The Preparation of 3,5-Disubstituted Tetrahydro-4*H*-1,3,5-oxadiazine-4-thiones, Tetrahydro-4*H*-1,3,5-thiadiazin-4-ones, and Tetrahydro-4*H*-1,3,5-thiadiazine-4-thiones

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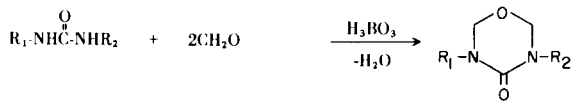
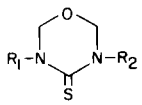
The reaction of 1,3-disubstituted thioureas with formaldehyde under acidic conditions with removal of water yielded 3,5-disubstituted tetrahydro-4*H*-1,3,5-oxadiazine-4-thiones. When hydrogen sulfide was bubbled through the reaction mixture, the corresponding tetrahydro-4*H*-1,3,5-thiadiazine-4-thiones were formed. Similarly, starting from 1,3-disubstituted ureas, a number of tetrahydro-4*H*-1,3,5-thiadiazine-4-ones were prepared. The latter compounds were also oxidized to the corresponding sulfoxides and sulfones.

3,5-Disubstituted tetrahydro-4*H*-1,3,5-oxadiazine-4-ones (urons, I) have been known since 1936 (1). The first practical method for their preparation is due to A. A. Eisenbraun and coworkers (2) who heated 1,3-dialkyl ureas with paraformaldehyde with or without boric acid while removing the water formed in the reaction. 1,3-Diarylureas and 1-aryl-3-alkylureas can also be transformed into urons at room temperature by the use of 85% sulfuric acid as reaction solvent (3). Sulfur-containing urons have not been previously reported.

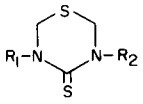


I

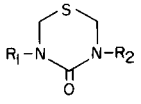
We now wish to report a method to prepare 3,5-disubstituted tetrahydro-4*H*-1,3,5-oxadiazine-4-thiones (II), tetrahydro-4*H*-1,3,5-thiadiazine-4-thiones (III), and tetrahydro-4*H*-1,3,5-thiadiazin-4-ones (IV). The method



II

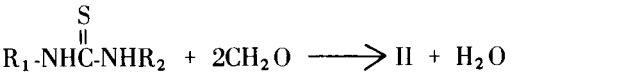


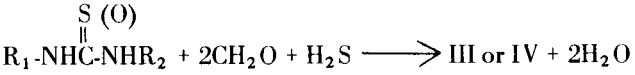
III



IV

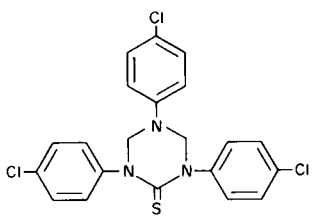
consists of refluxing the corresponding ureas with 2 moles of formaldehyde and a catalytic amount of *p*-toluenesulfonic acid in chloroform while removing the water of reaction in a reversed phase water separator. When hydrogen sulfide is bubbled through the reaction mixture, another mole of water separates and the compounds of general structure III and IV are formed.





It appears most likely that the hydrogen sulfide reacts with the bis-methylol derivative of the urea (or thiourea) forming a methylol methylthiol intermediate which then loses water and forms III or IV. If the hydrogen sulfide were to extensively react with formaldehyde the formation of some insoluble 1,3,5-trithiane would be expected, which was not observed. Preformed uron or II exposed to the reaction conditions react very slowly and incompletely with hydrogen sulfide forming small amounts of III or IV (detected by tlc) together with decomposition products.

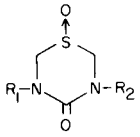
Four compounds of type II were prepared (see Table I); the compounds of type III are listed in Table II. The yields were lower when both substituents R_1 and R_2 were aryl. The attempted preparation of II (R_1 = R_2 = *p*-chlorophenyl) yielded none of the desired product. The compound isolated instead in 29% yield probably has structure V judging by its elemental analysis and spectral properties. The formation of tetrahydro-1,3,5-triazine-2-



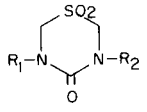
V

thiones from thioureas, aldehydes, and amines is well known (4). Evidently, under the influence of the acid catalyst, the thiourea had split into *p*-chloroaniline and *p*-chlorophenylisothiocyanate giving rise to a mixture of products of which only V was isolated.

In the case of IV compounds with 3,5-dialkyl and with 3-aryl-5-alkyl substitution could be made (see Table III). Oxidation of these compounds with *m*-chloroperbenzoic acid yielded the corresponding sulfoxides (VI) and sulfones (VII) depending on the amount of reagent used (Tables IV and V).



VI



VII

The ir spectra of all the compounds prepared showed characteristic bands in the 675-830 cm^{-1} region. These bands were observed at the following wave numbers (cm^{-1}):

Urons	755,815
II	675,720
III	795
IV	740,755
VI	740,775
VII	780,830

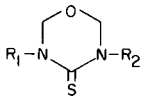
These bands are probably C-S and C-O stretching bands (5).

EXPERIMENTAL

All melting points are uncorrected. The microanalyses were carried out by Mr. C. W. Nash and his associates.

TABLE I

Tetrahydro-4*H*-1,3,5-oxadiazine-4-thiones

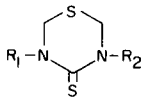


II

Compound	R_1	R_2	Emp. Formula	Yield (%)	M.p., °C	Analysis Calcd. over Found		
IIa	methyl	methyl	$C_5H_{10}N_2OS$	54	107.6	C 41.07	H 6.89	N 19.16
						C 41.03	H 6.80	N 18.97
IIb	ethyl	ethyl	$C_7H_{14}N_2OS$	49	77.1	C 48.24	H 8.09	N 16.08
						C 48.36	H 8.37	N 16.10
IIc	methyl	*n*-hexyl	$C_{10}H_{20}N_2OS$	41	58.9	C 55.51	H 9.32	N 12.95
						C 55.79	H 9.14	N 12.75
IId	methyl	*n*-octyl	$C_{12}H_{24}N_2OS$	18	b.p. 142-146 0.075 mm	C 58.97	H 9.90	N 11.47
						C 59.25	H 9.93	N 11.47

TABLE II

Tetrahydro-4*H*-1,3,5-thiadiazine-4-thiones

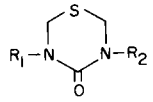


III

Compound	R_1	R_2	Emp. Formula	Yield (%)	M.p., °C	Analysis Calcd. over Found			
IIIa	methyl	methyl	$C_5H_{10}N_2S_2$	31	145-148	C 37.00	H 6.21	N 17.23	S 39.52
						C 36.99	H 6.09	N 17.30	S 39.39
IIIb	ethyl	ethyl	$C_7H_{14}N_2S_2$	60	94-97	C 44.20	H 7.36	N 14.75	S 33.68
						C 44.46	H 7.48	N 14.80	S 33.39
IIIc	methyl	phenyl	$C_{10}H_{12}N_2S_2$	74	112.1	C 53.54	H 5.39	N 12.49	S 28.59
						C 53.76	H 5.12	N 12.51	S 28.49
IIId	phenyl	phenyl	$C_{15}H_{14}N_2S_2$	19	137.2	C 62.90	H 4.93	N 9.78	
						C 63.02	H 4.84	N 9.89	
IIIe	phenyl	4-chlorophenyl	$C_{15}H_{13}ClN_2S_2$	5	180.0	C 56.15	H 4.08	N 8.73	
						C 56.40	H 3.98	N 8.89	

TABLE III

Tetrahydro-4*H*-1,3,5-thiadiazin-4-ones

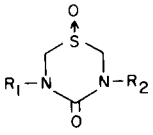


IV

Compound	R_1	R_2	Emp. Formula	Yield (%)	M.p., °C	Analysis Calcd. over Found		
IVa	methyl	methyl	$C_5H_{10}N_2OS$	48	b.p. 95-100 0.5 mm	C 41.07 C 40.96	H 6.89 H 7.15	N 19.16 N 18.94
IVb	methyl	*n*-propyl	$C_7H_{14}N_2OS$	89	b.p. 101 0.5 mm	C 48.24 C 47.96	H 8.09 H 7.91	
IVc	methyl	*i*-butyl	$C_8H_{16}N_2OS$	55	b.p. 90-95 0.075 mm	C 51.02 C 50.97	H 8.57 H 8.62	N 14.88 N 14.82
IVd	methyl	*n*-hexyl	$C_{10}H_{20}N_2OS$	78	b.p. 119-121 0.1 mm	C 55.51 C 55.44	H 9.32 H 9.14	N 12.95 N 12.66
IVe	methyl	*n*-octyl	$C_{12}H_{24}N_2OS$	28	b.p. 135-150 0.1 mm	C 58.97 C 59.09	H 9.90 H 9.83	N 11.47 N 11.52
IVf	cyclohexyl	cyclohexyl	$C_{15}H_{26}N_2OS$	80	90.4	C 63.78 C 63.72	H 9.28 H 9.27	N 9.90 N 9.72
IVg	methyl	3-chlorophenyl	$C_{10}H_{11}ClN_2OS$	50	b.p. 175-180	C 49.48 C 49.54	H 4.57 H 4.49	N 11.54 N 11.48
IVh	methyl	4-chlorophenyl	$C_{10}H_{11}ClN_2OS$	28	71-73	C 49.48 C 49.70	H 4.57 H 4.46	N 11.54 N 11.60

TABLE IV

Tetrahydro-4*H*-1,3,5-thiadiazin-4-one Oxides



VI

Compound	R_1	R_2	Emp. Formula	Yield (%)	M.p., °C	Analysis Calcd. over Found		
VIa	methyl	methyl	$C_5H_{10}N_2O_2S$	31	107-110	C 37.02 C 37.14	H 6.21 H 6.26	N 17.27 N 17.29
VIb	methyl	*i*-butyl	$C_8H_{16}N_2O_2S$	54	85-87	C 47.03 C 46.94	H 7.90 H 8.00	N 13.72 N 13.65
VIc	methyl	4-chlorophenyl	$C_{10}H_{11}ClN_2O_2S$	60	140-141.5	C 46.42 C 46.64	H 4.29 H 4.57	N 10.83 N 10.81
VId	cyclohexyl	cyclohexyl	$C_{15}H_{26}N_2O_2S$	51	146-149	C 60.36 C 60.53	H 8.78 H 8.81	N 9.39 N 9.41

3,5-Dimethyltetrahydro-4*H*-1,3,5-oxadiazine-4-thione (IIa) (Table I).

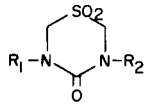
A solution of 26 g. (0.25 mole) of 1,3-dimethylthiourea, 15 g. (0.5 mole) of paraformaldehyde, and 2 g. of *p*-toluenesulfonic acid in 250 ml. of chloroform was refluxed for 2½ hours. A reversed phase water separator was used to separate the water of reaction. The solvent was then evaporated on a rotatory evaporator and the residue recrystallized from toluene, yield 19.8 g.

3,5-Diethyltetrahydro-4*H*-1,3,5-thiadiazine-4-thione (IIIb) (Table II).

A solution of 26.4 g. (0.2 mole) of 1,3-diethylthiourea, 12 g. (0.4 mole) of paraformaldehyde, and 5 g. of *p*-toluenesulfonic acid in 200 ml. of chloroform was refluxed while a slow stream of hydrogen sulfide was passed through. After 1½ hours the theoretical amount of water had been collected in the reversed phase water separator. The solvent was then removed using a

TABLE V

Tetrahydro-4*H*-1,3,5-thiadiazin-4-one Dioxides



VII

Compound	R_1	R_2	Emp. Formula	Yield (%)	M.p., °C	Analysis Calcd. over Found		
VIIa	methyl	methyl	$C_5H_{10}N_2O_3S$	62	131-133.5	C 33.69	H 5.66	N 15.72
						C 33.90	H 5.56	N 15.64
VIIb	methyl	*n*-propyl	$C_7H_{14}N_2O_3S$	90	68-71	C 40.75	H 6.84	N 13.58
						C 40.52	H 6.77	N 13.36
VIIc	methyl	*i*-butyl	$C_8H_{16}N_2O_3S$	81	92.6	C 43.61	H 7.32	N 12.72
						C 43.72	H 7.28	N 12.60
VIId	methyl	*n*-hexyl	$C_{10}H_{20}N_2O_3S$	70	40.2	C 48.36	H 8.12	N 11.28
						C 48.60	H 8.16	N 11.26
VIIe	cyclohexyl	cyclohexyl	$C_{15}H_{26}N_2O_3S$	92	141-143	C 57.29	H 8.34	N 8.91
						C 57.07	H 8.22	N 8.83
VIIf	methyl	3-chlorophenyl	$C_{10}H_{11}ClN_2O_3S$	78	178.1	C 43.71	H 4.04	N 10.20
						C 43.69	H 4.04	N 10.17
VIIg	methyl	4-chlorophenyl	$C_{10}H_{11}ClN_2O_3S$	78	169-171	C 43.71	H 4.04	N 10.20
						C 43.91	H 4.10	N 10.16

rotatory evaporator and the residue recrystallized twice from methylcyclohexane, yield 23 g.

The 3,5-disubstituted tetrahydro-4*H*-1,3,5-thiadiazin-4-ones listed in Table III were prepared in analogous fashion.

3,5-Dimethyltetrahydro-4*H*-1,3,5-thiadiazin-4-one Dioxide (VIIa) (Table V).

To an ice cooled stirred slurry of 43 g. (0.212 mole) of 85% *m*-chloroperoxybenzoic acid in 200 ml. of chloroform was added dropwise a solution of 14.6 g. (0.1 mole) of IVa in 50 ml. of chloroform. The mixture was left stirring at room temperature for one hour and then an excess of saturated sodium carbonate solution was added. The organic layer was separated, dried, and evaporated almost to dryness. Addition of hexane precipitated the product which was recrystallized from chloroform/hexane, yield 11 g.

The tetrahydro-4*H*-1,3,5-thiadiazin-4-one oxides listed in Table VI were prepared in analogous fashion using only one equivalent of peroxy acid.

Tetrahydro-1,3,5-tri-(*p*-chlorophenyl)-4*H*-1,3,5-triazine-2-thione (V).

A solution of 34.5 g. (0.116 mole) of 1,3-di-(*p*-chlorophenyl)-thiourea, 7 g. (0.234 mole) of paraformaldehyde, and 1 g. of *p*-toluenesulfonic acid in 200 ml. of chloroform was refluxed for 2 hours using a reverse phase water separator. The solution was then cooled, washed with 2 *N* sodium hydroxide and water and dried with anhydrous magnesium sulfate. After evaporation of the chloroform, the residue was treated with warm 2-propanol whereupon the product crystallized. It was filtered and washed with 2-propanol and dired, yield 10 g. (29%), m.p. 221-223°. Recrystallization from methylcellosolve raised the melting point to 237-238°.

Anal. Calcd. for $C_{21}H_{16}Cl_3N_3S$: C, 56.20; H, 3.59; N, 9.36. Found: C, 55.99; H, 3.89; N, 9.30.

Acknowledgment.

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