Synthesis of 4-Substituted 3-Hydroxy- and 3-amino-6*H*-1,2,6-thiadiazine 1,1-Dioxides

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Reaction of sulfamide with ethoxymethylene derivatives yielded 4-ethoxycarbonyl-, 4-cyano-, and 4-nitro-2*H*,6*H*-1,2,6-thiadiazine 1,1-dioxide. In some cases, the corresponding open chain sulfamidomethylene derivatives were isolated. Preparation of 4-amino- and 4-amino-5-methyl-2*H*,6*H*-1,2,6-thiadiazin-3-one 1,1-dioxide is also described. Reaction of sulfamide with ethyl 3,3-ethoxypropionate afforded 3,7-bis(ethoxycarbonylmethyl)perhydro-1,5,2,4,6,8-dithiatetrazocine 1,1,5,5-tetroxide.

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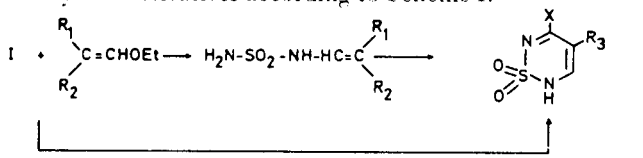
Whitehead (1) and more recently Prystas (2), have described syntheses of 5-substituted uracil and cytosine derivatives, by cyclization of ureidomethylene derivatives. In our effort to prepare *S*-dioxo analogs of pyrimidines (3), which could act as potential antimetabolites, we have studied the reaction of sulfamide (I) and several ethoxymethylene derivatives according to Scheme I.



II III IV

a, $R_1 = R_2 = CO_2Et$
b, $R_1 = CN, R_2 = CO_2Et$
c, $R_1 = R_2 = CN$
d, $R_1 = NO_2, R_2 = CO_2Et$
e, $R_1 = H, R_2 = CO_2Et$

a, $R_1 = R_2 = CO_2Et$
b, $R_1 = CN, R_2 = CO_2Et$
c, $R_1 = R_2 = CN$

a, $X = OH, R_3 = CO_2Et$
b, $X = OH, R_3 = CN$
c, $X = NH_2, R_3 = CN$
d, $X = OH, R_3 = NO_2$

Depending on the number and nature of the activating substituents R_1 and R_2 of the ethoxymethylene derivatives II, the reaction with sulfamide led, in basic medium, to the sulfamidomethylene derivatives III or to the 5-substituted 1,2,6-thiadiazine derivatives IV, which could also be obtained by further basic treatment of the corresponding open chain compounds III.

The reaction of the ethoxymethylene compounds IIa, IIb, IIc with sulfamide in dilute sodium hydroxide, at room temperature, yielded upon treatment with hydrochloric acid, diethyl sulfamidomethylenemalonate (IIIa), ethyl sulfamidomethylenecyanacetate (IIIb) and sulfamidomethylenemalononitrile (IIIc), respectively. All these open products exhibited very similar characteristics in their spectral data. Thus, the uv spectra showed absorption bands at wavelengths λ max (ethanol) 272-276 nm, and the ^{1}H nmr signals for the ethylenic protons appeared at δ 8.05-8.30.

The ^{1}H nmr spectrum of ethyl sulfamidomethylenecyanacetate (IIIb) showed a mixture of the (*Z*) and (*E*) isomers in a 1:5 ratio, as could be deduced from the two different signals for the ethylenic proton. The signal at higher field was attributed to the (*Z*) isomer, whilst the one at lower field to the (*E*) isomer, by estimation of the chemical shifts of protons in olefinic systems using additive increments for the substituents (4).

From the reaction of sulfamide with ethoxymethylenemalononitrile (IIc) two isomeric compounds were isolated, one was the expected sulfamidomethylenemalononitrile (IIIc) and the other one could be identified as the cyclic derivative IVc. Since in this case, both the open chain product and the cyclic compound have the same analytical data, the assignment of their structure was mainly based on the fact that on treating open chain isomer IIIc with sodium ethoxide, the cyclic one (IVc) was obtained. Both the uv and ^{1}H nmr spectral data confirmed this assignment, by comparison with those of other open chain and cyclic compounds here described.

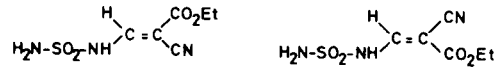
On treating ethyl ethoxymethylenenitroacetate (IId) with sulfamide, in the way mentioned above, no reaction took place. Neither could the corresponding sulfamidomethylene derivative be obtained by reaction of sulfamide, ethyl nitroacetate and triethyl orthoformate, according to the preparation of ethyl ureidomethylenenitroacetate (2). Nevertheless, under stronger basic conditions sulfamide and IId directly afforded the cyclic compound IVd.

All our attempts to bring into reaction sulfamide with ethyl ethoxymethyleneacetate (IIe) (3), under several conditions of basicity and temperature had no success.

The cyclization of the sulfamidomethylene derivatives IIIa, IIIb and IIIc was carried out by treatment with sodium ethoxide, in ethanol, at room temperature, yielding the corresponding 1,2,6-thiadiazine derivatives IVa, IVb and IVc. As in the case of the open chain products, these compounds had also many spectral features in common, and so, they all showed absorption bands at λ max 288 nm, and the proton at C-5 appeared at δ 7.70-8.36 in their ^{1}H nmr spectra.

The cyclization of ethyl sulfamidomethylenecyanacetate (IIIb) afforded only the uracil derivative, whilst none of the cytosine one could be traced. Since the *E*-isomer was the predominating form in the starting material, the fact that the uracil analog was obtained could only be explained by an isomerization to the *Z* form, prior to the cyclization. This is in agreement with the strong experimental conditions needed for the reaction to take place.

It must be pointed out that both the 4-nitro- and 4-cyanothiadiazine derivatives (IVb, IVd) prepared with



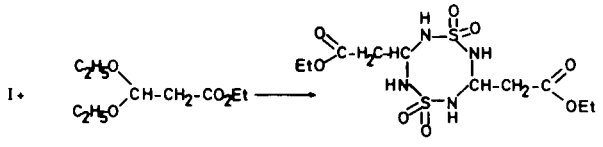
E Z

III b

sodium ethoxide, somehow bind, sodium, in such a way, that neither acid treatment nor resin exchange could release the free heterocyclic compounds. Moreover, attempts to displace the sodium by reaction of the sodium complex of IVb with silver nitrate, and treatment of the compound thus obtained with hydrogen sulfide, led to the unchanged starting material.

For the preparation of 4-cyano-2*H*,6*H*-1,2,6-thiadiazin-3-one 1,1-dioxide (IVb) and 4-nitro-2*H*,6*H*-1,2,6-thiadiazin-3-one 1,1-dioxide (IVd) sulfamide and the corresponding ethoxymethylene derivatives were refluxed in 2-propanol/methanol in the presence of potassium. Compounds IVb and IVd were isolated either by means of an Amberlite IR-120 (H^+) column, as in the case of IVd, or by treating with hydrochloric acid the monopotassium salt of IVb, obtained by addition of acetic acid to the reaction mixture.

Our interest in preparing 2*H*,6*H*-1,2,6-thiadiazin-3-one 1,1-dioxide, as an analog of uracil, led us to attempt the reaction of ethyl 3,3-diethoxypropionate with sulfamide, on the basis that 3-methylthiouracil had thus been obtained starting from *N*-methylthiourea (6). Furthermore, it was known that sulfamide reacted with aldehydes or acetals rending the corresponding alkylidene sulfamides (7). However, when this reaction was carried out in hydrochloric acid medium, 3,7-bis(ethoxycarbonylmethyl)-perhydro-1,5,2,4,6,8-dithiatetrazocine 1,1,5,5-tetroxide (V) was obtained.

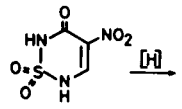


V

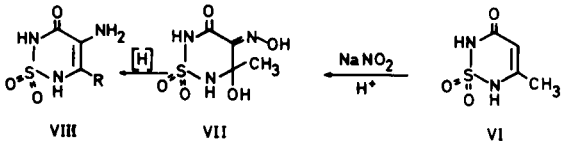
The structure of V was established according to its analytical and spectral data; thus the ^1H nmr spectrum showed two doublets, one at δ 2.60 with a coupling constant of J = 7 Hz corresponding to the CH_2 group, and another one at δ 7.40 with $J_{CH\text{-}NH}$ = 9 Hz, due to the NH group coupled with the CH. The multiplet at δ 5.12 attributed to the CH collapsed to a triplet upon addition of deuterium oxide.

The formation of this compound is due to a "dimerizing cyclocondensation" *via* an α-ureidoalkylation (8) as it had been previously observed (9).

It is worth mentioning that the desired analog of uracil, could neither be obtained by hydrolysis and decarboxylation of the ethyl ester derivative, nor by oxidation and decarboxylation of the 5-methylthiadiazine. This behaviour contrasted with that of 5-ethoxycarbonyluracil



IVd



VIII VII VI

a, R=H

b, R=CH_3

and 6-methyluracil which do undergo these reactions (10, 11).

The amino derivative VIIIa was obtained by catalytic hydrogenation of IVd. For the preparation of its 5-methyl derivative (VIIIb), 5-methyl-2*H*,6*H*-1,2,6-thiadiazin-3-one 1,1-dioxide (VI), previously synthesized in this laboratory (12), was treated with sodium nitrite in acetic acid solution. The oximino derivative thus prepared, was reduced, by catalytic hydrogenation, to the amino compound VIIIb. Compounds VIIIa and VIIIb had very similar spectroscopic features and physical properties. Thus, both were very insoluble in organic solvents, and the water solutions changed their colour from yellow to red (13).

The oxime VII was isolated with a molecule of water convalently bonded as could be deduced from its mass spectrum. Despite the steric hindrance of the methyl group at the 5 position, the electron-withdrawing effect of the oximino group (14) can account for the addition of water across the CN double bond.

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. Ultraviolet spectra were recorded on a Perkin-Elmer 350 and 402 spectrophotometer. Mass spectra were run on a Varian MAT-711 spectrometer.

Diethyl Sulfamidomethylenemalonate (IIIa).

Sodium hydroxide, 0.4 g. (0.01 mole) in 40 ml. of water was added, dropwise, to a well-stirred suspension of 0.96 g. (0.01 mole) of sulfamide and 2.16 g. (0.01 mole) of diethyl ethoxymethylenemalonate (IIa). After stirring for 12 hours at room temperature, the reaction mixture, which by then was completely uniform, was extracted, repeatedly, with ethyl acetate. The aqueous layer was cooled to 10°, and upon addition of concentrated hydrochloric acid, a white precipitate appeared. Recrystallization from ethyl acetate/petroleum ether yielded 1.08 g. of pure IIIa (41%), m.p. 148-149°; uv λ max (ethanol): 272 nm (ϵ, 18,100); ^1H nmr (DMSO-d_6, δ): 8.10 (s, 1H, CH), 8.00 (bm, 2H, NH_2), 4.20 (m, 4H, CH_2), 1.24 (t, 6H, CH_3); ir (nujol, ν): 1675 (C=O).

Anal. Calcd. for $C_8H_{14}N_2O_6S$: C, 36.09; H, 5.26; N, 10.52; S, 12.03. Found: C, 36.00; H, 5.15; N, 10.26; S, 12.21.

(*E*) (*Z*) Ethyl Sulfamidomethylenecyanacetate (IIIb).

This compound was obtained by the procedure described above starting from 0.96 g. (0.01 mole) of sulfamide and 1.69 g. (0.01 mole) of ethyl ethoxymethylenecyanacetate (IIb). The final product was purified by tlc using 40:2:1 chloroform, ethanol, acetic acid. The major band, after recrystallization from ethyl acetate/petroleum ether afforded 0.6 g. of IIIb (30%), m.p. 150-152° dec.; uv λ max (ethanol): 275 nm (ε, 18,400); ^{1}H nmr (DMSO-d_6, δ): 8.35 (bm, 3H, NH and NH_2), 8.30 (s, CH (E)), 8.05 (s, CH (Z)), 4.25 (q, 2H, CH_2), 1.25 (t, 3H, CH_3); ir (nujol, ν): 2220 (CN), 1675 (C=O).

Anal. Calcd. for $C_6H_9N_3O_4S$: C, 32.88; H, 4.13; N, 19.18; S, 14.59. Found: C, 33.10; H, 4.21; N, 19.08; S, 14.59.

Sulfamidomethylenemalononitrile (IIIc).

The synthesis of this compound was accomplished, as before, starting from 0.96 g. (0.01 mole) of sulfamide and 1.22 g. (0.01 mole) of ethoxymethylenemalononitrile (IIc). The precipitate obtained, at the end, was a mixture of two products, one of which was insoluble in ethyl acetate. The other one, which was a white solid, was recrystallized from ethyl acetate/petroleum ether furnishing 0.57 g. of pure IIIc, (33%), m.p. 167-168°; uv λ max (ethanol): 276 nm (ε, 22,400); ^{1}H nmr (DMSO-d_6, δ): 8.05 (s, 1H, CH), 7.92 (s, 3H, NH_2 and NH); ir (nujol, ν): 2250 cm^{-1} (CN).

Anal. Calcd. for $C_4H_4N_4O_2S$: C, 27.91; H, 2.34; N, 32.55. Found: C, 28.11; H, 2.33; N, 32.48.

The insoluble solid in ethyl acetate, was filtered off and recrystallized from water to give 0.15 g. (10%) of 3-amino-4-cyano-6*H*-1,2,6-thiadiazine 1,1-dioxide (IVc).

4-Ethoxycarbonyl-2*H*,6*H*-1,2,6-thiadiazin-3-one 1,1-Dioxide (IVa).

A sodium ethoxide solution was prepared by adding 0.5 g. (0.02 mole) of sodium to 150 ml. of ethanol. Once the solution had cooled it was added dropwise to a well-stirred suspension of 2.66 g. (0.01 mole) of IIIa in 50 ml. of ethanol. On stirring at room temperature for 12 hours, the reaction mixture was concentrated to dryness *in vacuo*. The residue was dissolved in water and acidified with hydrochloric acid. The solid which then appeared was collected by filtration and recrystallized from ethyl acetate/petroleum ether to give 1.41 g. of IVa (65%), m.p. 178-179°; uv λ max (ethanol): 244 nm (ε, 11,900), 288 nm (ε, 7,700); ^{1}H nmr (DMSO-d_6, δ): 11.40 (s, 2H, NH), 8.36 (s, 1H, H-5), 4.25 (q, 2H, CH_2), 1.25 (t, 3H, CH_3); ir (nujol, ν): 1680 cm^{-1} (CONH), 1640 cm^{-1} (C=O).

Anal. Calcd. for $C_6H_8N_2O_5S$: C, 32.73; H, 3.66; N, 12.72; S, 14.54. Found: C, 32.82; H, 3.66; N, 12.65; S, 14.25.

4-Cyano-2*H*,6*H*-1,2,6-thiadiazin-3-one 1,1-Dioxide (IVb).

A potassium alkoxide solution was prepared by adding 0.78 g. (0.02 mole) of potassium to 10 ml. of 2-propanol and diluting the solution with 10 ml. of methanol. After the solution had cooled, 0.96 g. (0.01 mole) of sulfamide in 10 ml. of methanol were added dropwise with stirring to give a white suspension. Ethyl ethoxymethylenecyanacetate (IIb) 1.69 g. (0.01 mole) was added, dropwise, with stirring, and the resulting suspension was refluxed gently and stirred for 10 hours. After cooling, the solid was filtered and dissolved in water, and treated with acetic acid. The monopotassium salt of IVb, thus obtained, was filtered off, dissolved in water and acidified with hydrochloric acid to give free compound IVb (35%), m.p. 209-210° (nitromethane); uv λ max (water): 290 nm (ε, 11,000); ^{1}H (DMSO-d_6, δ): 9.25 (s, 2H, NH), 7.84 (s, 1H, H-5); ir (nujol, ν): 2250 cm^{-1} (CN), 1650 cm^{-1} (C=O).

Anal. Calcd. for $C_4H_3N_3O_3S$: C, 27.75; H, 1.74; N, 24.27. Found: C, 27.68; H, 1.95; N, 24.51.

Monopotassium Salt of IVb.

This compound had m.p. 250-251° dec. (water); ^{1}H nmr (DMSO-d_6, δ): 7.68 (s, 1H, H-5); ir (nujol, ν): 3500 cm^{-1} (OH), 2240 cm^{-1} (CN).

Anal. Calcd. for $C_4H_3N_3O_3SK \cdot H_2O$: C, 20.86; H, 2.17; N, 18.26. Found: C, 21.15; H, 2.08; N, 18.40.

3-Amino-4-cyano-6*H*-1,2,6-thiadiazine 1,1-Dioxide (IVc).

a) Condensation of Sulfamide and Ethoxymethylenemalononitrile (IIc).

To a stirred suspension of 1.22 g. (0.01 mole) of ethoxymethylenemalononitrile (IIc) and 0.96 g. (0.01 mole) of sulfamide in 50 ml. of ethanol, sodium ethoxide (0.5 g. of sodium in 100 ml. of ethanol, 0.02 mole) was added dropwise. After stirring for 12 hours at room temperature, the reaction mixture was concentrated *in vacuo*, dissolved in water and acidified with hydrochloric acid. The solid thus obtained was collected by filtration and recrystallized from water to give 0.7 g. of IVc (41%), m.p. 235-236° dec.; uv λ max (ethanol): 288 nm; ^{1}H nmr (DMSO-d_6, δ): 8.32 (s, 1H, H-5), 7.40 (m, 4H, NH_2 and NH); ir (nujol, ν): 2230 cm^{-1} (CN).

Anal. Calcd. for $C_4H_4N_4O_2S$: C, 27.91; H, 2.34; N, 32.55. Found: C, 27.90; H, 2.64; N, 32.31.

b) Cyclization of Sulfamidomethylenemalononitrile (IIIc).

Cyclization of IIIc, 1.72 g. (0.01 mole), under the same conditions as those described for IIIa, gave 0.9 g. (52%) of a compound identical to that obtained by method a.

4-Nitro-2*H*,6*H*-1,2,6-thiadiazin-3-one 1,1-Dioxide (IVd).

This compound was prepared starting from ethyl ethoxymethylenenitroacetate (IId), 1.89 g. (0.01 mole), in a similar manner as described for IVb. After filtering the precipitate, it was dissolved in water and passed through 30 ml. (wet volume) of Amberlite IR-120 (H^+) column. Elution with water provided the free compound IVa which was recrystallized from nitromethane to give 0.7 g. (35%), m.p. 152-153° dec.; uv λ max (ethanol): 267 nm (ε, 5,100), 337 nm (ε, 14,100); ^{1}H nmr (DMSO-d_6, δ): 8.82 (s, 2H, NH), 8.75 (s, 1H, H-5); ir (nujol, ν): 1530 and 1350 cm^{-1} (NO_2).

Anal. Calcd. for $C_3H_3N_3O_5S$: C, 18.66; H, 1.56; N, 21.76. Found: C, 18.56; H, 1.80; N, 21.70.

3,7-Bis(ethoxycarbonylmethyl)perhydro-1,5,2,4,6,8-dithiatetrazocine 1,1,5,5-Tetroxide (V).

Ethyl 3,3-ethoxypropionate (15), 1.9 g. (0.01 mole), were added, dropwise, to a solution of 0.96 g. (0.01 mole) of sulfamide in 25 ml. of dilute hydrochloric acid. The reaction mixture was stirred at room temperature for 24 hours. The white solid which had precipitated was filtered off and recrystallized from nitromethane to give 0.7 g. of V (36%), m.p. 178-179°; uv λ max (ethanol): 255 nm; ^{1}H nmr (DMSO-d_6, δ): 7.40 (d, 4H, NH, J = 9 Hz), 5.12 (m, 2H, CH), 4.01 (q, 4H, CH_2), 2.60 (d, 4H, CH_2, J = 7 Hz), 2.15 (t, 6H, CH_3).

Anal. Calcd. for $C_{10}H_{20}N_4O_8S_2$: C, 30.93; H, 5.19; N, 14.43; S, 16.50. Found: C, 31.07; H, 5.38; N, 14.27; S, 16.86.

5-Hydroxy-4-hydroxyimino-5-methyl-2*H*,4*H*,6*H*-1,2,6-thiadiazin-3-one 1,1-Dioxide (VII).

A stirred solution of 1.62 g. (0.01 mole) of 5-methyl-2*H*,6*H*-1,2,6-thiadiazin-3-one 1,1-dioxide (VI) (12), and 0.69 g. (0.01 mole) of sodium nitrite in 35 ml. of water, at ice bath temperature, was acidified with acetic acid. The reaction mixture was stirred at room temperature for 4 hours, and then passed through an Amberlite IR-120 (H^+) column. The solution so obtained was concentrated to dryness *in vacuo* (bath temperature below 35°),

and the residue recrystallized from acetonitrile/chloroform yielding 1.6 g. (77%), m.p. 138-139° dec.; ^{1}H nmr (DMSO-d_6, δ): 13.20 (m, 1H, OH), 11.90 (m, 1H, OH), 7.68 (s, 2H, NH), 2.32 (s, 3H, CH_3); ir (potassium bromide, ν): 3410, 3370, 3280 and 3150 cm^{-1} (OH, NOH, NH); ms, m/e (%): 209 (10) M^+, 191 (15).

Anal. Calcd. for $C_4H_7N_3O_5S$: C, 22.96; H, 3.34; N, 20.09. Found: C, 22.80; H, 3.41; N, 20.00.

4-Amino-2*H*,6*H*-1,2,6-thiadiazin-3-one 1,1-Dioxide (VIIIa).

A solution of 0.96 g. (0.005 mole) of IVd in 35 ml. of water was hydrogenated with 30 psi in the presence of platinum oxide, at room temperature. The precipitate was filtered and yielded, after recrystallization, from water 0.35 g. of VIIIa (45%), m.p. 175-176° dec.; uv λ max (water): 285 nm; ^{1}H nmr (DMSO-d_6, δ): 7.92 (bm, 4H, NH_2 and NH), 7.20 (s, 1H, H-5); ir (nujol, ν): 3250, 3130 cm^{-1} (NH_2, NH).

Anal. Calcd. for $C_3H_5N_3O_3S$: C, 22.00; H, 3.09; N, 25.76. Found: C, 22.02; H, 3.43; N, 26.03.

4-Amino-5-methyl-2*H*,6*H*-1,2,6-thiadiazin-3-one 1,1-Dioxide (VIIIb).

A solution of 1.04 g. (0.005 mole) of VII in 35 ml. of ethanol was hydrogenated with 40 psi in the presence of platinum oxide, at room temperature. The white solid was filtered and recrystallized from water/ethanol affording 0.3 g. of VIIIb (34%), m.p. 197-198° dec.; uv λ max (ethanol): 290 nm; ^{1}H nmr (DMSO-d_6, δ): 8.80 (bm, 4H, NH_2 and NH), 1.95 (s, 3H, CH_3); ir (nujol, ν): 3270, 3150 cm^{-1} (NH_2, NH).

Anal. Calcd. for $C_4H_7N_3O_3S$: C, 27.12; H, 3.98; N, 23.72; S, 18.06. Found: C, 26.90; H, 3.98; N, 23.44; S, 17.76.

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