

6-1965

The Preparation of 2-Aryl-3-Methyl-4-Metathiazanones and 2-Aryl-3-Methyl-4-Thiazolidones

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THE PREPARATION OF
2-ARYL-3-METHYL-4-METATHIAZANONES AND
2-ARYL-3-METHYL-4-THIAZOLIDONES

by

John Charles Wilson UC 1965

Senior Thesis Submitted
in Partial Fulfillment
of the Requirements of Graduation

DEPARTMENT OF CHEMISTRY
UNION COLLEGE
MAY 1965



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This Thesis

Submitted by

John Wilson

to the

Department of Chemistry of Union College

in partial fulfillment of the requirements of the degree of

Bachelor of Science with a Major in Chemistry

is approved by

Howard E. Shaffer

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ACKNOWLEDGEMENT

I wish to express my sincere gratitude to Professor Howard Sheffer, Professor of Chemistry at Union College for his assistance and suggestions throughout my work.

My thanks also go to Messrs. Surrey and Bailey of Sterling Winthrop Laboratories, Rensselaer, New York, for their suggestions, analytical equipment and permission to allow me to share in their work.

And to my wife, Barbara, my congratulations for learning how to type metathiazanone blindfolded.

HISTORICAL BACKGROUND

Based upon an article, Central Nervous System Depressants. The Preparation of Some 2-Aryl-4-metathiazanones, by Alexander R. Surrey, William G. Webb, and Robert M. Gesler (3), the following history of previous work was obtained.

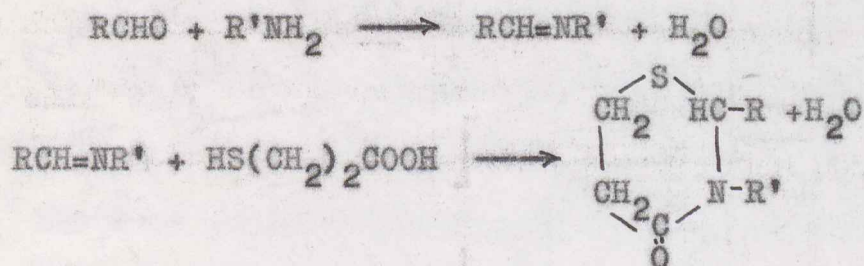
Abstract

It had been found that 3-mercaptopropanoic acid would react readily with ammonia or primary amines yielding Schiff bases which when reacted with aryl aldehydes would give 2 and 2,3 disubstituted 4-metathiazanones. The report included a variety of substituted benzaldehydes, pyridyl and thienyl carboxaldehydes, ammonia, and alkyl and aralkylamines. The corresponding 1-oxides (sulfoxides) and 1-dioxides (sulfones) were also prepared. The sulfones held good promise as effective skeletal muscle relaxants.

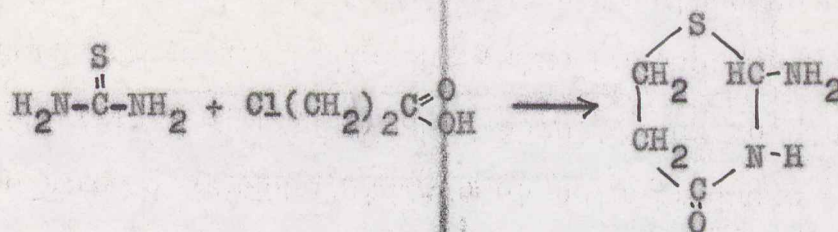
Article

Based upon previous work done by Surrey's group dealing with the addition of sulfhydryl compounds to Schiff bases, interest was directed to determining the reactivity of 3-mercaptopropanoic acid with Schiff bases to yield substituted metathiazanone derivatives.

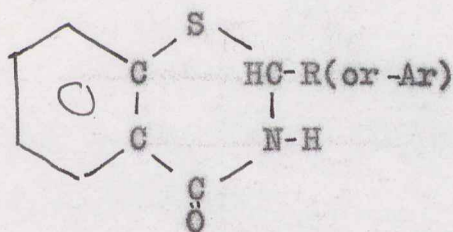
HISTORICAL BACKGROUND (cont.)



At the time, most 4-metathiazanones (1,3-thiazin-4-ones) from the literature had contained the 2-imino group prepared from thiourea and 3-chloropropanoic acid derivatives.

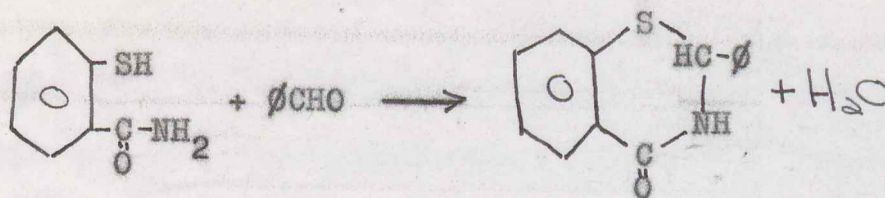


Recently some 2-alkyl and 2-aryl-5, 6-benzo-4-metathiazanones had been reported.

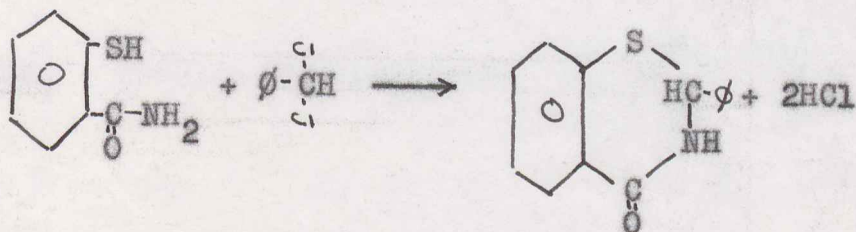


In 1953, Bahme and Schmidt showed that thiosalicylamide would condense with aldehydes or ketones in alcoholic solution in the presence of dry hydrogen chloride.

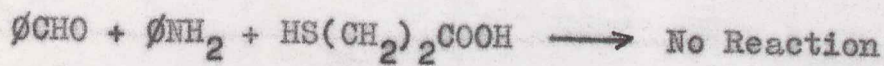
HISTORICAL BACKGROUND (cont.)



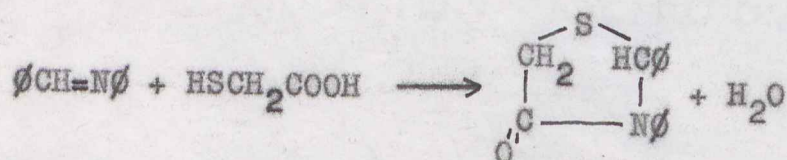
The same product was obtained by Baudet's reaction of thiosalicylamide with benzylidene chloride in pyridine.



Surrey initially worked with aniline, benzaldehyde (or benzylideneaniline) and 3-mercaptopropanoic acid with no success in preparing the 2,3-disubstituted 4-metathiazanones.

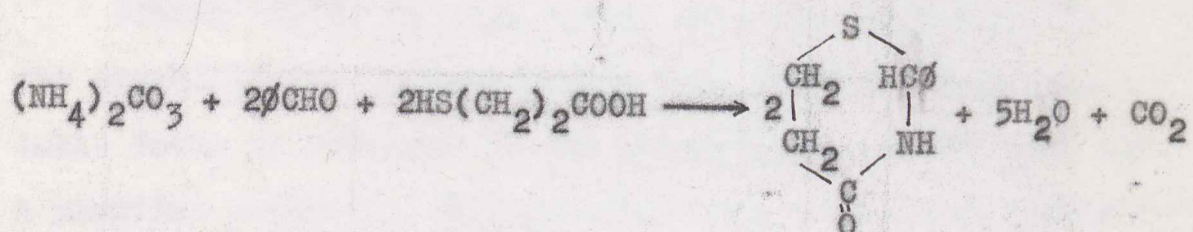


In contrast, thioglycolic acid was found to react readily with benzylideneaniline to give the cyclic amide 2,3-diphenyl-4-thiazolidone.



HISTORICAL BACKGROUND (cont.)

Under similar conditions, when ammonium carbonate was refluxed in benzene with benzaldehyde and 3-mercaptopropanoic acid, two moles of water were eliminated per mole of product in a smooth reaction yielding 2-phenyl-4-metathiazanone.



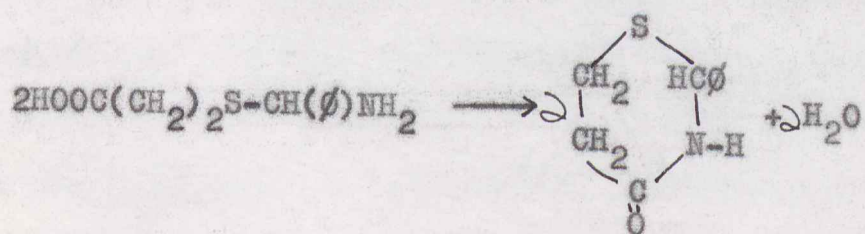
The reaction was believed to occur in steps with the initial formation of an azomethine (Schiff base).



The sulfhydryl group then adds to the $-\text{C}=\text{N}-$ linkage



followed by dehydration to give the cyclic amide



HISTORICAL BACKGROUND (cont.)

A variety of substituted benzaldehydes and 2- and 3-pyridyl- and 2-thienyl carboxaldehydes were also employed. The table on page 6 lists most of the 2-aryl-4-metathiazanones prepared in the authors' work.

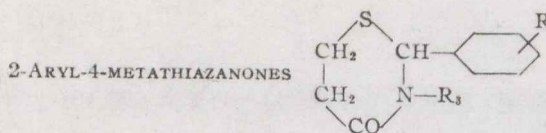
Schiff bases, in most cases, were not isolated. It was suggested that better yields than those given in the table could be obtained if the intermediate Schiff base was a purified material. For example, when 4-chlorobenzylidene-methylamine was isolated and purified from the reaction



and reacted with 3-mercaptopropanoic acid, the yield of 2-(4-chlorophenyl)-3-methyl-4-metathiazanone was 63% as compared to 11% when 4-chlorobenzaldehyde and methylamine were used directly with 3-mercaptopropanoic acid.

In general, the amount of water collected during the reactions at reflux for twenty-four hours varied from 75 to 100% of theory. In some cases, a reflux of 72 hours did not appreciably change the amount of water collected. An excess of 3-mercaptopropanoic acid gave favorable effects upon the yields. This was evident in 3-benzyl-2-phenyl-4-metathiazanone preparations.

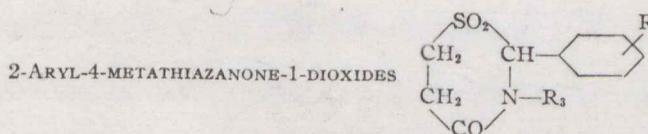
TABLE I



R	R ₃	Yield, %	M.p., °C.	Formula	Sulfur, %		Chlorine, %	
					Calcd.	Found	Calcd.	Found
H	H	34	179.3-180.7	C ₁₀ H ₁₁ NOS	16.58	16.34	7.25	7.18
4-OCH ₃	H	39	193.2-193.8	C ₁₁ H ₁₃ NO ₂ S	14.36	14.44	6.28	6.30
4-Cl	H	25	174.9-175.7	C ₁₀ H ₁₀ ClNOS	14.08	14.19	15.57	15.20
4-Br	H	34	184.3-185.5	C ₁₀ H ₁₀ BrNOS	11.78	11.86	29.36 ^a	29.25 ^a
2,4-Cl ₂	H	25	166.9-168.7	C ₁₀ H ₉ Cl ₂ NOS	12.23	12.32	27.05	27.50
3,4-Cl ₂	H	36	149.3-151.1	C ₁₀ H ₉ Cl ₂ NOS	12.23	12.15	27.05	27.20
H	CH ₃	74	95.2-96.2	C ₁₁ H ₁₃ NOS	15.46	15.50	6.75	6.97
4- <i>i</i> -Pr	CH ₃	28	110.0-112.1	C ₁₄ H ₁₉ NOS	12.86	12.72	67.44 ⁱ	67.41 ⁱ
							7.68 ^j	7.74 ^j
4-OCH ₃	CH ₃	59	67.2-69.6 ^a	C ₁₂ H ₁₅ NO ₂ S	13.51	13.35	5.90 ^k	6.12 ^k
2-Cl	CH ₃	39	76.4-79.6 ^b	C ₁₁ H ₁₂ ClNOS	54.67 ⁱ	54.70 ⁱ	14.68	14.54
					5.01 ^j	4.86 ^j		
3-Cl	CH ₃	59	57.2-60.6 ^c	C ₁₁ H ₁₂ ClNOS	54.67 ⁱ	54.45 ⁱ	14.68	14.72
					5.01 ^j	5.04 ^j		
4-Cl	CH ₃	11	^d	C ₁₁ H ₁₂ ClNOS	13.27	13.24	14.67	14.43
2,4-Cl ₂	CH ₃	65	117.8-122.3	C ₁₁ H ₁₁ Cl ₂ NOS	11.61	11.36	25.67	25.50
3,4-Cl ₂	CH ₃	70	81.8-83.2	C ₁₁ H ₁₁ Cl ₂ NOS	11.61	11.99	25.67	25.50
4-Cl	C ₂ H ₅	37	106.0-107.7	C ₁₂ H ₁₄ ClNOS	5.48 ^k	5.14 ^k	13.86	13.90
3,4-Cl ₂	C ₂ H ₅	37	63.2-67.4 ^e	C ₁₂ H ₁₃ Cl ₂ NOS	11.17	10.73	24.43	24.33
4-Cl	C ₃ H ₇	25	^f	C ₁₃ H ₁₆ ClNOS	11.87	12.04	13.13	12.98
H	C ₆ H ₅ CH ₂	31	82.9-84.5	C ₁₇ H ₁₇ NOS	11.31	11.41	4.94 ^k	5.18 ^k
H	C ₆ H ₅ (CH ₂) ₂	45	75.4-83.8	C ₁₈ H ₁₉ NOS	10.78	10.93	4.71 ^k	4.76 ^k

^a B.p. 176-179° (0.5 mm.), n_D^{25} 1.5937. ^b B.p. 156-158° (0.5 mm.), n_D^{25} 1.6072. ^c B.p. 178-180° (0.1 mm.), n_D^{25} 1.6060. ^d B.p. 172-175° (0.2 mm.), n_D^{25} 1.6072. ^e B.p. 150-158° (0.5 mm.), n_D^{25} 1.6044. ^f B.p. 164-167° (0.2 mm.). ^g Bromine, %. ^h Carbon, %. ⁱ Hydrogen, %. ^j Nitrogen, %.

TABLE II

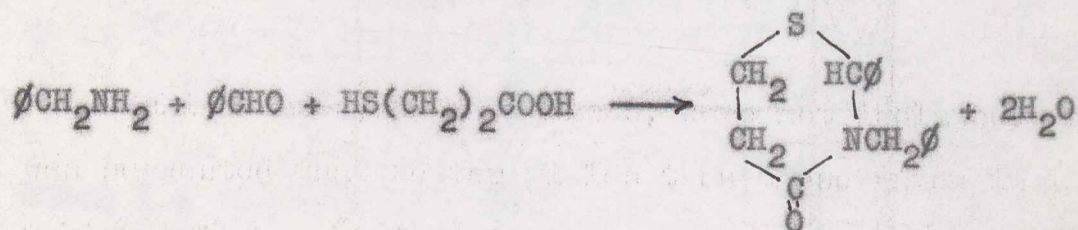


R	R ₃	Yield, %	M.p., °C.	Formula	Sulfur, %		Chlorine, %	
					Calcd.	Found	Calcd.	Found
H	H	27	153.9-155.5	C ₁₀ H ₁₁ NO ₃ S	14.23	13.94	6.21 ^b	6.23 ^b
4-Cl	H	95	173.0-173.6	C ₁₀ H ₁₀ ClNO ₃ S	12.34	12.20	13.65	13.41
4-Br	H	89	176.1-177.1	C ₁₀ H ₁₀ BrNO ₃ S	10.54	10.48	26.27 ^c	25.95 ^c
3,4-Cl ₂	H	81	184.3-185.3	C ₁₀ H ₉ Cl ₂ NO ₃ S	10.90	11.19	24.10	24.15
H	CH ₃	67	174.9-175.7 ^a	C ₁₁ H ₁₃ NO ₃ S	13.40	13.27	5.85 ^b	5.95 ^b
4-CH(CH ₃) ₂	CH ₃	67	152.9-157.3	C ₁₄ H ₁₉ NO ₃ S	11.39	11.18	59.75 ^d	59.98 ^d
							6.80 ^e	6.80 ^e
4-OCH ₃	CH ₃	60	132.4-133.4	C ₁₂ H ₁₅ NO ₃ S	11.92	11.78	5.20 ^b	5.20 ^b
2-Cl	CH ₃	86	172.8-175.4	C ₁₁ H ₁₂ ClNO ₃ S	11.71	11.80	12.95	12.65
3-Cl	CH ₃	75	153.4-156.2	C ₁₁ H ₁₂ ClNO ₃ S	11.71	11.75	12.95	12.96
4-Cl	CH ₃	46	116.2-118.6	C ₁₁ H ₁₂ ClNO ₃ S	11.71	11.88	12.95	13.20
2,4-Cl ₂	CH ₃	79	135.4-137.7	C ₁₁ H ₁₁ Cl ₂ NO ₃ S	10.40	10.62	23.01	22.70
3,4-Cl ₂	CH ₃	61	122.5-126.1	C ₁₁ H ₁₁ Cl ₂ NO ₃ S	42.86 ^d	42.70 ^d	23.01	22.60
					3.60 ^e	3.99 ^e		
4-Cl	C ₂ H ₅	66	157.6-159.8	C ₁₂ H ₁₄ ClNO ₃ S	4.87 ^b	4.90 ^b	12.32	12.47
3,4-Cl ₂	C ₂ H ₅	66	137.2-139.8	C ₁₂ H ₁₃ Cl ₂ NO ₃ S	9.95	9.99	22.01	22.04
4-Cl	C ₃ H ₇	90	110.4-112.2	C ₁₃ H ₁₆ ClNO ₃ S	10.62	10.62	11.74	11.67
3,4-Cl ₂	C ₃ H ₇	55	85.8-91.4	C ₁₃ H ₁₅ Cl ₂ NO ₃ S	9.53	9.83	21.09	21.34
H	C ₆ H ₅ CH ₂	61	158.4-161.2	C ₁₇ H ₁₇ NO ₃ S	10.17	10.04	64.73 ^d	64.47 ^d
							5.43 ^e	4.95 ^e
4-Cl	C ₆ H ₅ CH ₂	41	180.0-187.4	C ₁₇ H ₁₆ ClNO ₃ S	9.16	9.23	10.14	9.94
4-Cl	C ₆ H ₅ (CH ₂) ₂	49	133.2-137.2	C ₁₈ H ₁₈ ClNO ₃ S	8.81	8.80	9.74	9.83
3,4-Cl ₂	C ₆ H ₅ (CH ₂) ₂	50	149.8-151.8	C ₁₈ H ₁₇ Cl ₂ NO ₃ S	8.04	8.11	17.80	17.68

^a Dimorphic form, m.p. 162.6-166.0°. ^b Nitrogen, %. ^c Bromine, %. ^d Carbon, %. ^e Hydrogen, %.

HISTORICAL BACKGROUND (cont.)

Benzaldehyde and benzylamine were refluxed in benzene for 1.5 hours and an equivalent amount of 3-mercaptopropanoic acid was added. Reflux followed for forty-eight hours where 83% of the theoretical water was collected.



At the end of this time no further water evolved. A 30% excess of 3-mercaptopropanoic acid was added, followed by reflux for an additional twenty-four hours, at which time 92% of the water was collected.

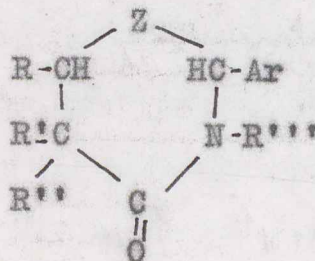
Room temperature reactions leading to the preparation of metathiazanones were slow. 3-methyl-2phenyl-4-metathiazanone was obtained in 22% yield following a week of reaction time at 25°C.

Oxidation of the 2-aryl-4-metathiazanones to the corresponding 1-dioxides were carried out in acetic acid with potassium permanganate with satisfactory yields as indicated in Table II (page 6).

United States Patent 3,082,209 (4) includes some of the forementioned ideas, more specifically, the preparation

HISTORICAL BACKGROUND (cont.)

of 4-metathiazanone derivatives of the general form



Where Z = =S, =SO, or =SO₂

Ar = lower aromatic radical

R = hydrogen, a lower aliphatic hydrocarbon radical having an aliphatic carbon atom linked to the ring - nitrogen atom, a lower -cycloalkyl radical, a lower -cycloalkylalkyl radical or a (lower -mono-cyclic-aromatic)-(lower-alkyl) radical.

R', R'', R''' = hydrogen or a lower alkyl radical

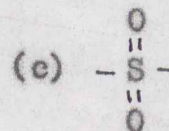
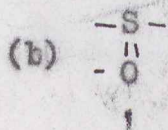
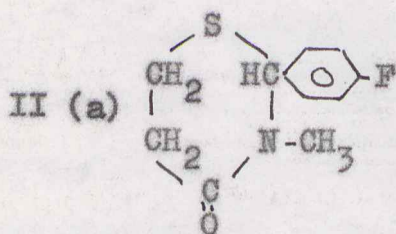
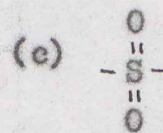
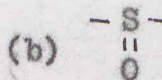
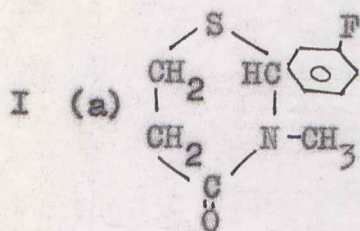
With a few modifications, experimental techniques for my research work were derived from this patent and the fore-mentioned article (3).

EXPERIMENTAL

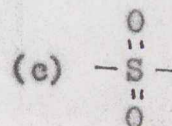
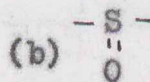
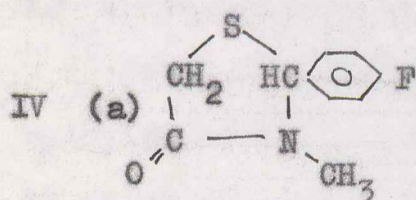
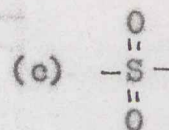
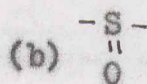
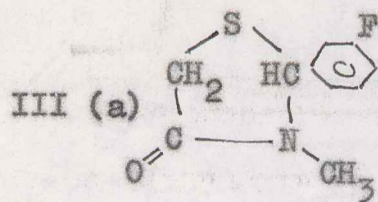
The research work previously performed on the preparation of 2-aryl-4-metathiazanones, 1-oxides and 1-dioxides, and their derivatives was done in the light of promising studies which showed that this synthetic series has unusual and interesting central nervous system depressant properties. Experiments indicated that they were effective paralyzing agents and exhibited anticonvulsant activity.

The research I have done is an extension of the preparation of this series with the hope that the pharmacological properties which result are at least equally effective.

At the suggestion of Mr. Surrey, several structures which were of apparent interest were delegated to me for synthesis and purification. They are:



EXPERIMENTAL (cont.)



- I (a) 2-(3-fluorophenyl)-3-methyl-4-metathiazanone
 (b) the 1-oxide of (a)
 (c) the 1-dioxide of (a)
- II (a) 2-(4-fluorophenyl)-3-methyl-4-metathiazanone
 (b) the 1-oxide of (a)
 (c) the 1-dioxide of (a)
- III (a) 2-(3-fluorophenyl)-3-methyl-4-thiazolidone
 (b) the 1-oxide of (a)
 (c) the 1-dioxide of (a)
- IV (a) 2-(4-fluorophenyl)-3-methyl-4-thiazolidone
 (b) the 1-oxide of (a)
 (c) the 1-dioxide of (a)

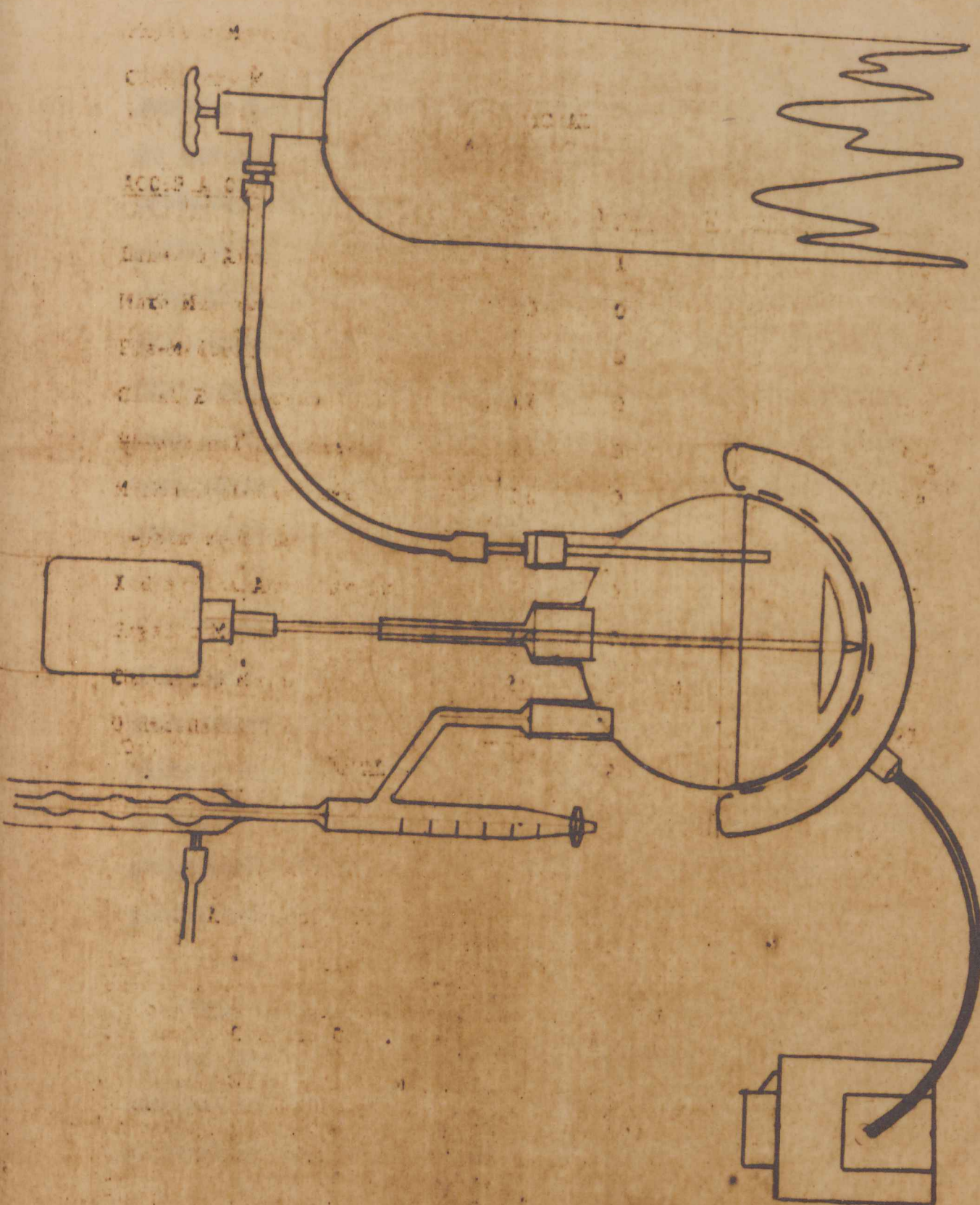
In an effort to arrive at a smooth and efficient procedure and at the risk of losing time, previously prepared structures were synthesized and purified until competence was achieved.

EXPERIMENTAL (cont.)

Part I - Practice Experiments

1. Preparation of 2-(4-chlorophenyl)-3-methyl-4-metathiazanone

Based upon the stoichiometry of the preparation of 3-methyl-2(3-pyridyl)-4-metathiazanone performed by Surrey (4) in which 43.2 g. (.40 mole) of 3-pyridinecarboxaldehyde was reacted with 42.5 g. (.40 mole) of 3-mercaptopropanoic acid and 14 g. (.40 mole + 12.5% excess) of methylamine in 200 ml. benzene, 14 g. (.10 mole) of p-chlorobenzaldehyde, 10.6 g. (.10 mole) of 3-mercaptopropanoic acid and 56 ml. of benzene were delivered to a 2000ml. three-necked round bottom flask equipped with mechanical stirrer and teflon paddle on a glass rod, Dean Stark trap (calibrated in milliliters) with stop-cock, reflux condenser, heating mantle, variac, and tubing (Tygon) from the methylamine pressure tank as illustrated on page 12. The reactants were stirred, followed by gradually administering 3.5 g. (.10 mole + 12.5% excess) methylamine gas at a rate of 4-5 bubbles per second. The mantle was secured under the flask which then was heated to a point short of reflux where the reaction was shut down for twenty-four hours. The contents which were initially clear were a yellow color one day later. The flask was brought to reflux and water collected in the Dean Stark trap. Reflux was continued for twenty-four hours at which time 3.9 ml. of water had collected.



EXPERIMENTAL (cont.)

Another twenty-four hours of heating was attempted where at the end of this period the flask was a dark color, probably due to heat effects which resulted when a good portion of the benzene solvent had vaporized into the atmosphere through loosened glass joints during the night. An observant eye remedied the situation by replenishing the solvent in the amount of 100 ml. With the darkening of the flask, some yellow material came over into the trap. Crystals were observed here and in the flask. A total of 5.3 ml. of water collected in the trap.

Theory indicates that 0.2 mole of water should evolve (0.1 mole from formation of the Schiff base and 0.1 mole from formation of the cyclic amide structure) or 3.6 ml. of water. The excess of 1.7 ml. of water was attributed to the excessive decomposition of the product. The reaction was abandoned when efforts to remove the remaining product proved too difficult.

The initial 3.9 ml. reading which was 0.3 ml. in excess of the theoretical amount was attributed in part to wet solvent and apparatus. The additional heating time was allowed in an effort to insure complete reaction.

In subsequent experiments, care was taken to develop a better sealed reaction system.

EXPERIMENTAL (cont.)

2. Preparation of 2-(2-chlorophenyl)-3-methyl-4-metathiazanone

Referring to Table I (page 6), the use of 2-chlorobenzaldehyde has yielded products at 39% of theory as compared with 11% for parachlorobenzaldehyde's product, the preparation of which was attempted in Experiment 1. Therefore, o-chlorobenzaldehyde was tried next. A greater amount of solvent was also employed to reduce the chance of complete loss of solvent.

Following the same procedure as in Experiment 1, the flask was loaded with 14 g. (.10 mole) o-chlorobenzaldehyde, 10.6 g. (.10 mole) of 3-mercaptopropanoic acid, and 200 ml. of benzene, stirred, heated and bubbled with methylamine. Initial cloudiness was observed probably due to formation of water and its resultant immiscibility in the benzene. After four days of reflux a constant volume of 2.9 ml. of water (80.5%) was obtained, after which the system was shut down.

The excess 3-mercaptopropanoic acid (assumed present) was neutralized with NH_4OH (a 3 molar solution in water) by washing in a separatory funnel after cooling of the reaction mixture. The product did not crystallize upon neutralization as per directions. An emulsion resulted

EXPERIMENTAL (cont.)

from the aqueous basic solution and the benzene. This was partially broken by a saturated solution of sodium chloride. Separation of the organic layer and subsequent filtration yielded no crystals.

A vacuum distillation arrangement was set up which included a three necked round bottom flask equipped with flask thermometer, boiling chips, capillary tubing to the atmosphere via rubber tubing and clamp, take off head, head thermometer, water condenser, vacuum arm, receiver, mantle, variac, and vacuum pump. Under a reduced pressure of 8-9 mm. of mercury, water and benzene were stripped off. A flask temperature of 230°C was reached without noticeable distillation of the product. Upon examination of the water-benzene distillate the odor of o-chlorobenzaldehyde was detected, possibly due to decomposition of the product or the presence of unreacted starting material. With a new receiver, the flask contents were reheated under vacuum by flame until the product began coming over as an orange-brown opaque oil of high viscosity. Upon standing for a few days the viscous distillate began to crystallize. Crystals were found in greater abundance with time, having a melting point of 73-78°C. The crystals dissolved in hot ethanol. Upon cooling and standing, recrystallization was not successful.

EXPERIMENTAL (cont.)

The solution was concentrated by evaporation of most of the solvent on a hot plate with crystallization upon cooling yielding discolored crystals. A series of solvents were tried for the recrystallization before settling on the ether-ligroin pair. (Soluble in ether, insoluble in ligroin). Recrystallization of the entire product yielded crystals of a melting point 77-78.5°C. This value compares well with the literature value of 76.4-79.6°C. The crystals were collected to give 2.52 g. (15.90%) of product.

3. Preparation of 2-phenyl-3-methyl-4-metathiazanone

A relatively larger supply of benzaldehyde (unsubstituted) was on hand and this prompted its use in this and many of the following practice experiments.

Based upon information from Table I (page 6), 2-phenyl-3-methyl-4-metathiazanone had been prepared in 74% yield.

With the same apparatus of the previous experiments, 21.2 g. (.20 mole) of benzaldehyde, 21.2 g. (.20 mole) of 3-mercaptopropanoic acid, 100 ml. of benzene, and gaseous methylamine were delivered to the flask. The reaction was started and continued at reflux for 4 to 5 days until a continuous volume of 4.3 ml. of water had collected. This represented 72% of the theoretical water. The reaction

EXPERIMENTAL (cont.)

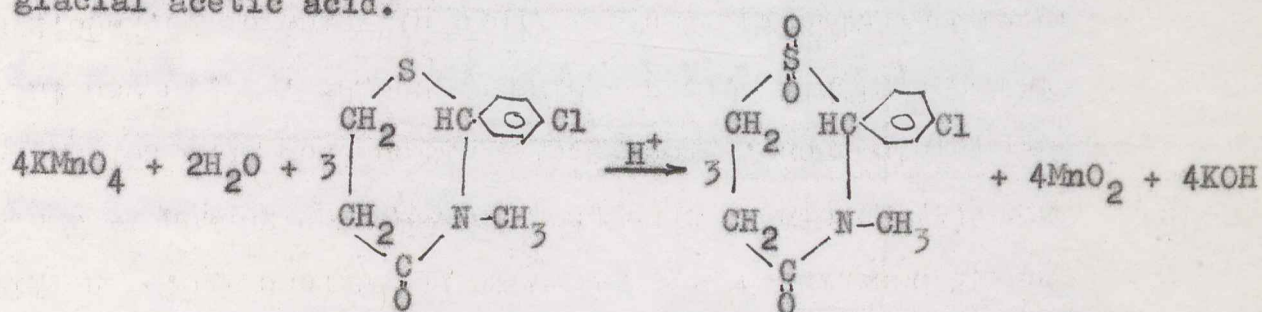
mixture was worked up to the stage where water and benzene were stripped off. Further heating resulted in vaporization of the product and subsequent collection in the receiver. Because of its highly viscous properties, the product could not be effectively freed from the reaction flask and take off head without some form of contamination from the flask impurities. The collected product was allowed to stand for twelve days, afterwhich crystallization was observed with marked decolorization indicating an impure product. Although a hot 10% solution of HCl was effective in dissolving a sample of the product, subsequent cooling yielded crystals on a test tube scale. It was feared that the crystals may have been contaminated with the hydrochloride of any Schiff base which may have remained unreactive. The literature (4) gave n-heptane as a solvent for 2-phenyl-3-methyl-4-metathiazanone. Recrystallization from this solvent gave crystals with a melting point of 95-96°C. This was in agreement with the Table I (page 6) value of 95.2-96.2°C.

4. Oxidation of 2-(2-chlorophenyl)-3-methyl-4-metathiazanone to the sulfone derivative

Based upon Example 44, column 12 of United States Patent 3,082,209, where 10 g. (.04 mole) of 2-(4-chlorophenyl)-3-methyl-4-metathiazanone in 50 ml. of glacial acetic acid

EXPERIMENTAL (cont.)

were oxidized with 11.2 g. (.07 mole) potassium permanganate in 100 ml. of warm water, 2.52 g. (.016 mole) potassium permanganate were dissolved in 20 ml. of warm water and added dropwise to a solution of 2.25 g. ($.93 \times 10^{-2}$ mole) of 2-(2-chlorophenyl)-3-methyl-4-metathiazanone in 12 ml. of glacial acetic acid.



External cooling was necessary to hold the reaction below 30°C due to the resultant exotherm. Stirring was necessary to aid the reaction. The characteristic brown color of manganese dioxide was viewed until the end of permanganate addition where the purple color of permanganate persisted, indicating complete oxidation had taken place. These mild conditions were maintained in the hope of not defacing the remaining parts of the molecule. A saturated aqueous solution of sodium bisulfite was prepared and added to the oxidized product mixture to remove the manganese dioxide. The product was extracted with chloroform and the extract washed several times with water.

EXPERIMENTAL (cont.)

In a reduced pressure distillation arrangement, the chloroform was evaporated yielding the pure product which was recrystallized from n-propanol.

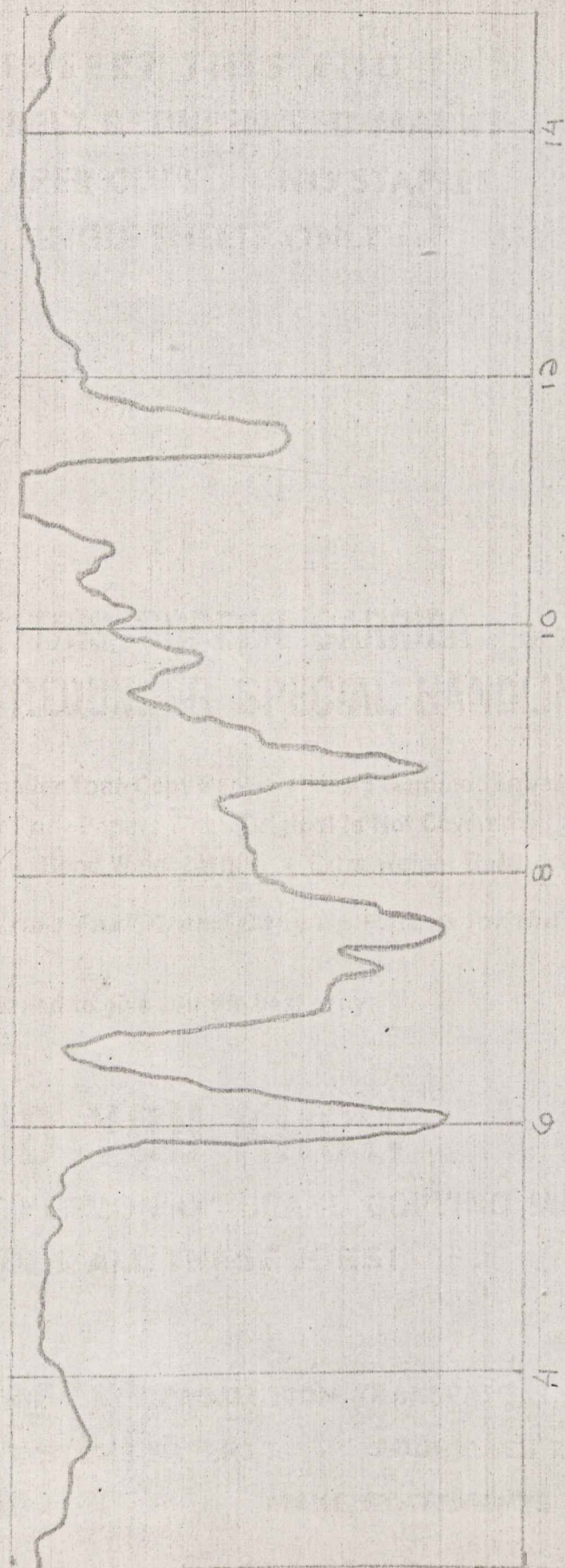
An infrared spectrum was taken of a 10% solution of the sulfone in chloroform in NaCl cells. Peaking at 6.0-6.1 microns indicated the disubstituted amide structure, while peaking at 7.3, 7.5-.6, and 8.9 microns showed sulfone vibrations (page 20).

5. Preparation of 2-(2-chlorophenyl)-3-methyl-4-metathiazanone (intended for sulfoxide preparation)

In view of the fact that success was met in Experiment 2, the same procedure was repeated in the hope that the product would be oxidized to the sulfoxide.

To the 2000 ml. reaction flask, 14 g. (.10 mole) of o-chlorobenzaldehyde, 10.6 g. (.10 mole) of 3-mercaptopropanoic acid, 200 ml. of benzene and methylamine were added and heated to reflux. During the night a power failure automatically shut down the reaction with the accumulation of methylamine as ventilation pumps for the hood became inactivated. However, the reaction mixture was

2-(2-CHLOROPHENYL)-3-METHYL-4-METHYL-
THIAZANONE-1-DIOXIDE



WAVELENGTH (MICRONS)

EXPERIMENTAL (cont.)

worked up in an effort to salvage the product. At the point of solvent stripping, more procedural and technical information was obtained via phone conversation with Sterling Winthrop Laboratories. In the light of the following, the present experiment was abandoned.

The following data were obtained from Experiments 1, 2 and 3.

<u>Experiment</u>	<u>Vol. Water Collected</u>	<u>Theoretical</u>	<u>%</u>
1	3.9 ml.	3.6 ml.	108.0
2	2.9	3.6	80.5
3	4.3	7.2	72.0

The water yield from Experiment 1 has already been described as partly due to wetness of solvent and apparatus and to decomposition of the product. The water yields of Experiments 2 and 3, although relatively high as far as chemical reactions go, are actually low when one considers that Schiff base formation and lactam formation usually proceed very readily.

Two reasons were conceived to account for these reduced yields. First, the 3-mercaptopropanoic acid may be suffering a premature oxidation to the sulfoxide, or sulfone. The

EXPERIMENTAL (cont.)

disulfide may also result from the air oxidation which can be represented as $R-SH + \text{air} \longrightarrow R-S-S-R$. Secondly, the Schiff base may be undergoing oxidation or trimerization. To minimize these effects, the Schiff base was formed first, followed by addition of the 3-mercaptopropanoic acid in 5% excess under a cover of inert nitrogen gas.

6. Preparation of 2-phenyl-3-methyl-4-metathiazanene

Following the new technique, 21.2 g. (.20 mole) of benzaldehyde were dissolved in 200 ml. of benzene with stirring. The usual apparatus was employed. Methylamine was bubbled into the reaction flask which was brought to reflux. The bubbling was continued until the theoretical amount of water, 3.6 ml., had collected in the Dean Stark trap. At this point, a continuous flowing nitrogen blanket was administered followed by addition of 22.26 g. (.20 mole + 5% excess) of 3-mercaptopropanoic acid. The nitrogen was dried by bubbling through two glycerol traps to minimize the volume error in water determination. Reflux was continued. Again the ground glass joints were loosened from the stirrer resulting in solvent leakage and resultant charring of flask contents. The reaction was abandoned.

EXPERIMENTAL (cont.)

7. Preparation of 2-phenyl-3-methyl-4-metathiazanone

Experiment 6 was repeated with the same reactant weights. Glass joints were well greased and sealed tightly. Apparatus arranged on three separate ring stands reinforced the vibrational effects of the stirrer. A single-body rack construction would be ideal and later efforts were directed at this problem.

The 200 ml. of benzene were delivered directly to the flask. An additional 30-40 ml. were often added to the Dean Stark trap in order not to reduce the volume of solvent in the reaction flask at reflux.

The benzaldehyde was weighed and delivered to the benzene in the flask. Following attachment of the methylamine delivery tube, the flask was brought to reflux and methylamine was bubbled into the system. The Schiff base formed rapidly (less than one hour) with theoretical water evolved. After standing for forty-eight hours in air, 3-mercapto-propanoic acid was weighed and delivered with a nitrogen blanket. A total of 4.6 ml. of water was collected without further increase. In order to complete the ring closure, more drastic energizing of the reaction system was attempted by slowly bleeding out the benzene and replacing it with a

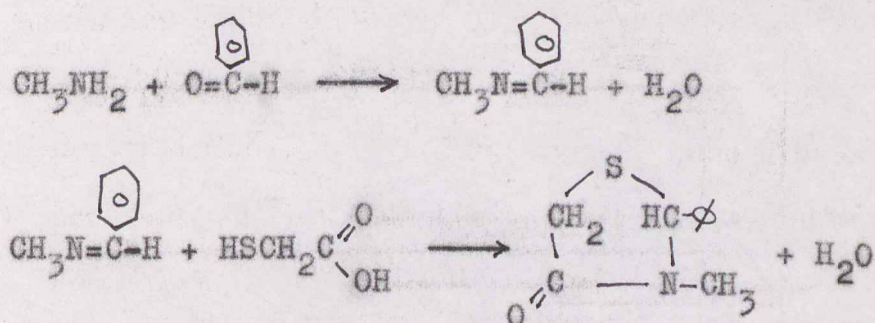
EXPERIMENTAL (cont.)

higher boiling commercial grade of xylene. At higher temperatures a strong stream of odorous vapors were seen emerging from the top of the reflux condenser. No attempt was made to identify the vapor, but obviously the system was not efficient enough to trap and return this emerging gas. The experiment was abandoned.

8. Preparation of 2-phenyl-3-methyl-4-thiazolidone

Due primarily to a dwindling supply of 3-mercaptopropionic acid and a good supply of thioglycolic acid, five membered heterocyclic structures were attempted.

The reaction was similar to those of the metathiazanone type as shown by the following equations.



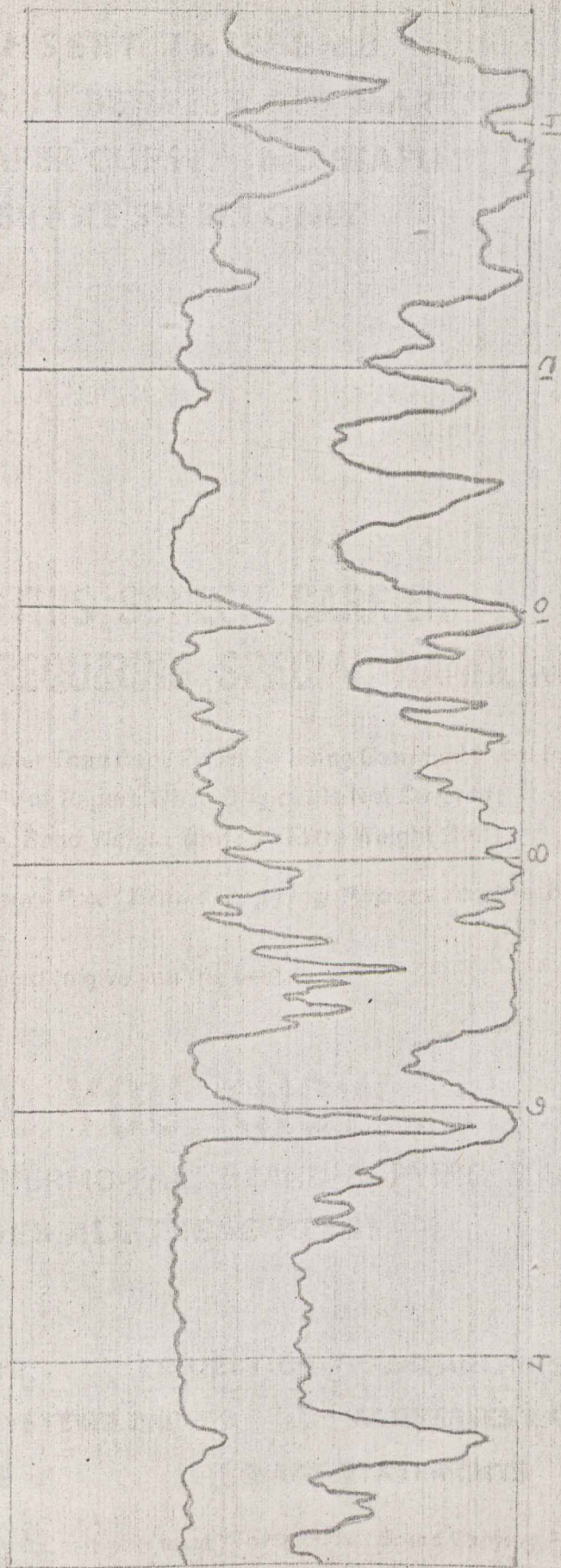
Benzaldehyde, 21.2g. (.20 mole), was weighed and dissolved in 200 ml. of benzene followed by bubbling and reflux heating of methylamine. The theoretical 3.6 ml. of water collected within an hour and nitrogen replaced the

EXPERIMENTAL (cont.)

methylaniline to prevent oxidation of the Schiff base. The thioglycolic acid, 19.32 g. (.20 mole + 5% excess), was added and under a continuous blanket of nitrogen the reaction mixture was reheated to reflux. The theoretical additional water was collected (3.6 ml. or 7.2 ml. total) and the flask was allowed to cool in an ice bath (ether was added to prevent benzene from crystallizing). Any unreactive Schiff base was taken up with a dilute (4 parts H_2O : 1 part conc. HCl) aqueous HCl wash while excess thioglycolic acid and HCl were extracted with 10% Na_2CO_3 solution. The resultant mixture was washed several times with water to remove the Na_2CO_3 . Benzene and water were stripped out of the reaction mixture and the product was chilled in an ice bath. Twenty-four hours standing in the refrigerator failed to produce crystals of the thiazolidone. The oil was distilled over in vacuo and received in two portions, one a clear yellow oil, the second a translucent discolored oil. Fraction one was recorded as coming over at a head temperature of 115°C at 2 mm. of pressure. Fraction two saw a range of temperatures up to $180\text{--}185^\circ\text{C}$ at 16 mm. of pressure. The difference in pressures was due to a leak in the system which developed. The two fractions were separated at two different times with an interval of five days. A sample was taken from each distillate and analyzed by infrared spectroscopy (pages 26 & 27).

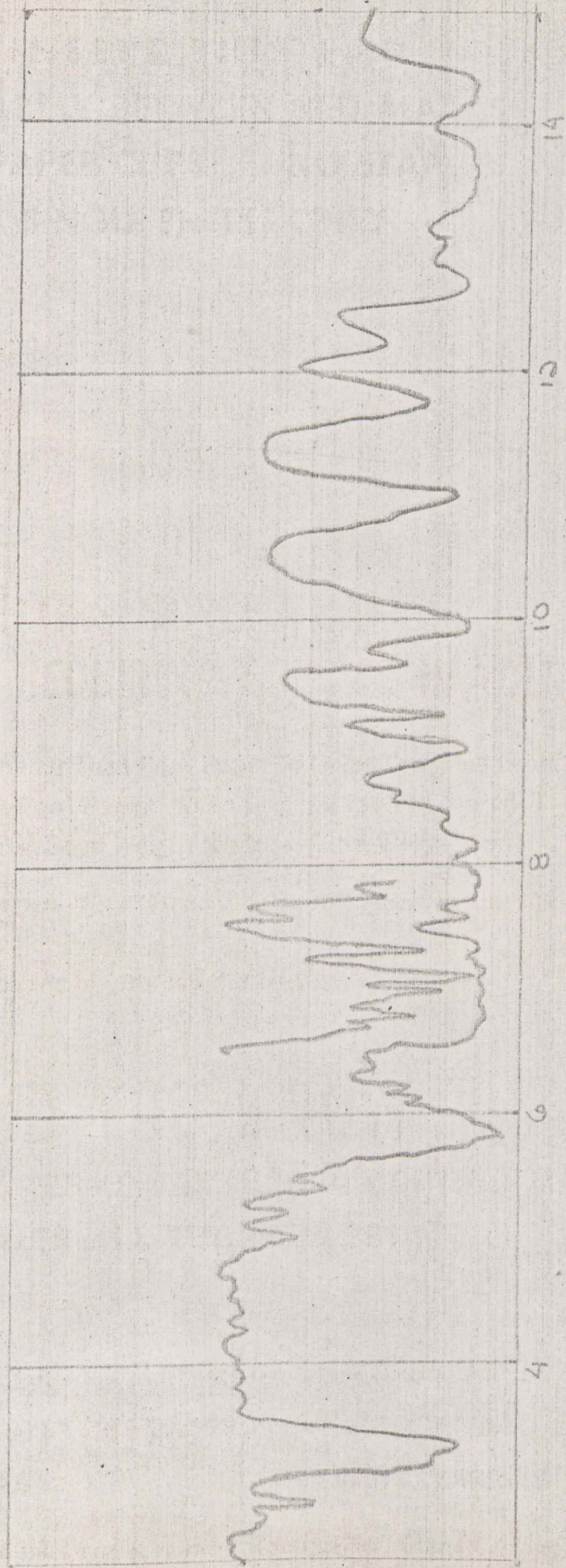
DISTILLATE ONE

2-PHENYL-3-METHYL-4-THIAZOLIDONE



WAVELENGTH (MICRONS)

DISTILLATE T300
O-PHENYL-3-METHYL-4-THIAZOLIDONE



WAVELENGTH (MICRONS)

EXPERIMENTAL (cont.)

Both spectra were found to be identical and showed disubstituted amide absorption at 5.9-6.0 microns and sulfide absorption at 13.5-13.9 microns. Polymerization may have taken place and the next step would have led to a molecular weight determination via freezing point depression.

This experiment terminated the series of practice runs which resulted in development of valuable and time saving techniques which were employed extensively in the following organic syntheses.

Part II - Original Organic Syntheses

Hereafter, reaction weights were reduced considerably due to the expense of the fluoroaldehydes.

9. Preparation of 2-(3-fluorophenyl)-3-methyl-4-metathiazanone

The apparatus was arranged with 11.58 g. (.093 mole) of fluorobenzaldehyde in solution with 150 ml. of benzene. Methylamine was bubbled while the flask was brought to reflux with stirring. The theoretical 1.67 ml. (.093 mole) of water was collected in the trap. 3-mercaptopropanoic acid, 10.34 g. (.093 + 5% excess), was added followed by the inert nitrogen blanket and reflux was continued. After three hours no noticeable water had collected. The reaction

EXPERIMENTAL (cont.)

was continued overnight with no water being formed. The reaction was shut down and abandoned.

The Schiff base was believed to have been ineffectively covered with the nitrogen blanket resulting in oxidation or trimerization of the Schiff base.

10. Preparation of 2-(3-fluorophenyl)-3-methyl-4-metathiazanone

To prevent any oxidation or trimerization of the Schiff base, the reaction time of the Schiff base was cut first by dissolving the methylamine (in excess) in benzene, followed by the aldehyde and acid and nitrogen blanket. The benzene was added to an Erlenmeyer flask and cooled in a porcelain evaporating dish containing salt, ice and acetone. The flask, benzene and evaporating dish were weighed and methylamine was bubbled until 2.73 g. (.08 mole + 10% excess) were delivered. The methylamine, now in benzene solution was added to the reaction flask with 9.33 g. (.08 mole + 10% excess) of 3-mercaptopropanoic acid, 10 g. (.08 mole) of m-fluorobenzaldehyde and nitrogen blanket. After twenty-four hours of reflux, a constant volume of 0.80 ml. of water was collected which represented 27.8% of theory (2.88 ml.).

EXPERIMENTAL (cont.)

Crystallization was observed upon cooling and standing. The crystals were collected in a Buchner funnel and dried to give 0.1 g. (.05%) of product.

11. Preparation of 2-(3-fluorophenyl)-3-methyl-4-thiazolidone
10 g. (.08 mole) of metafluorobenzaldehyde were weighed and dissolved in sufficient volume of benzene in the reaction flask. Methylamine was bubbled into the refluxing flask mixture until 1.44 ml. (.08 mole) of water had collected in the trap. 7.36 g. (.08 mole) of thioglycolic acid was added with an accompanying nitrogen cover. Within three hours, a total of 2.30ml. of water had collected which represented 80% of theoretical water. The reaction was continued overnight with development of a leak in the refluxing system. As a result, the flask contents were charred and the reaction was abandoned.

12. Preparation of 2-(3-fluorophenyl)-3-methyl-4-thiazolidone
The procedure and measures of Experiment 11 were repeated, however a system of crosslinked racks was set up to prevent motor vibrations from loosening ground glass joints. Also a 5% excess of acid was used here. 2.00 ml. of cloudy water had been trapped from Schiff base formation which was still not at a constant level when the thioglycolic acid was added.

EXPERIMENTAL (cont.)

A nitrogen blanket followed the acid and the flask was heated again to reflux. A total of 2.70 ml. of water had collected within an hour. The system was cooled and covered with nitrogen while standing for two days. The flask was reheated after two days without further evolution of water. In fact, the water level which in its cloudy state registered 2.70 ml. had settled to 2.0 ml. (69.4%).

13. Oxidation of 2-(3-fluorophenyl)-3-methyl-4-thiazolidone to the one-sulfone (or one-dioxide)

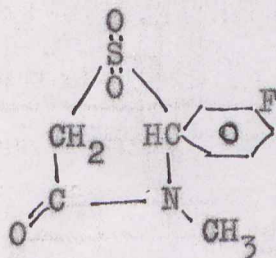
Benzene and water were stripped off the product of Experiment 12 at atmospheric pressure leaving an oil believed to be 2-(3-fluorophenyl)-3-methyl-4-thiazolidone contaminated with the corresponding Schiff base and unreacted thioglycolic acid. Based upon data given in Patent 3,082,209, column 12, example 44, the above product was oxidized to the sulfone.

21.7 g. (.14 mole) of potassium permanganate was dissolved in 196 ml. of water which was warmed and delivered dropwise to a well-stirred solution of 16.9 g. (.08 mole) of the thiazolidone in 97 ml. of acetic acid and held below 30°C with external cooling. After complete addition of KMnO_4 , a saturated solution of sodium bisulfite was added to remove the manganese dioxide. Immediately the dark

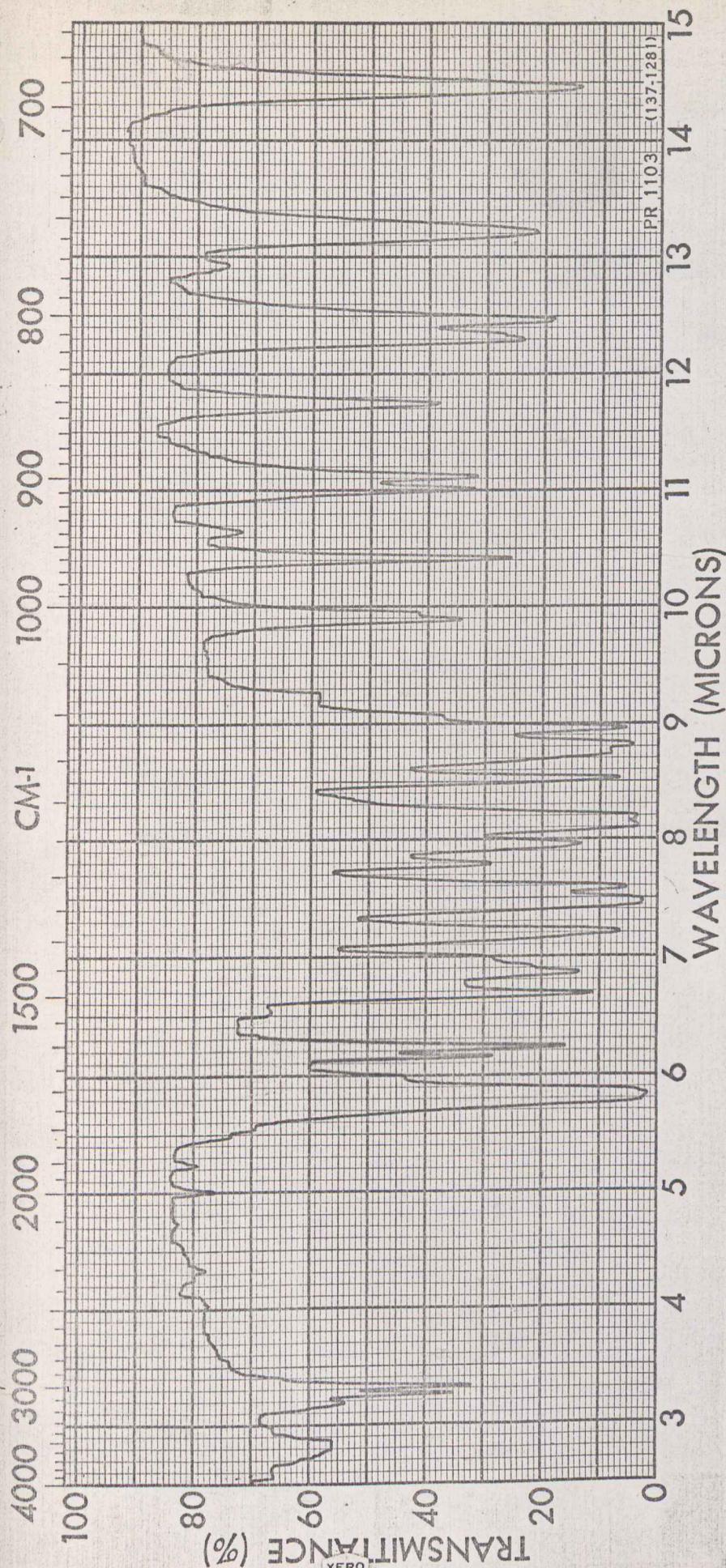
EXPERIMENTAL (cont.)

brown color disappeared. A thick white oil separated out, and the entire mixture was transferred to a separatory funnel with the aid of a chloroform rinse. The white oil solidified and was taken up in a chloroform extract. This extract was washed with water to remove sodium bisulfite and stripped of chloroform under reduced pressure. A white solid was recovered. The solid was recrystallized from isopropanol twice. After the first crystallization and drying, 3.79 g. was recovered corresponding to a 53.60% yield, m.p. 138-39°C. An infrared spectrum was taken showing sulfone absorption (page 33). A sample of the product was sent out for elemental analysis and corrected melting point determination. After the second recrystallization, the melting point was 139-140°C.

Results of the analysis performed by Sterling Winthrop Laboratories of Rensselaer, New York confirmed that 2-(3-fluorophenyl)-3-methyl-4-thiazolidone-1-dioxide had been prepared.



corrected m.p. - 142.2-
143.8°C



SPECTRUM NO. _____
SAMPLE _____

SPECTRUM NO. _____	ORIGIN _____	LEGEND _____	REMARKS _____
SAMPLE <chem>CC(=O)N1CCSC1c2ccccc2F</chem>	PURITY _____	1. _____	_____
META	PHASE KBr Disc	2. _____	_____
	THICKNESS 1%	DATE 3/11/65	_____
		OPERATOR J. Wilson	_____

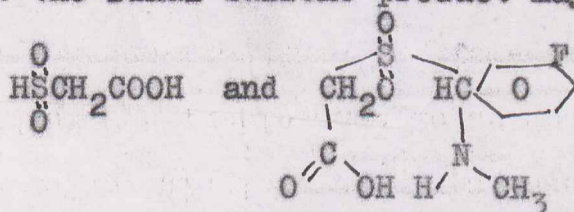
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GRAPHIC CONTROLS CORPORATION
BUFFALO, NEW YORK

2-(3-FLUOROPHENYL)-3-METHYL-4-THIAZOLIDONE-1-DIOXIDE

EXPERIMENTAL (cont.)

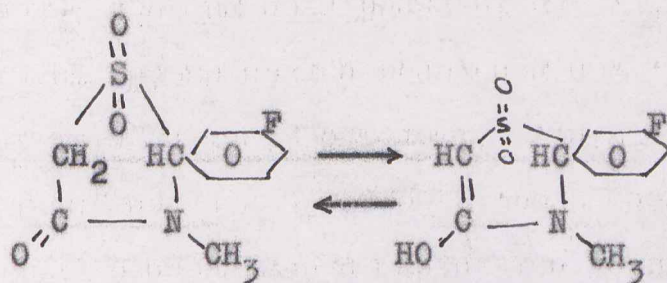
	<u>Calculated</u>	<u>Found</u>
% Nitrogen	5.75	5.50
% Sulfur	13.17	13.65

It was thought that the final sulfone product may have been contaminated with



when it

was found that the product of this experiment was soluble in 10% NaOH and since Schiff Base and acid were not removed before oxidation. After receiving the above elemental analysis, it was clear that the acidity of the molecule was due to keto-enol tautomerism with the enol form contributing



largely to the molecule's acidity.

14. Preparation of 2-(4-fluorophenyl)-3-methyl-4-thiazolidone

The procedure for Experiment 12 was repeated, replacing metafluorobenzaldehyde with p-fluorobenzaldehyde. The same reaction weights were employed.

EXPERIMENTAL (cont.)

A total volume of 2.8 ml. of cloudy water collected within an hour. The reaction mixture was cooled to room temperature and washed with 10% HCl, 10% Na_2CO_3 and water to remove any Schiff base or acid which remained unreacted. Benzene and water were stripped off at atmospheric pressure yielding the oily product.

15. Preparation of 2-(4-fluorophenyl)-3-methyl-4-thiazolidone-1-dioxide

The procedure of Experiment 13 was repeated with 2-(4-fluorophenyl)-3-methyl-4-thiazolidone. Again assuming 100% yield of Experiment 14's thiazolidone, .08 mole should have been prepared. On this basis, 16.9 g. (.08 mole) of 2-(4-fluorophenyl)-3-methyl-4-thiazolidone was dissolved in 97.1 ml. of acetic acid reacted with 21.7 g. (0.14 mole) of KMnO_4 in 196 ml. of water.

The oxidation was carried out as before. The white oil, however, did not solidify during the chloroform extraction. Evaporation of the chloroform under reduced pressure once again gave a white solid which was recrystallized twice from isopropanol.

Melting point after 1st crystallization - 143.5-144.5°C

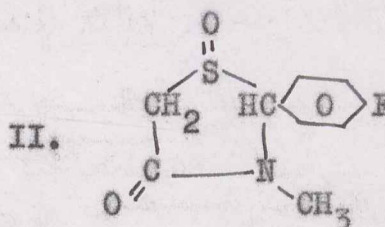
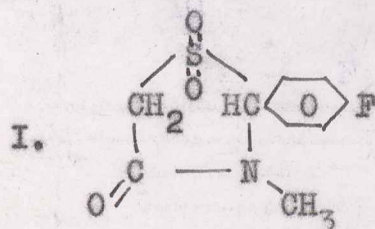
Yield - 5.94 g. = 33%

Melting point after 2nd crystallization - 146.5-147.5°C

EXPERIMENTAL (cont.)

A sample was sent to Sterling Winthrop for elemental analysis and corrected melting point determination.

Results of this analysis indicated that the 1-sulfoxide had been prepared rather than the 1-sulfone.

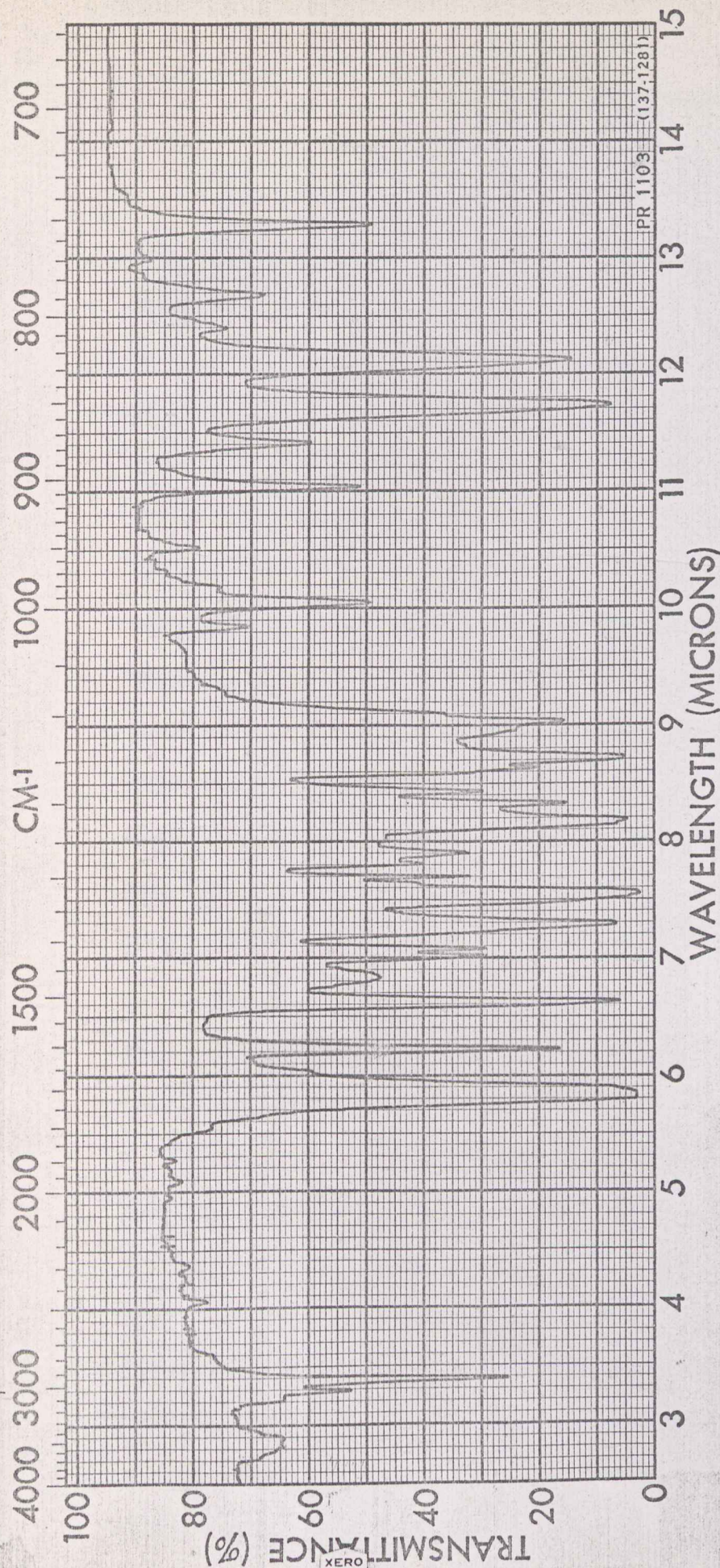


	<u>Calculated</u>	<u>Found</u>
I.		
% Sulfur	13.17	13.90
% Fluorine	7.82	7.99
II.		
% Sulfur	14.14	13.90
% Fluorine	8.36	7.99

The formation of the sulfoxide is made more likely by the fact that oxidation was performed over a shorter time than in Experiment 13 and also by a comparison of infrared spectra (page 37). Absorption showed double peaking, characteristic of sulfoxide, where the sulfone bond occurs.

Corrected yield - 35%

Corrected melting point - 148-151°C



SPECTRUM NO. _____
SAMPLE _____

37.

SPECTRUM NO. _____	ORIGIN _____	LEGEND _____	REMARKS _____
SAMPLE _____	PURITY _____	1. _____	_____
<chem>Cc1ccc(cc1)C(=O)N</chem>	PHASE <u>KBr Disc</u>	2. _____	_____
<u>para</u>	THICKNESS <u>10%</u>	DATE <u>3/22/65</u>	_____
		OPERATOR <u>J. Wilson</u>	_____

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BUFFALO, NEW YORK

2-(4-FLUOROPHENYL)-3-METHYL-4-THIAZOLIDONE-1-OXIDE

EXPERIMENTAL (cont.)

16. Preparation of 2-(3-fluorophenyl)-3-methyl-4-metathiazanone

10 g. (.08 mole) of m-fluorobenzaldehyde was reacted with bubbled methyl amine and 8.90 g. (.08 mole + 5% excess) of 3-mercaptopropanoic acid in a sufficient volume of benzene. Following the normal procedure, 2.2 ml. of cloudy water collected from Schiff base formation. Upon addition of 3-mercaptopropanoic acid and nitrogen cover, water ceased to evolve. At this point, it was thought that water evolution was a poor barometer of reaction progress. Therefore, the reaction mixture was worked up in the usual manner. Schiff base and acid were removed with 10% HCl, 5% NaHCO₃ and water. Water and benzene were stripped off at atmospheric pressure to give the oily product.

17. Preparation of 2-(3-fluorophenyl)-3-methyl-4-metathiazanone-1-dioxide

28.10 g. (.08 mole) of 2-(3-fluorophenyl)-3-methyl -4-metathiazanone in 97.1 ml. of acetic acid was reacted with KMnO₄, 21.7 g. (0.14 mole), in 196 ml. of water. The oil was dissolved in acetic acid to which was added the aqueous solution of potassium permanganate. Manganese dioxide was removed by addition of sodium bisulfite with no appreciable white oil formation. Two chloroform extractions were performed with subsequent evaporization of the solvent under

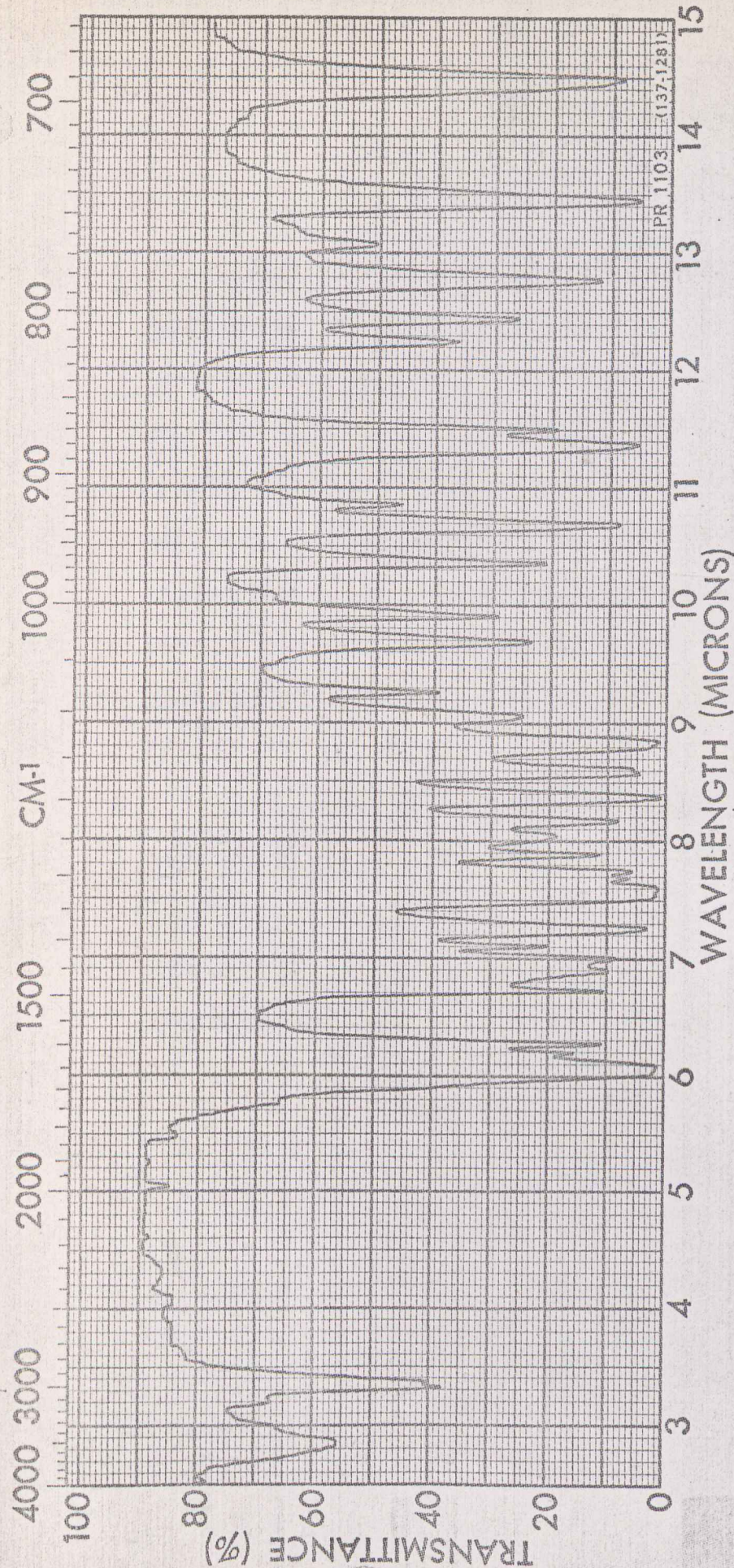
EXPERIMENTAL (cont.)

reduced pressure yielding a yellow solid. The yellow crystals were actually a slurry in a viscous oil. Cooling of the oil resulted in its crystallization. The product was recrystallized twice from isopropanol. Each crystallization required cooling of the mother liquor for 24-48 hours at standard refrigeration temperatures. Following the first crystallization, 3.6 g. (18.50%) yield was obtained, melting point 154-56.5°C. A 1.9 g. yield followed the second crystallization. An infrared spectrum was taken showing sulfone bands (page 40). The entire 1.9 g. of sample was sent to Sterling Winthrop Laboratories for elemental analysis and corrected melting point determination.

Sulfur and fluorine analysis of the above product confirmed a successful preparation. This data as well as a corrected melting point determination are shown below.

	<u>Calculated</u>	<u>Found</u>
% Sulfur	12.46	12.61
% Fluorine	7.41	7.21

Corrected melting point - 154-156.5°C.



SPECTRUM NO. _____
SAMPLE

SPECTRUM NO. _____	ORIGIN _____	LEGEND _____	REMARKS _____
SAMPLE _____	PURITY _____	1. _____	_____
<chem>CC(C)C(=O)N(C)Cc1ccc(F)cc1</chem>	PHASE KBr Disc	2. _____	_____
	THICKNESS 1%	DATE 4/10/65	_____
		OPERATOR J. Wilson	_____

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GRAPHIC CONTROLS CORPORATION
BUFFALO, NEW YORK

2-(3-FLUOROPHENYL)-3-METHYL-4-METHYLARAZONE-1-DIOXIDE

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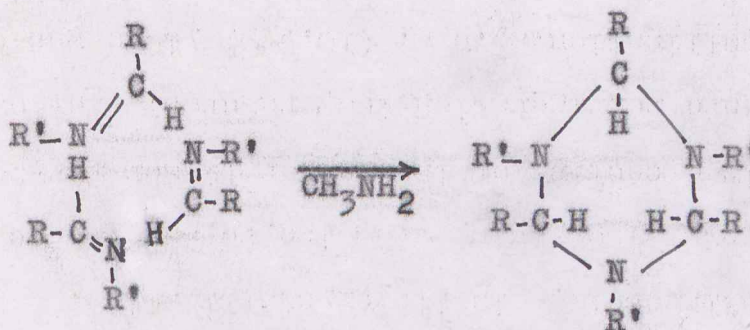
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CONCLUSIONS

From the work performed for this thesis, three general questions of a chemical nature evolved which demand a more precise treatment. Probably the most important of these was the low reactivity of the intermediary Schiff base with the sulfhydryl acids. Second, there exists the question of the ease of formation of the five membered heterocyclic system over the six membered heterocyclic. Finally, there was the problem of water evolution which may very well be one of engineering rather than chemistry.

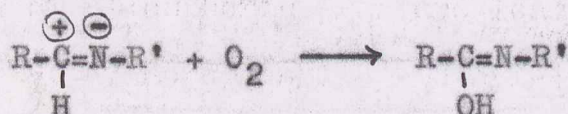
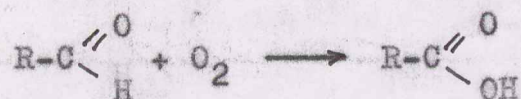
Two possible explanations account for this reduced activity of the azomethines. The first may be in a base catalyzed trimerization or polymerization. Such a reaction would follow the non-detailed path where CH_3NH_2 serves as the base catalyst.



CONCLUSIONS (cont.)

Formaldehyde behaves similarly with resultant trimerization. The trimer is predicted over the polymer due to stability considerations of the six membered ring.

Secondly, much the same as an aldehyde undergoes oxidation to the corresponding acid, so the azomethine in the presence of oxygen probably may be oxidized to the hydroxy azomethine. The reaction and its analogue are represented

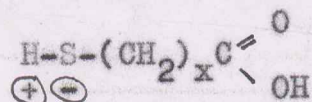


Formerly, the azomethine, or Schiff base possessed a double bond which was very negative at nitrogen and relatively positive at the carbon terminal. With the formation of the hydroxy group on the terminal carbon, the positive charge is greatly reduced. This charge difference between carbon and nitrogen appears to be important since the sulfhydryl addition to the carbon nitrogen double bond is probably a four centered mechanism influenced by electrostatic forces. This can be represented as

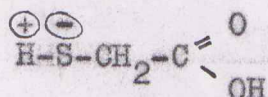


CONCLUSIONS (cont.)

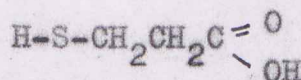
From the proposed mechanism it is seen that the charge difference on the sulfhydryl bond is as important as the charge separation of the azomethine double bond. Now considering 3-mercaptopropanoic acid and thioglycolic acid as members of the sulfhydryl acid series with the general representative formula of



where $x =$ integer, it is clear that any electron withdrawing group on the aliphatic chain will increase the acidity of the hydrogen on sulfur. The carboxy group is such an electron withdrawing group. As to the matter of which acid will have the more acidic hydrogen on sulfur, thioglycolic acid would appear to be the choice due to the relatively greater proximity of the carboxy electron withdrawing activity to sulfur.



more acidic at sulfur



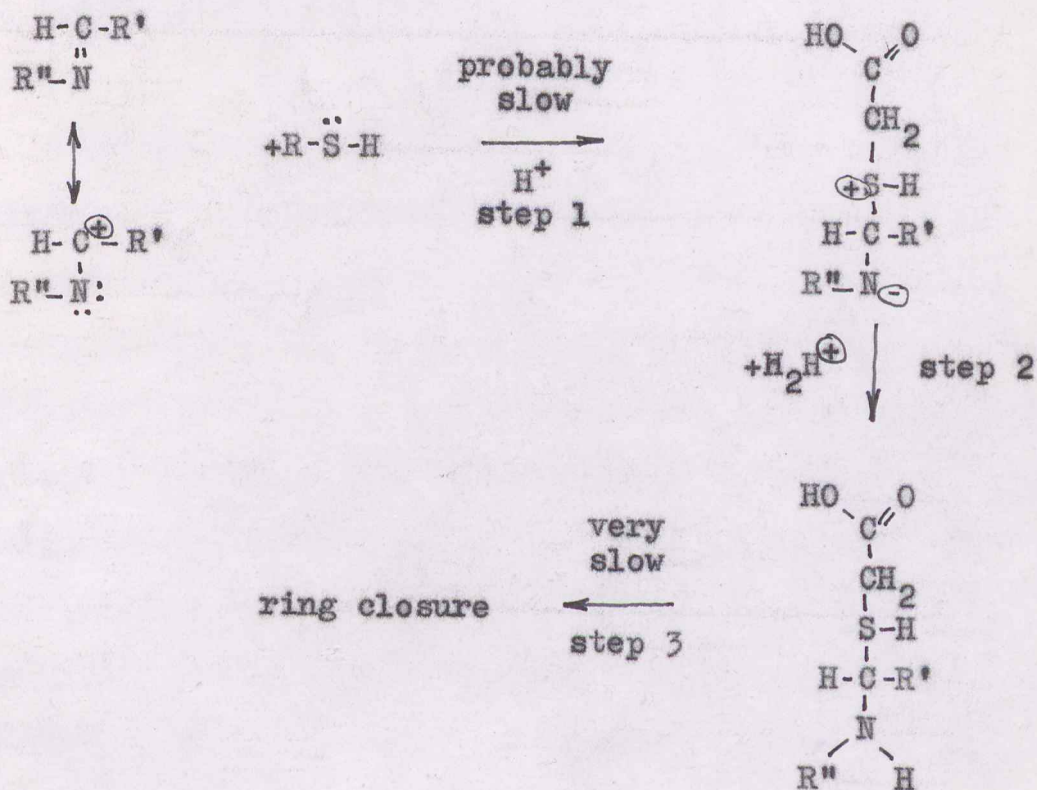
less acidic at sulfur

The greater acidity of this hydrogen may explain the greater reactivity of thioglycolic acid and therefore the greater tendency to form the thiazolidone.

CONCLUSIONS (cont.)

Professor Howard Sheffer of the Union College Chemistry Staff has offered another view on sulfhydryl addition to Schiff bases. "It is well known that in the addition of nucleophiles to carbonyl groups the rate determining step is the addition of the nucleophile to positive carbon which corresponds to step 1 below and not the redistribution of protons in step 2.

However, in this reaction the slow step is probably the subsequent dehydration and formation of lactam."



CONCLUSIONS (cont.)

This mechanism seems more probable since it is of the two centered type in contrast to the forementioned four centered mechanism.

The various air oxidation possibilities for the sulfhydryl compound have already been mentioned (pages 21-22).

Once the Schiff base has satisfactorily bonded with the sulfhydryl acid, the subsequent ring closure results in a cyclic amide or lactam. The study of structural three dimensional models showed no steric hindrance to either five or six membered systems.

A general organic chemistry text (5) was consulted to compare the lactam formation abilities of ϵ -aminobutyric acid and δ -aminovaleric acid to give the five and six membered systems respectively. It was found that heating readily produced the corresponding lactams rather than the polymeric products reported formed by ϵ -aminocaproic acid. This tends to reinforce the argument that the ring production is dependent upon sulfhydryl addition to Schiff base. This discovery also throws light on an earlier problem discussed in Experiment 8 (pages 24-28) where a ten membered ring was suspected. Thus such a ten membered heterocyclic does not seem to be a probable structure.

CONCLUSIONS (cont.)

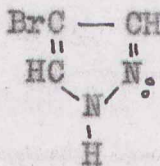
Based upon an article (1) in the March 15, 1965 issue of Chemical and Engineering News, pages 40-41, entitled Bifunctional Catalysts, a study was done on aminolysis of amines and esters to form peptides or polyamides. It is known that acids and bases individually catalyze the aminolysis of amino acid esters to form peptide linkages. It was theorized "that the bifunctional molecules such as 1,2,4-triazole that contain both a weakly acidic and a weakly basic center (properly situated) act through the formation of a cyclic transition state with the ester. The fact that bifunctional molecules such as imidazole and 3-hydroxy pyridine have a much weaker catalytic effect than 1,2,4-triazole, for example, bears out our theory that the aminolysis path involves a concerted displacement mechanism." To displace even a non-acidic group which would be alkoxy groups of the esters, a proton must be available at the correct position on the catalyst molecule. Examples of catalytic structures are given below.

(1)



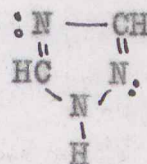
Pyrazole

(2)



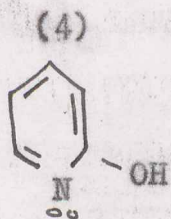
4-Bromopyrazole

(3)

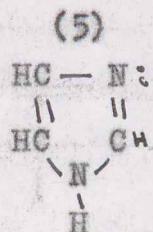


1,2,4-Triazole

CONCLUSIONS (cont.)



2-Hydroxypyridine



Imidazole

Note that in the first four molecules acidic ($=\text{NH}$, $-\text{OH}$) and basic ($=\text{N}$) groups are in adjacent positions to catalyze aminolysis. In imidazole the acidic and basic groups are not properly oriented and a lower catalytic action is to be expected.

The point of the above argument is that extension of it to the existing problem of ring closure to form the lactam may very well be the answer. 2-hydroxypyridine, a relatively mild catalyst in the above scheme, seems attractive to the present work and should be tested.

Although the metathiazanone and thiazolidone formation necessarily results in a splitting out of two moles of water per mole of product, techniques were not developed efficient enough to account for all the water which had formed. This is particularly evident in the metathiazanone reactions where a product was obtained with little or no water separating in

CONCLUSIONS (cont.)

in the trap.

It is suggested that more time be spent in this area since the resultant splitting out of water is probably the most precise and simplest method of determining the progress of reactions.

A number of factors must be improved upon. More specifically, benzene was found to be only moderately satisfactory as a solvent. Water was discovered to be soluble in benzene as represented by the following table (6).

<u>°C</u>	<u>% Wt. H₂O</u>
5.4	0.0335
10.0	0.041
20.0	0.057
30.0	0.082
40.0	0.114
50.0	0.155
60.0	0.205
70.0	0.270

Since reactions were run at reflux which corresponds to a temperature of 80°C, it would be expected that a 500 g. reaction mixture would be expected to contain water in excess of 135 milliliters which is ~~not~~ very significant.

CONCLUSIONS (cont.)

A serious problem encountered with benzene was its great ability to form cloudy emulsions with water in the trap making reading of the meniscus between water and benzene extremely difficult. Heating of this cloudy area readily cleared the field with cloudiness again developing on cooling. Since this emulsion system is stabilized by electrostatic repulsions, it may be broken by mechanical agitation or by addition of electrolytes such as sodium chloride. The application of an external static charge to the system offers another route for destabilization of the emulsion. It should be added that previous work has shown that diminished yields were obtained by using no solvent and such solvents as "toluene, ethanol, isopropanol, n-hexane and the like."⁽⁴⁾ Commercial xylene was used here also but proved to be too high of a boiler (pages 23-24).

Pharmacology

As stated earlier the aim of the research project which is an extension of previous work was to develop a series of compounds which would be tested as to their practicability as central nervous system depressant agents. Preliminary testing of earlier products has shown them to be effective paralyzing agents exhibiting anticonvulsant activity which

CONCLUSIONS (cont.)

appears similar to the activity of mephenesin.

"Compounds containing a lower alkyl group at the 3 position of the metathiazanone or the metathiazanone-1-dioxide and a chloro substituted phenyl group at the 2 position exhibited optimal antielectroshock, antichemoshock, paralyzing, and hypothermic activities. The metathiazanones (sulfones) appear to differ principally from the corresponding metathiazones (sulfides) in pattern of activity rather than profile of action." (2)

Pharmacological tests performed with the three new members, i.e. 2-(3-fluorophenyl)-3-methyl-4-thiazolidone-1-dioxide, 2-(4-fluorophenyl)-3-methyl-4-thiazolidone-1-sulfoxide, and 2-(3-fluorophenyl)-3-methyl-4-metathiazanone-1-dioxide were incomplete as of June 1965.

SUMMARY

Technical and procedural information was obtained from a number of practice experiments where non-substituted and chloro substituted 2-aryl-3-methyl-4-metathiazanones and 2-aryl-3-methyl-4-thiazolidones were prepared.

Three new molecules were successfully prepared:

2-(3-fluorophenyl)-3-methyl-4-thiazolidone-1-dioxide

melting point 142.2-143.8°C

2-(4-fluorophenyl)-3-methyl-4-thiazolidone-1-sulfoxide

melting point 148-151°C

2-(3-fluorophenyl)-3-methyl-4-metathiazanone-1-dioxide

melting point 154-156.5°C

Testing of these new synthetic structures was still in progress at the time of this report.

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