The Preparation of 2-Aryl-3-Methyl-4-thiazolidinone 1,1-Dioxides and 2-Arylperhydro-3-methyl-4*H*-1,3-thiazin-4-one 1,1-Dioxides.

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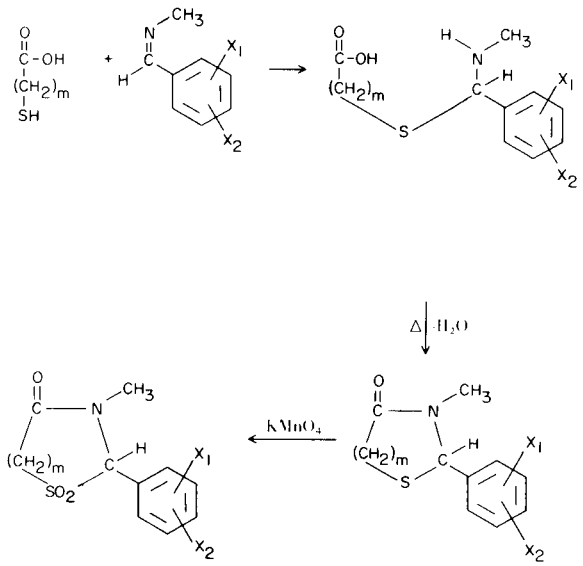
Compounds containing a small alkyl group at the 3-position and a chlorophenyl group at the 2-position of perhydro-4-*H*-1,3-thiazin-4-ones or their 1,1-dioxides exhibit optimal antielectroshock, antichemoshock, paralyzing, and hypothermic activities (3). The object of this synthetic work was to prepare the dioxides of 2-fluorophenyl- or 2-dichlorophenyl-substituted-3-methylthiazinones and thiazolidinones to submit to Sterling-Winthrop Research Institute for pharmacological testing.

The thiazolidinone 1,1-dioxides (**3a** and **3b**) (Scheme I) were prepared by adding mercaptoacetic acid to a preformed Schiff base, heating the adduct (**1**) to effect ring closure, and oxidizing with permanganate (4). The thiazinones (**3c**, **3d** and **3e**) were prepared in a similar fashion using 3-mercaptopropanoic acid (4).

The procedure used for preparation of both thiazinones and thiazolidinones was essentially the one given by Surrey (6). After several unsuccessful attempts to prepare these compounds by simultaneously reacting the mercapto acid, aldehyde, and methyl amine, the syntheses were completed by preforming the Schiff base and then adding the mercapto acid. A nitrogen atmosphere was used to prepare thiazolidinones. In all cases the oils (**2**) were oxidized to crystalline dioxides (**3**) without isolation.

SCHEME I



	m	X_1	X_2
a	1	3-F	H
b	1	4-F	H
c	2	3-F	H
d	2	2-F	H
e	2	2-Cl	6-Cl

EXPERIMENTAL

2-(3-Fluorophenyl)-3-methyl-4-thiazolidinone 1,1-Dioxide (**3a**).

Through a solution of 10 g. (0.08 mole) of *m*-fluorobenzaldehyde in 150 ml. of refluxing dry benzene was bubbled methylamine until 0.08 mole of water had collected in a Dean Stark trap. Then 7.8 g. (0.08 mole) of thioglycolic acid was added and the reflux continued for one hour while 70% of the theoretical amount of water was collected. The solvent was stripped to give an oil. A solution of 21.7 g. (0.14 mole) of potassium permanganate in 196 ml. of water was added dropwise to a well-stirred solution of the oil in 97 ml. of acetic acid keeping the temperature below 30°.

After removing manganese dioxide with sodium bisulfite, a thick colorless oil separated which soon solidified. Extraction with chloroform followed by evaporation gave a solid that was recrystallized from isopropyl alcohol. The analysis of **3a** is summarized in Table I: ir 7.45, 7.6, 7.8 μ; nmr (deuteriochloroform), δ 7.27 (4, m), 5.66 (1, s), 3.96 (2, s), 3.03 (3, s).

2-(4-Fluorophenyl)-3-methyl-4-thiazolidinone 1,1-Dioxide (**3b**).

By a similar procedure the 1-dioxide (**3b**) was obtained; ir 7.55, 8.2 μ; nmr (deuteriochloroform), δ 7.40 (4, m), 5.60 (1, s), 3.90 (2, s), 2.98 (3, s).

2-(3-Fluorophenyl)-perhydro-3-methyl-4*H*-1,3-thiazin-4-one 1,1-Dioxide (**3c**).

The reaction of 0.08 mole of *m*-fluorobenzaldehyde with methylamine in boiling benzene gave 0.08 mole of water, but after adding 3-mercaptopropanoic acid under nitrogen very little additional water was collected in the trap after refluxing. Apparently hot benzene dissolved considerable water. Extraction of the benzene layer with dilute hydrochloric acid and dilute bicarbonate was followed by evaporation of the benzene. Oxidation as before gave **3c**; ir 7.5-7.65 broad, 7.70, 7.75 μ; nmr (DMSO) δ 7.57 (4, m), 6.31 (1, s), 3.6 (2, m), 3.3 (2, m), 2.90 (3, s).

2-(2-Fluorophenyl)-perhydro-3-methyl-4*H*-1,3-thiazin-4-one 1,1-Dioxide (**3d**).

A solution obtained by bubbling 3.4 g. (0.11 mole) of methyl amine into 100 ml. of cold benzene was added to 13.7 g. (0.11 mole) of *o*-fluorobenzaldehyde dissolved in 50 ml. of benzene. During Schiff base formation by refluxing 1.8 ml. of water formed

TABLE I

3	m	X_1	X_2	Yield %	M.p. °C	Molecular Formula
a	1	3-F	H	54	142.2-143.8	$C_{10}H_{10}FNO_3S$
b	1	4-F	H	35	146.5-147.5	$C_{10}H_{10}FNO_3S$
c	2	3-F	H	19	154-156.5	$C_{11}H_{12}FNO_3S$
d	2	2-F	H	27	160-162	$C_{11}H_{12}FNO_3S$
e	2	2-Cl	6-Cl	30	220-221	$C_{11}H_{11}Cl_2NO_3S$

3	Carbon % Calcd.	Found	Hydrogen % Calcd.	Found	Nitrogen % Calcd.	Found	Sulfur % Calcd.	Found	Fluorine % Calcd.	Found	Chlorine % Calcd.	Found
a	49.37	49.11	4.14	3.96	5.75	5.50	13.17	13.65				
b	49.37	49.51	4.14	4.17			13.17	13.90	7.80	7.99		
c	51.34	51.53	4.70	4.77			12.46	12.61	7.41	7.21		
d	51.34	51.46	4.70	4.92	5.45	5.26	12.46	12.94	7.39	7.44		
e	42.86	42.37	3.60	3.68			10.41	10.36			23.01	23.19

and during ring closure after adding 0.11 mole of 3-mercaptopropanoic acid 1.6 ml. of additional water was obtained. Several washes with dilute ammonium hydroxide and dilute hydrochloric acid were followed by evaporation of the solvent. Oxidation of the thiazinone was accomplished by adding slowly 31.6 g. (0.20 mole) of potassium permanganate in 550 ml. of water to the oil dissolved in 140 ml. of acetic acid. Sodium bisulfite was used to decolorize the solution. The crystalline dioxide (**3d**) was recrystallized from isopropyl alcohol; ir 7.55-7.65 broad, 7.8 μ; nmr (DMSO) δ 7.50 (4, m), 6.26 (1, s), 3.6 (2, m), 3.1 (2, m), 2.82 (3, s).

2-(2,6-Dichlorophenyl)-perhydro-3-methyl-4*H*-1,3-thiazin-4-one 1,1-Dioxide (**3e**).

Using the same procedure as was used for **3d**, 0.11 mole of 2,6-dichlorobenzaldehyde gave 1.7 ml. of water during Schiff base formation and only 0.95 ml. during ring closure. To facilitate the aqueous ammonia wash, salt was added to break the emulsion; the nmr of **3e** (deuteriochloroform), δ 7.52 (3, m), 6.62 (1, s), 3.7 (2, m), 3.2 (2, m), 2.89 (3, s).

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