Tetrahydro-2-thioxo-2*H*-1,3,5-thiadiazin-4-ones and their Derivatives Representing a Novel Heterocyclic Ring System

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The cyclization reaction between *N*-substituted dithiocarbamates (**1**) and *N*-substituted *N*-chloromethylcarbamoyl chlorides (**2**) gives 3,5-disubstituted tetrahydro-2-thioxo-2*H*-1,3,5-thiadiazin-4-ones (**3**). In order to decide among the theoretically possible structures **3-5**, the compounds **6a,b**, containing a thioxo group instead of an oxo group as in **3a,b**, as well as the *S*-oxide derivative of **3a** was also established by X-ray structure determination.

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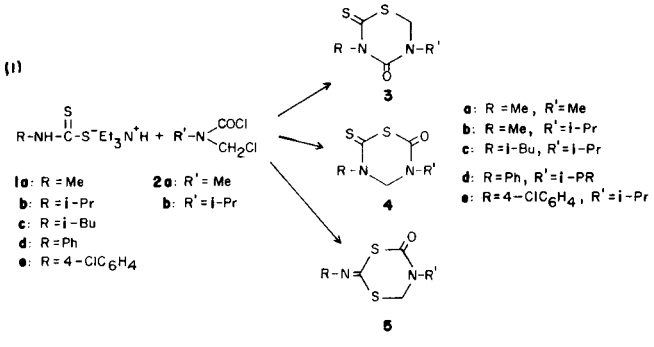
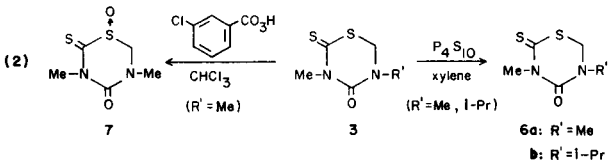
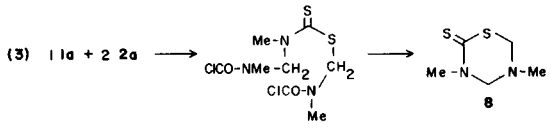
Although the first representatives of the fully saturated 1,3,5-thiadiazines were synthesized as early as the last century, their correct structure was not assigned until 1944 (2). Only a few authors have researched the synthesis of new perhydro-1,3,5-thiadiazine derivatives (3-7). Recently, new derivatives have been synthesized using *N*-chloromethylcarbamoyl chlorides to cyclize thioureas (8-10).

We have investigated the cyclization reaction of *N*-substituted *N*-chloromethylcarbamoyl chlorides (**2**) with *N*-substituted dithiocarbamic acid triethylammonium salts (**1**). Theoretically, three different products can form (equation 1).



The cyclization probably takes place in two consecutive steps. It is logical that the chloromethyl group reacts first with the sulfur of the dithiocarbamate, considering both the difference in reactivity between the chloromethyl and the carbamoyl chloride groups, and the fact that thiols are generally stronger nucleophilic agents than amino groups. It has been proved that the chloromethyl group of **2** reacts with certain nucleophiles (*e.g.*, mercaptans, alcohols, *etc.*) in preference to the carbonyl chloride group (11). The ring is closed by the carbonyl chloride group reacting either at the nitrogen atom or at the alternate sulfur atom *via* tautomerisation, to give tetrahydro-2-thioxo-2*H*-1,3,5-thiadiazin-4-ones (**3**) or dihydro-2-imino-2*H*,4*H*-1,3,5-dithiazin-4-ones (**5**), respectively. The formation of tetrahydro-2-thioxo-2*H*-1,3,5-thiadiazin-6-ones (**4**) by a reverse cyclization is less probable.





We have carried out the reactions in acetone in the presence of an additional mole of triethylamine as an acid acceptor. No reaction took place when treating *N*-isopropyldithiocarbamate (**1b**) with **2a** or **2b**. A major and a minor product was obtained from the reaction between *N*-methyl-dithiocarbamate (**1a**) and **2a**.

In order to decide among the theoretically possible structures **3-5**, we have synthesized (with phosphorus pentasulfide in xylene) the compounds **6**, which contain a

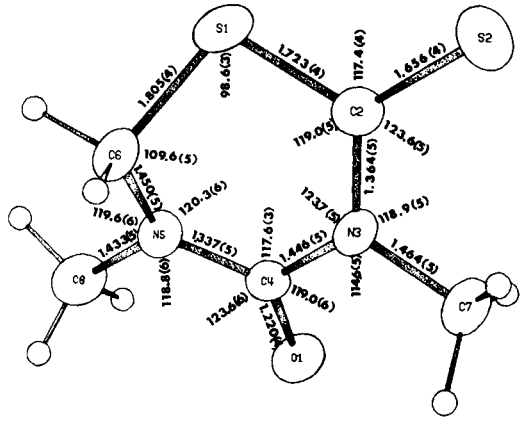


Figure. The perspective diagram of the molecule **3a** with the numbering of atoms, bond lengths (Å) and angles (°).

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Table 1

Spectroscopical Data of Tetrahydro-2*H*-1,3,5-thiadiazines **3a-e**, **6a,b**, **7** and **8**

Compound No.	Ir data [cm^{-1}] in Potassium Bromide Discs		^{1}H Nmr Data in Deuteriochloroform [δ TMS = 0 ppm]					
	ν C=O	ν C=S	δ CH_3 (a) d (b) (6H)	δ NCH_3, s (3H) 3rd	5th	δ CH_2, s (2H)	δ CH (a), sp (b) (1H)	Other Signals
3a	1680	1325	—	3.55	3.20	4.50	—	—
3b	1665	1310	1.30	3.60	—	4.40	4.65	—
3c	1675	1350 1325	1.25	—	—	4.35	4.60	δ CH_3 (c) 0.90 d (b) (6H) δ CH_2 (c), 4.40, d (b) (2H) δ CH (c), 2.10, m (1H)
3d	1690	1310	1.25	—	—	4.45	4.60	ν ArH 420-450 Hz, m, (5H)
3e	1690	1310	1.25	—	—	4.50	4.60	δ ArH (2,6) 7.35 (d) (2H) δ ArH (3,5) 7.15 (d) (2H)
6a	—	1320 1245	—	3.85	3.60	4.60	—	—
6b	—	1300 1280	1.35	3.90	—	4.55	5.60	—
7 (e)	1715	1345	-	3.15 (f)	3.20 (f)	4.60	—	—
8	—	1335	—	3.50	2.65	4.40 (g) 4.35 (g)	—	—

(a) Isopropyl group. (b) J = 7 Hz. (c) Isobutyl group. (d) Part A and B, respectively, of the AA' BB'-type multiplet, J_{AB} = 9 Hz; (e) νS → O = 1040 cm^{-1}. (f) It is possible for the assignment to be reversed. (g) Methylene groups in the position 4 and 6, respectively.

thioxo group instead of an oxo group, from the main product of the reaction of **1a** and **2a**, as well as **6b** from the reaction product of **2b**. For the same purpose we have prepared the *S*-oxide derivative **7** of **3a**, using *m*-chloroperbenzoic acid as an oxidant (equation 2).

Comparing the ^{1}H nmr data (Table I) of the ring closed product with the thioxo and *S*-oxide derivatives, **3a**, **6a** and **7**, respectively, seemed to be the most probable structures. Namely, in the ^{1}H nmr spectrum of **6a**, two *N*-methyl signals are shifted downfield to about the same extent (0.3 and 0.4 ppm, respectively) compared to the spectral data of **3a**, showing that the oxo group exchanged for the thioxo group is adjacent to both *N*-methyl groups. In cases of structures **4** and **5**, the shift of only one *N*-methyl signal can be expected.

In the spectrum of the *S*-oxide derivative **7**, one of the *N*-methyl signals is shifted upfield by 0.4 ppm, while the other is unchanged. The methylene signal is shifted downfield (0.1 ppm) relative to the ^{1}H nmr spectrum of the starting material of the proposed structure **3a**. These facts support again structure **3a**, since in **4** the two *N*-methyl groups are symmetrical to the sulfoxide group; consequently both *N*-methyl signals are expected to shift in the same direction and to about the same extent. Again, in the case of structure **5**, presumably a mixture of isomers (differing partly in the position of the *S*-oxide group and partly in the *E-Z* configuration, respectively, of the methylimino group) would form, resulting in doubled ^{1}H nmr signals. The fact that there are no split signals in the spectra of compounds **3**, due to the isomerism of the alkylimino groups, shows *ab ovo*, that no cyclization results leading to structure **5**.

For the same reason, *i.e.*, because isomers do not form the theoretically possible oxidation of the thioxo sulfur atom of **3a** or **4a**, leading to *E-Z* isomers of the sulfine type derivatives, can be excluded, since in this case all of the ^{1}H nmr signals or at least one of the *N*-methyl signals would split.

The by-product, which has already been known from the literature (2,12,13), is the 3,5-dimethyl-tetrahydro-2*H*-1,3,5-thiadiazin-2-thione (**8**). The elemental analysis, melting point, ir and ^{1}H nmr spectral data of the compound obtained by us are identical with those described. The formation of this product can be explained by the reaction of one mole of **1a** with two moles of **2a**, assuming that the intermediate product is a *N,S*-dialkylated derivative (equation 3). We have not observed the formation of any by-products in the other cyclization reactions.

Steric hindrance may be responsible for the failure of cyclization in the reaction of **1b** with **2a,b**. The isopropyl group hinders the carbonyl chloride moiety and the nitrogen atom from approaching each other. It has been

Table 2

Fractional Atomic Coordinates for the Heavy Atoms (x 10^4) and the Hydrogen Atoms (x 10^3) with Their e.s.d. Values

	x	y	z		x	y	z
S(1)	6351(2)	2323(1)	1842(1)	C(2)	6229(5)	1491(4)	394(4)
S(2)	6430(2)	−264(1)	367(1)	C(4)	6435(5)	3784(4)	−756(3)
O(1)	6874(4)	4255(3)	−1776(3)	C(6)	5495(6)	4026(4)	1402(4)
N(3)	5981(4)	2298(3)	−661(3)	C(7)	5734(5)	1583(5)	−1875(4)
N(5)	6346(4)	4568(3)	297(3)	C(8)	6724(7)	6057(5)	227(4)
H(7a)	500(5)	86(3)	−84(4)	H(6b)	462(3)	86(3)	212(3)
H(7b)	529(5)	225(3)	−243(5)	H(8a)	625(5)	225(3)	89(5)
H(7c)	680(5)	140(4)	−221(4)	H(8b)	581(5)	140(4)	−35(6)
H(6a)	428(5)	379(4)	131(4)	H(8c)	669(6)	379(4)	−20(5)

Table 3

Yields, Melting Points, and Analyses of Tetrahydro-2*H*-thiadiazines **3a-e, 6a,b, 7** and **8**

Compound No.	Yield %	M.p. °C	Analytical Data									
			Found					Calculated				
3a	41	74-75 (a)	33.92	4.54	15.78	18.27	—	34.07	4.58	15.89	18.19	—
3b	49	81-82 (b)	41.32	6.15	13.78	31.15	—	41.15	5.92	13.71	31.39	—
3c	45	83 (b)	48.44	7.47	11.54	25.98	—	48.75	7.36	11.37	26.03	—
3d	61	184-185(c)	54.56	5.53	10.56	24.15	—	54.11	5.30	10.52	24.07	—
3e	53	217-219 (c)	48.07	4.45	9.38	21.41	11.35	47.91	4.36	9.31	21.32	11.79
6a	21	108-110 (d)	31.29	4.26	14.59	49.81	—	31.23	4.19	14.57	50.02	—
6b	23	122 (e)	38.19	5.41	12.83	43.55	—	38.15	5.49	12.71	43.65	—
7	31	127-128 (e)	31.15	4.17	14.35	33.61	—	31.24	4.19	14.57	33.36	—
8	5-7	104-106 (a)	36.88	6.08	16.93	39.32	—	37.01	6.21	17.26	39.52	—

The compounds were crystallized from: (a) methanol; (b) 2-propanol; (c) 2-propanol-chloroform 4:1; (d) carbon tetrachloride; (e) acetone.

shown that the exchange of the isopropyl group for isobutyl group, resulting in a shift of the branching with one carbon atom from the nitrogen atom, leads to ring closure.

The analogous structures of **3b-e** follow unambiguously from the spectral data.

The structure of **3a** was also established by crystal structure determination [*Crystal data:* $C_5H_8N_2OS_2$, M = 176.3, a = 8.121(1), b = 9.389(2), c = 10.584(2) Å, V = 870.0(4) Å^3, D_x = 1.451 mg./m^3, $\mu(MoK_{\overline{\alpha}}$, λ = 0.71073 Å) = 0.58 mm^{-1}, Z = 4, space group $P2_12_12_1$].

Nine hundred thirty five unique reflexions were collected on an Enraf-Nonius CAD4 computer controlled diffractometer, with θ-2θ scan, in the $3 < 2\theta < 50°$ range (approximate crystal size was 0.07 x 0.13 x 0.28 mm). The structure was determined by direct methods and was refined by anisotropic full-matrix least squares. Hydrogen atoms were located in a difference map and were refined in the last two least-squares cycles. The final R values are 0.037 for 822 observed [$I \geq 1.0\sigma(I)$, where $\sigma(I)$ is the standard deviation of the intensity, based on counting statistics] and 0.049 for all reflexions. Atomic coordinates are given in Table II, the diagram of the molecule with the numbering of atoms, bond lengths and angles are shown in the Figure.

EXPERIMENTAL

The *N*-alkyl-*N*-chloromethylcarbamoyl chlorides (**2**) were prepared from the appropriate 1,3,5-trialkylhexahydro-*s*-triazine and phosgene (14). The ir spectra were recorded on a Perkin-Elmer 577 grating spectrometer in potassium bromide pellets. The ^{1}H nmr spectra were recorded on a JEOL 60-HL instrument at 60 MHz in deuteriochloroform at room temperature, using TMS as an internal standard. The yields, melting points (uncorrected), and elemental analysis data are collected in the Table III. The purity of all the compounds were controlled by tlc carried out on silica gel HF_{254}, using benzene-acetone (9:1) for developing.

General Procedure for the Preparation of 3,5-Disubstituted Tetrahydro-2-thioxo-2*H*-1,3,5-thiadiazin-4-ones (**3**).

To a stirred and ice-water cooled mixture of 0.05 mole of triethyl ammonium dithiocarbamate (**1**) and 0.05 mole of triethylamine in 250 ml. of dry acetone was added 0.0525 mole of chloromethyl-carbamoyl chloride (**2**) in fifteen minutes. The stirring was continued for one hour with ice-water cooling, and then for an additional two hours at room temperature. The triethylammonium chloride was filtered off by suction, and the filtrate was evaporated under reduced pressure. The residue was taken up in chloroform. The chloroform solution was washed with water and dried. After evaporating the solvent, the remaining material was crystallized from the appropriate solvent (see Table III) to give pure yellow **3**. In the case **a**, the by-product (thick white needles) could be manually separated easily from the main product (thick yellow plates). The separated products were recrystallized again to obtain the pure **3a** and **8**, respectively.

3,5-Dialkyltetrahydro-2*H*-1,3,5-thiadiazin-2,4-dithiones (**6**).

Compound **3** (0.01 mole) and 0.05 mole (11 g.) of phosphorus penta

sulfide in 40 ml. of dry xylene were refluxed with stirring for twelve hours. The hot xylene solution was decanted and the remaining solid was washed with hot benzene. The combined xylene-benzene solution was evaporated under reduced pressure. The residue was eluted on alumunium oxide (benzene-acetone, 9:1) to remove the inorganic materials. The reaction product was purified further by tlc carried out on silica gel PF_{254} and developed with benzene-acetone (9:1).

3,5-Dimethyltetrahydro-2-thioxo-2*H*-1,3,5-thiadiazin-4-one 1-Oxide (**7**).

To a stirred and ice-water cooled solution of 0.01 mole (1.72 g.) of **3a** in 20 ml. of chloroform was added 0.0105 mole (2.07 g.) of 85% *m*-chloroperbenzoic acid dissolved in 20 ml. of chloroform in fifteen minutes, then the stirring was continued for twenty minutes at room temperature. The *m*-chlorobenzoic acid was filtered by suction. The filtrate was washed with sodium hydrogencarbonate solution and water, dried then evaporated. The residue was crystallized from methanol. The traces of the non-oxidized material could be removed only by tlc (silica gel PF_{254}, benzene-acetone-chloroform, 1:1:1).

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