Syntheses of Pyrimidine and Purine Analogs Derived from 1,2,6-Thiadiazine 1,1-Dioxide

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5-Amino-3-oxo-2*H*,4*H*-1,2,6-thiadiazine 1,1-dioxide and the monopotassium salt of 3,5-dioxo-2*H*,4*H*,6*H*-1,2,6-thiadiazine 1,1-dioxide was obtained by condensation of sulfamide and ethyl cyanacetate and diethyl malonate, respectively. 7-Oxo-1*H*,4*H*,6*H*-imidazo[2,3-c]-1,2,6-thiadiazine 5,5-dioxide was prepared by a multi-step reaction sequence from 5-amino-3-oxo-2*H*,4*H*-1,2,6-thiadiazine 1,1-dioxide.

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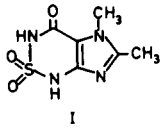
Following our work in the preparation of *S*-dioxo analogs of uracil (1,2), we now wish to report the syntheses of 5-amino-3-oxo-2*H*,4*H*-1,2,6-thiadiazine 1,1-dioxide (II) and the monopotassium salt of 3,5-dioxo-2*H*,4*H*,6*H*-1,2,6-thiadiazine 1,1-dioxide (VIII), the latter being an analog of barbituric acid.

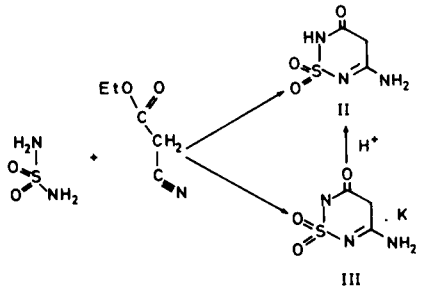
Compound II is the key intermediate needed for the synthesis of 7-oxo-1*H*,4*H*,6*H*-imidazo[2,3-c]-1,2,6-thiadiazine 5,5-dioxide (VII) as is reported in the present paper. Recently, Edenhofer and Meister reported the synthesis of I, a methyl analog of VII, by a different route, starting from appropriate derivative of imidazole (3).



I

Preparation of 5-Amino-3-oxo-2*H*,4*H*-1,2,6-thiadiazine 1,1-Dioxide.

Compound II was synthesized by condensation of sulfamide with ethyl cyanacetate in the presence of potassium methoxide. Treatment of an aqueous solution of the crude reaction mixture with Amberlite IR-120(H^+) resin afforded directly free compound II. However, when the above aqueous solution was acidified with acetic acid, the monopotassium salt III was isolated as could be observed by its analytical data. Free compound II could be also obtained from III by treatment with Amberlite IR-120 (H^+) resin.

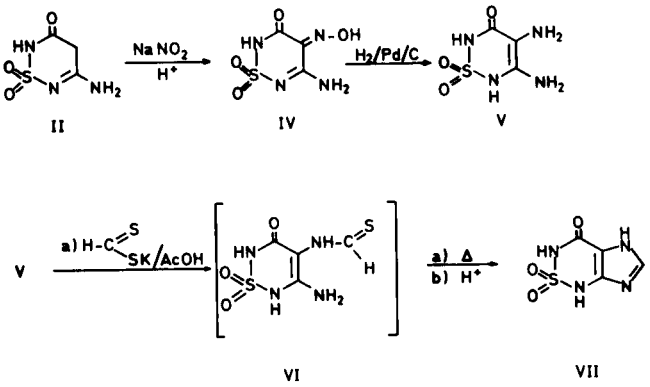


II III

The ^{1}H nmr spectrum of II exhibited a singlet at δ 3.60 for the two protons at C-4 and two broad signals for the NH protons. All these signals disappeared on adding deuterium oxide.

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

The synthetic approach for the preparation of this compound is based on that used for the obtention of 7-amino-1*H*,4*H*-imidazo[2,3-c]-1,2,6-thiadiazine 5,5-dioxide starting from 3,5-diamino-4*H*-1,2,6-thiadiazine 1,1-dioxide (2), according to the following pathway.



II IV V

VI VII

Compound II was smoothly converted to the oxime IV, upon treatment with sodium nitrite in acetic acid solution. The compound which crystallized from the reaction mixture was the monosodium salt of the oxime, as could be confirmed by its analytical data. When the aqueous suspension of this salt was acidified with concentrated hydrochloric acid to *p*H = 0, first the salt was dissolved and then free compound IV crystallized as yellow needles. The absence of the signal for the protons at position 4 in the ^{1}H nmr spectrum of IV, which was in that of II, indicated that the attack had taken place in this position. The ir spectrum of IV showed a broad hydroxyl absorption band at 3160 cm^{-1} and a carbonyl band at 1720 cm^{-1}.

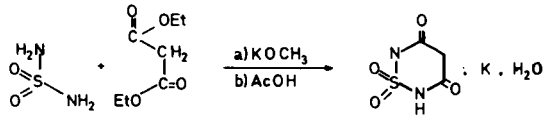
Catalytic hydrogenation of IV resulted in smooth conversion to the diamino derivative V. Attempts to reduce oxime IV with sodium dithionite did not give the expected V but a compound which was probably a sulfo derivative of V (4). Nevertheless, both, this sulfoderivative and V, treated in the same reaction conditions, led to VII.

Treatment of V with potassium dithioformate followed by ring closure, in acidic medium, of the non isolate

thioformamido derivative VI, yielded the imidazo-thiadiazine VII. The structure of VII was evident from the method of synthesis (Traube synthesis) (5), the analytical, nmr and mass spectrometry data, and the absence of the ir absorption bands for the amino group, indicated that the ring closure had taken place at this group. The ^1H nmr spectrum of VII exhibit a singlet at δ 8.75 attributed to the imidazole ring proton and a very broad multiplet at δ 9.6 for the NH protons.

Preparation of the Monopotassium Salt of 3,5-Dioxo-2*H*,4*H*,6*H*-thiadiazine 1,1-Dioxide.

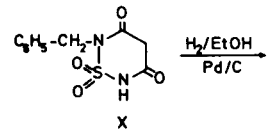
Although the synthesis of 3,5-dioxo-2*H*,4*H*,6*H*-1,2,6-thiadiazine 1,1-dioxide has been described by Walter (6), the attempts we made for the preparation of this compound were unsuccessful. Thus, hydrolysis of 3,5-diamino-4*H*-1,2,6-thiadiazine 1,1-dioxide (6), led us to obtain sulfamide or the unchanged starting material when milder hydrolysis conditions were used (6). Reaction of sulfamide with either malonic acid or some reactive functional derivatives, yielded open chain compounds bearing a molecule of sulfamide and one (XI) or two molecules of malonic acid, as was described by Paquin (7) and not the cyclic 1,2,6-thiadiazine as was reported in the review by Lawson and Tinkler (8). The reaction of sulfamide and diethyl malonate, following a procedure similar to the synthesis of 3,4-dihydroxy-1,2,5-thiadiazole 1,1-dioxide by Carmack and coworkers (9), after treatment with acetic acid, afforded the hydrated monopotassium salt of the cyclic 1,2,6-thiadiazine desired VIII which was dehydrated simply by drying it *in vacuo* over phosphorus pentoxide.



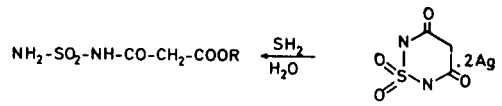
VIII

The ir spectrum of the dehydrated VIII showed three absorption bands at 1625, 1660 and 1715 cm^{-1}. The ^1H nmr spectrum exhibited one singlet at δ 3.1 for the two protons at position 4 and a broad signal at δ 3.4 for the NH proton. The crystal structure of the monopotassium salt VIII has been determined by single crystal x-ray diffraction techniques. The crystal packing (10) is built up with two crystallographically independent water molecules. Two types of potassium cations can be distinguished in the unit cell, as far as a first sphere of coordination of less of 3Å is concerned (11). One includes within this sphere four oxygen atoms and two nitrogen atoms of symmetrically related molecule plus two water oxygen. The other one has seven oxygen atoms, four of them belong to symmetry related SO_2 groups, and one is a water oxygen.

All our efforts to obtain the free cyclic thiadiazine from the monopotassium salt failed. Thus, treatment of VIII with either hydrochloric acid or Amberlite IR-120 (H^+) resin afforded the inaltered salt VIII in both cases. Attempts to liberate the disilver salt (IX), which was prepared from the monopotassium salt, with hydrogen sulfide gave the open chain compound (XI) identical in all respects with that obtained by the method of Paquin (7). Another attempt to obtain the free cyclic thiadiazine by debenzylation of X, which was synthesized from benzylsulfamide and malonyl chloride (7), yielded by catalytic hydrogenation in ethanol, the ethyl ester XII.



X



XI : R=H
XII : R=C_2H_5

IX

From all these facts, it can be deduced that, in spite of previous reports (8,9) compound 3,5-dioxo-2*H*,4*H*,6*H*-1,2,6-thiadiazine 1,1-dioxide is only isolable as salt form.

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 and mass spectra on a Varian MAT-711 spectrometer.

5-Amino-3-oxo-2*H*,4*H*-1,2,6-thiadiazine 1,1-Dioxide (II).

A potassium alkoxide solution was prepared by adding 5.87 g. (0.15 mole) of potassium to 30 ml. of 2-propanol and diluting the solution with 30 ml. of methanol. After the solution had cooled, 7.2 g. (0.075 mole) of sulfamide in 60 ml. of methanol was added dropwise with vigorous mechanical stirring to give a white suspension. Ethyl cyanacetate (8.47 g., 0.075 mole) was added dropwise with stirring and the resulting suspension was refluxed gently for 16 hours, with stirring. After cooling, the solid was filtered and dissolved in water. The aqueous solution was passed through 50 ml. (wet volume) of Amberlite IR-120 (H^+) cation-exchange resin, and eluted with water. The eluent was concentrated to 10 ml. and cooled in a refrigerator yielding 3.5 g. (30%) of II as colorless needles, m.p. 235° dec.; uv λ max (water): 210 (ϵ, 14,100), 220 (sh) (ϵ, 12,500) and 295 nm (ϵ, 750); ^1H nmr (DMSO-d_6, δ): 3.60 (s, 2H, CH_2), 4.30 (b.m. 1H, NH); 8.50 (b.s. 2H, NH_2); ir (nujol, ν): 3410, 3310, 3120 (NH_2, NH), and 1700, 1630 cm^{-1} (C=O, C=N).

Anal. Calcd. for $C_3H_5N_3O_3S$: C, 22.08; H, 3.06; S, 19.63. Found: C, 22.13; H, 3.13; S, 19.67.

Monopotassium Salt of 5-Amino-3-oxo-2*H*,4*H*-1,2,6-thiadiazine 1,1-Dioxide (III).

The aqueous solution mentioned above was acidified with acetic acid to *p*H 5 and was chilled in a refrigerator. The resulting precipitate was collected by filtration and recrystallized from

water to give 5.25 g. (35% yield) of III, m.p. 254-257°; ir (nujol, ν): 3330, 3200 (NH_2), 1650, 1620 and 1580 cm^{-1} (C=O, C=N).

Anal. Calcd. for $C_3H_4N_3O_3SK$: C, 17.91; H, 1.99; S, 15.92. Found: C, 17.64; H, 2.19; S, 15.65.

5-Amino-4-hydroximino-3-oxo-2*H*,4*H*-1,2,6-thiadiazine 1,1-Dioxide (IV).

A stirred solution of 3 g. (0.018 mole) of II and 1.25 g. (0.018 mole) of sodium nitrite in 20 ml. of 1.5 *N* sodium hydroxide at ice bath temperature was treated dropwise with 3 ml. of glacial acetic acid. The mixture was then stirred at room temperature for 1 hour. The yellow solid, which appeared, was filtered, washed with ethanol and dried *in vacuo* over calcium chloride to give 3.25 g. of the monosodium salt of IV. This salt was suspended in water and acidified with concentrated hydrochloric acid to *p*H = 0 and then it was cooled at 0° overnight. The yellow needles which crystallized from this solution were collected by filtration, washed with water and dried *in vacuo* over sodium hydroxide yielding free compound IV, m.p. 180° dec.; uv λ max (water): 203 (ϵ, 5,150) and 254 nm (ϵ, 4,900); ^1H nmr (DMSO-d_6, δ): 8.6, 9.6 and 11.4 (m, NH and NOH); ir (nujol, ν): 3400, 3300, 3160, 3030 (NH_2, NH, NOH), 1720, 1680, 1630 cm^{-1} (C=O, C-N).

Anal. Calcd. for $C_3H_4N_4O_4S$: C, 18.75; H, 2.06; S, 16.66. Found: C, 18.60; H, 2.08; S, 16.50.

Monosodium salt of IV, m.p. 265° dec.; uv λ max (water): 207 (ϵ, 6,200), 258 nm (ϵ, 7,150); ^1H nmr (DMSO-d_6, δ): 7.4 (m, NH_2, NH); ir (nujol, ν): 3410, 3300, 3120 (NH_2, NH), 1650, 1610 cm^{-1} (C=O, C=N).

Anal. Calcd. for $C_3H_3N_4O_4SNa$: C, 16.82; H, 1.41; S, 14.95. Found: C, 17.01; H, 1.54; S, 14.72.

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

A suspension of 2 g. of IV in 100 ml. of ethanol was hydrogenated with 50 psi of hydrogen in the presence of palladium/carbon 10% catalyst at room temperature. After 2 hours, the reaction mixture was evaporated to dryness *in vacuo*. The residue was dissolved in water and the catalyst was separated by filtration. The solution was concentrated and chilled in a refrigerator, the resulting precipitate was collected by filtration and dried *in vacuo* over calcium chloride yielding 0.75 g. of pure V, m.p. 198-200° dec. (water); uv λ max (water): 211 (ϵ, 7,300) and 286 (sh), nm (ϵ, 1,700); ^1H nmr (DMSO-d_6, δ): 5.9 (m, 2H, NH) and 7.4 (b.m. 4H, NH_2); ir (nujol, ν): 3460, 3360, 3240 (NH, NH_2), 1640, 1600, 1570 cm^{-1} (C=O, C=N).

Anal. Calcd. for $C_3H_6N_4O_3S$: C, 20.22; H, 3.37; N, 31.45; S, 17.96. Found: C, 20.16; H, 3.39; N, 31.17; S, 17.85.

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

A suspension of 4 g. of V in 500 ml. of water at 40° was treated with 6 g. of potassium dithioformate and allowed to stand for 7 hours. The mixture was acidified with glacial acetic acid and filtered off. The filtrate was evaporated *in vacuo* to 60 ml., heated to reflux for 3 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 solution in a refrigerator and filtration gave 2.0 g. (50% yield) of VII, m.p. 244-246° dec. (water); uv λ max (water): 207 (ϵ, 10,000), 227 (sh) (ϵ, 5,800) and 289 nm (ϵ, 7,900); ^1H nmr (DMSO-d_6, δ): 8.75 (s, 1H, CH imidazole ring), 9.65 (b.m., 3H, NH); ir (nujol, ν): 3130 (NH), 1650, 1600 cm^{-1} (C=O, C=N); ms: m/e (%): 188 (33) M^+, 109 (39), 108 (33), 96 (5), 81 (20), 80 (9), 64 (72), 54 (44), 53 (10), 48 (22), 44 (90), 43 (28), 32 (28), 28 (100).

Anal. Calcd. for $C_4H_4N_4O_3S$: C, 25.53; H, 2.12; S, 17.02. Found: C, 25.38; H, 2.16; S, 17.23.

Monopotassium Salt of 3,5-Dioxo-2*H*,4*H*,6*H*-1,2,6-thiadiazine 1,1-Dioxide (VIII).

To the suspension of potassium alkoxide and sulfamide described for compound II, 7.12 g. (0.075 mole) of diethyl malonate were added, dropwise, with stirring, and the resulting suspension was refluxed gently for 16 hours. After cooling, the white solid was filtered, washed with methanol and dried in vacuum to give 13 g. of crude product. The solution prepared with 2 g. of crude reaction product and 20 ml. of water was acidified with acetic acid to *p*H 5 and stored at 0-5° overnight. The colorless plates which precipitated were collected by filtration, washed with ethanol and dried over phosphorus pentoxide whereupon they turned to white, yielding 0.75 g. (30%) of analytically pure product, m.p. 252-253° dec.; uv λ max (water): 208 nm (ϵ, 5,700), ^1H nmr (DMSO-d_6, δ): 3.00 (m, 1H, NH), 3.07 (s, 2H, CH_2); ir (nujol, ν): 3050 (NH), 1700, 1650 and 1610 cm^{-1} (C=O, C=N).

Anal. Calcd. for $C_3H_3N_2O_4SK$: C, 17.82; H, 1.48; N, 13.86; S, 15.84. Found: C, 17.79; H, 1.54; N, 13.56; S, 15.93.

Disilver Salt of 3,5-Dioxo-2*H*,4*H*,6*H*-1,2,6-thiadiazine 1,1-Dioxide (IX).

A solution of 3 g. of silver nitrate in 30 ml. of water was added dropwise to a stirred solution of VIII (2 g., 0.01 mole) in 50 ml. of water at 90°. After the addition was complete, the mixture was boiled for 15 minutes and filtered hot. The white solid was washed with 50 ml. of hot water and dried over phosphorus pentoxide to give 2.95 g. (90%), m.p. > 350° dec.; ir (nujol, ν): 1620 cm^{-1} (C=O).

Anal. Calcd. for $C_3H_2N_2O_4SAg_2$: C, 9.53; H, 0.52; N, 7.40; S, 8.46. Found: C, 9.78; H, 0.75; N, 7.46; S, 8.24.

2-Benzyl-3,5-dioxo-4*H*,6*H*-1,2,6-thiadiazine 1,1-Dioxide (X).

To a solution of 1.86 g. (0.01 mole) of benzylsulfamide in 50 ml. of warm, dry toluene, 1.45 g. (0.01 mole) of malonyl chloride were added. This mixture was kept at 50° for ½ hour, then it was stirred for 14 hours at 70°. The solid which precipitated was filtered, washed with benzene and dried *in vacuo* to give 2.2 g. (96%) of X, m.p. 174° (ethanol-petroleum ether); ^1H nmr (DMSO-d_6, δ): 3.80 (s, 2H, CH_2 (4)), 4.90 (s, 2H, CH_2 benzylic), 7.35 (m, 5H, aromatic protons), 11.10 (m, 1H, NH); ir (nujol, ν): 3100 (NH), 1740, 1690 cm^{-1} (C=O, C=N).

Anal. Calcd. for $C_{10}H_{10}N_2O_4S$: C, 47.25; H, 3.92; N, 11.03; S, 12.64. Found: C, 47.40; H, 3.83; N, 10.92; S, 12.83.

Ethyl Ester of Malonilsulfamide (XI).

A solution of 2 g. (0.008 mole) of X in 100 ml. of ethanol was hydrogenated with 40 psi of hydrogen in the presence of 10% palladium/carbon catalyst at 50°. After 5 hours, the catalyst was filtered off and the resulting solution was evaporated to dryness *in vacuo*. The residue was dissolved in ethanol and purified by thin layer chromatography, developed in an 8:1 mixture of chloroform and ethanol. After recrystallization with ethanol/petroleum ether 0.35 g. (50%) of XI were obtained, m.p. 125-126°; ^1H nmr (DMSO-d_6, δ): 1.20 (t, 3H, CH_3), 3.35 (s, 2H, CH_2 (4)), 4.15 (c, 2H, CH_2O), 7.20 (b.m., 3H, NH); ir (nujol, ν): 3400, 3250, 3180 (NH_2, NH), 1720 and 1690 cm^{-1} (C=O).

Anal. Calcd. for $C_5H_{10}N_2O_5S$: C, 28.57; H, 4.76; N, 13.33; S, 15.23. Found: C, 28.53; H, 4.59; N, 13.25; S, 15.01.

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