CYCLIZATION OF N-ALLYLTHIOAMIDES AND THEIR HOMOLOGS WITH PARTICULAR ATTENTION TO THIAZOLINE SYNTHESIS

by
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To
Bernice, Mother, and Dad

ACKNOWLEDGMENTS

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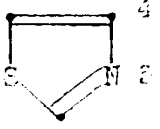
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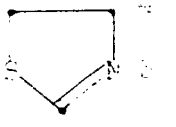
HISTORICAL INTRODUCTION

The thiazoline ring system was defined by Hantzsch[1] in 1888 as the dihydrothiazole system or as the system containing the pentavalent thiazoline nucleus, $(C_3SN)^V$. The thiazole ring, I, contains three non-consecutive carbon atoms, one sulfur atom, one nitrogen atom, and two conjugated double bonds. The numbering system starts with the sulfur as 1 and proceeds to the nitrogen as 3.



I

Two types of dihydrothiazoles are known. Derivatives of 2,3-dihydrothiazole (called Δ^4-thiazolines or simply 4-thiazolines) are known only in cases in which the double bond is part of a fused benzene ring, and as tautomers of thiazoles, the 2-position being doubly bonded to oxygen, sulfur, or nitrogen[2]. Derivatives of 4,5-dihydrothiazole, II, (called Δ^2-thiazolines or simply 2-thiazolines) are well known compounds about which a good part of this work is concerned.



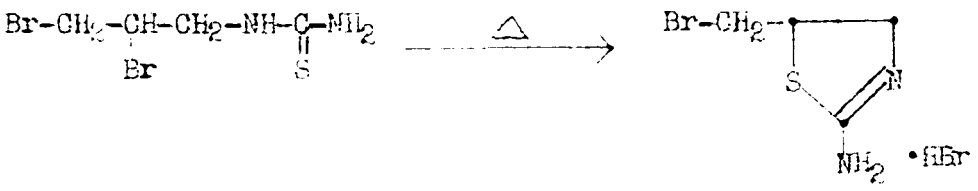
II

In the older literature[3], Green labels the ring to [illegible] to the carbon atoms, the 4 position being designated as α, the 5 as β, and the 2 as μ. The older name for the 2-thiazoline ring system is μ-thiazoline; 2-amino-2-thiazoline was often called ethylene-pseudothiourea (ethylene-Ψ-thiourea).

The 2-thiazolines are weakly basic substances capable of forming salts with strong acids. The picrates are particularly useful derivatives because of their ease of preparation and purification.

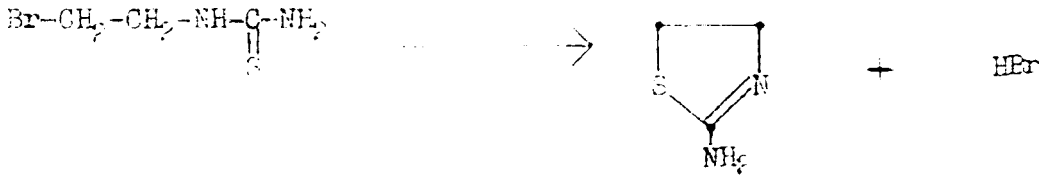
The 2-thiazolines have been of particular interest in recent years because of the possibility of fusing a β-lactam ring across the double bond to give rise to the penicillin ring system.

The first preparation of a 2-thiazoline recorded in the literature is that of the hydrobromide of 2-amino-5-bromomethyl-2-thiazoline, prepared by Maly[4] in 1866 by heating the bromine addition product of N-allylthiourea.



Although Maly did not realize the actual structure of the compound, he did recognize it to be the hydrobromide of a bromine-containing base.

In 1888, Gabriel[3] carried out an analogous cyclization of N-(β-bromoethyl)thiourea and isolated 2-amino-2-thiazoline.

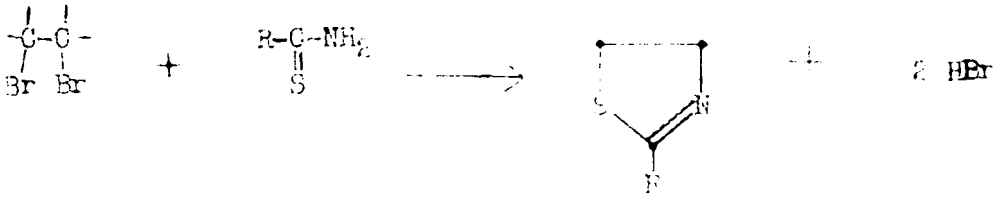


In the same paper, Gabriel points out the true structure of Maly's compound.

The methods for the preparation of 2-thiazolines can be divided into two categories: (1) methods in which two compounds interact to supply the ring atoms, and (2) methods in which the cyclization of a single compound produces the thiazoline ring. The division is arbitrary, because those reactions falling into category (1) undoubtedly proceed through intermediates whose final cyclization falls into category (2).

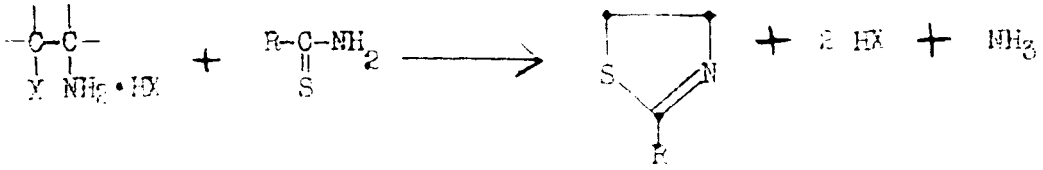
In all examples of the first category, a carbonyl or thiocarbonyl compound is used to supply atoms 1, 2, and 3 of the thiazoline ring and a difunctional compound supplies atoms 4 and 5. The following instances are examples:

(a) Reaction of thioamides with olefin dibromides[5-8].



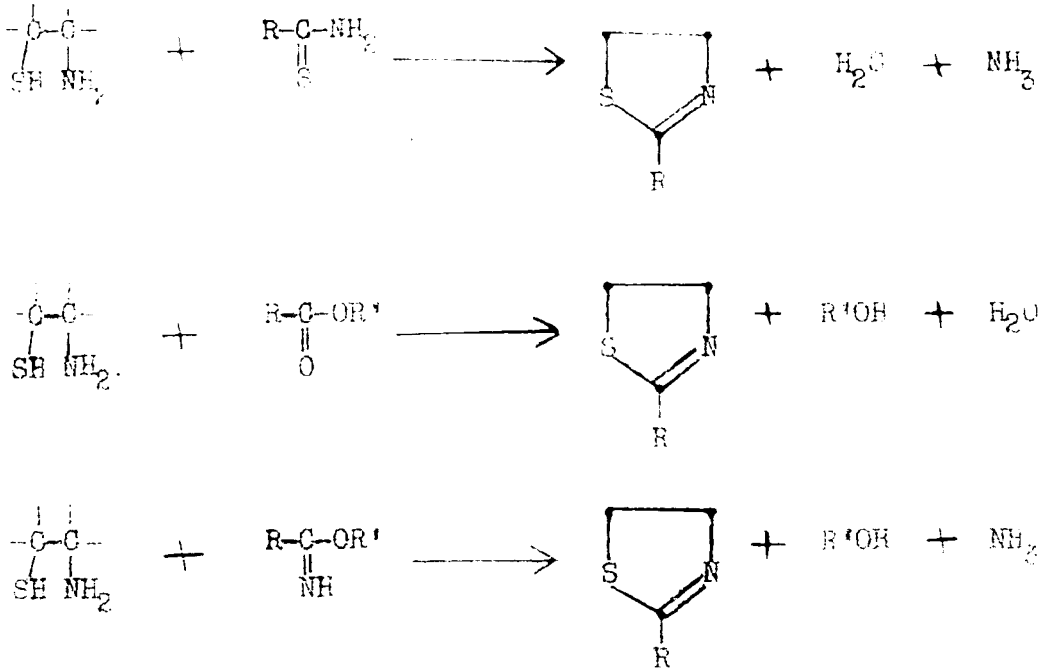
This method has been used in a fairly large number of cases, but yields are generally below 50%.

(b) Reaction of thioamides with 2-haloalkylamine salts[7, 9-14].

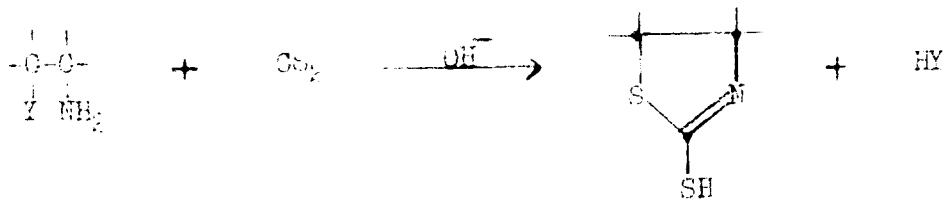


This method has been used quite widely, and yields vary from good to poor with specific examples.

(c) Reactions of 2-mercaptoalkylamines with thioamides, esters, and imino esters[15-18]. This method is particularly successful with cysteine and its derivatives[15-17].

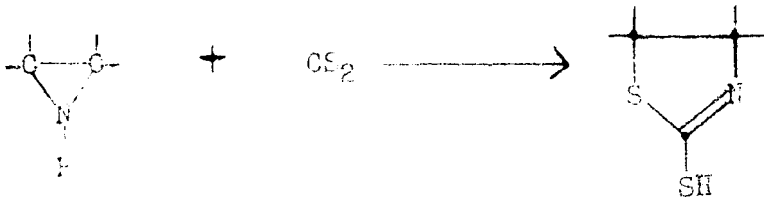


(d) Reaction of carbon disulfide with N-substituted alkylamines.



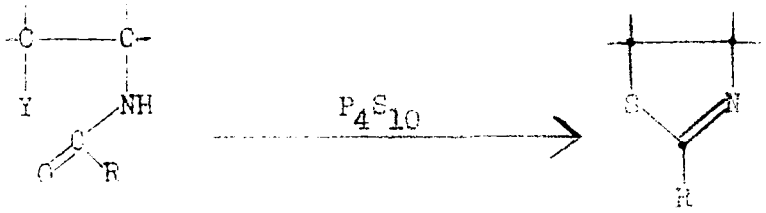
Where Y is halogen[3, 10, 19-21] or hydroxy[23-28], the reaction has been carried out in good yield in a large number of cases. Of limited importance are the examples where Y is mercapto[29] and hydrogen sulfate (OSO_3H)[30-32].

(e) Reaction of ethyleneimines with carbon disulfide[19, 28, 33-35].



The second category, methods employing a cyclization of a single compound to supply the ring atoms, can be subdivided as follows:

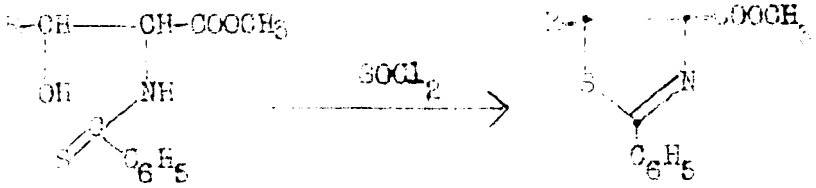
(a) Cyclization of N-(2-substitutedalkyl) amides.



The Y group can be halogen[12, 36, 37], hydroxy[17a, 17c, 38], acetoxy[39], mercapto[40, 41], or disulfide[33, 42, 43]. The yields are generally good, and the reaction has been widely applied with Y as halogen or hydroxy.

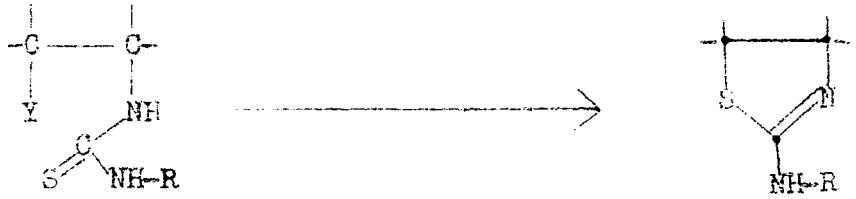
(b) Cyclization of N-(2-substitutedalkyl) thioamides.

1) Cyclization of N-thiobenzoyl derivatives of serine[44, 45].



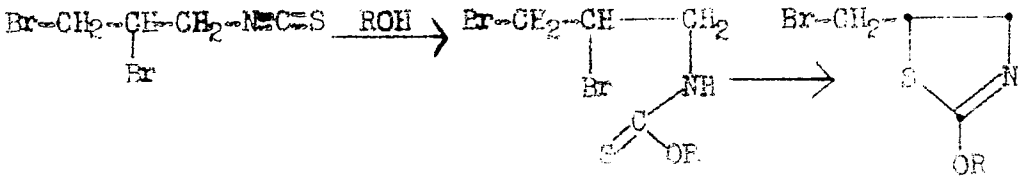
The scope of the reaction is very limited.

2) Cyclization of N-(2-substitutedalkyl) thioureas.



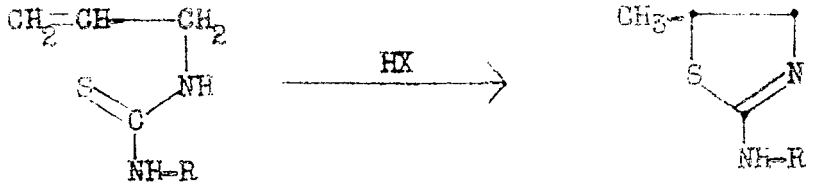
This method is widely applicable and gives good yields. The Y group can be halogen[3, 19-22, 46, 47], hydroxy[48-51], or ethoxy[52].

3) The bromine addition product of allyl isothiocyanate cyclizes in the presence of alcohols, undoubtedly through the 2,3-dibromopropylthiourea intermediate[53].



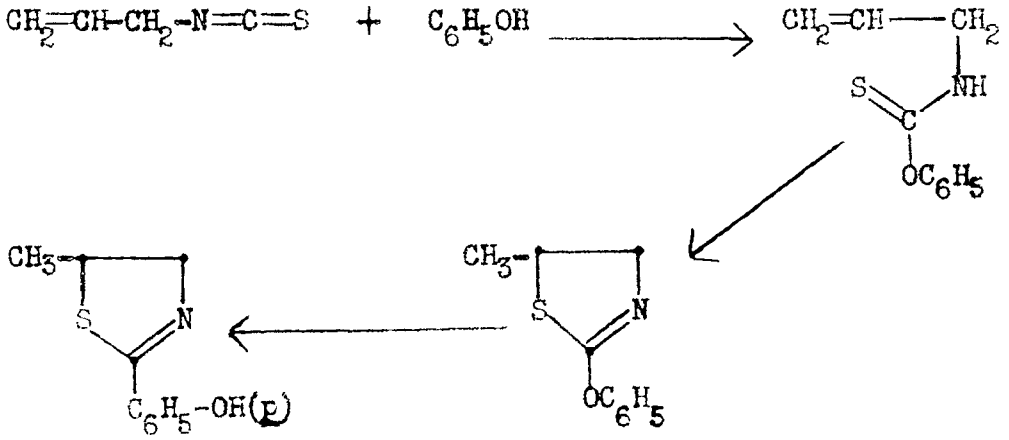
(c) Cyclization of N-alkenylthioamides.

1) Cyclization of N-allylthioureas[54-63].

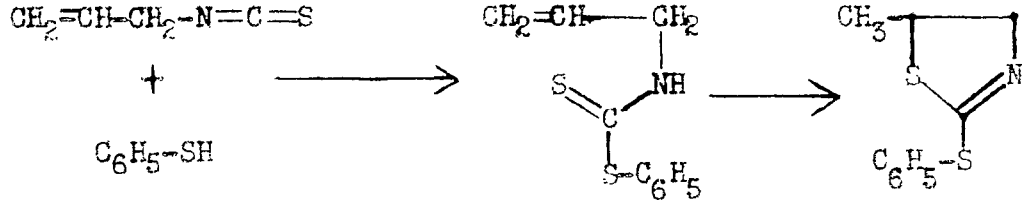


This reaction has been widely used because of the availability of starting materials obtained by the reaction of allyl isothiocyanate with amines or ammonia.

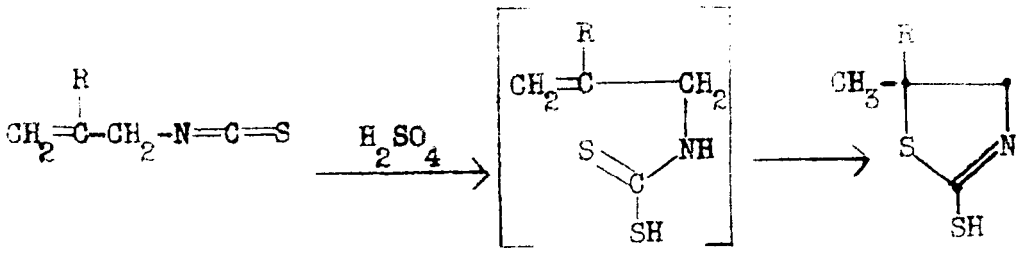
2) Cyclization of allyl isothiocyanates in the presence of various reagents. With phenols or thiophenols[23, 64], the reaction proceeds through the mono- and dithiourethans, respectively. Cyclization is brought about by sulfuric acid or dry hydrogen chloride. In the case of the monothiourethan, the initial product, the thiazolinephenyl ether, rearranges to a thiazolinephenol.



The reaction with thiophenol is analagous except that the final rearrangement does not occur.

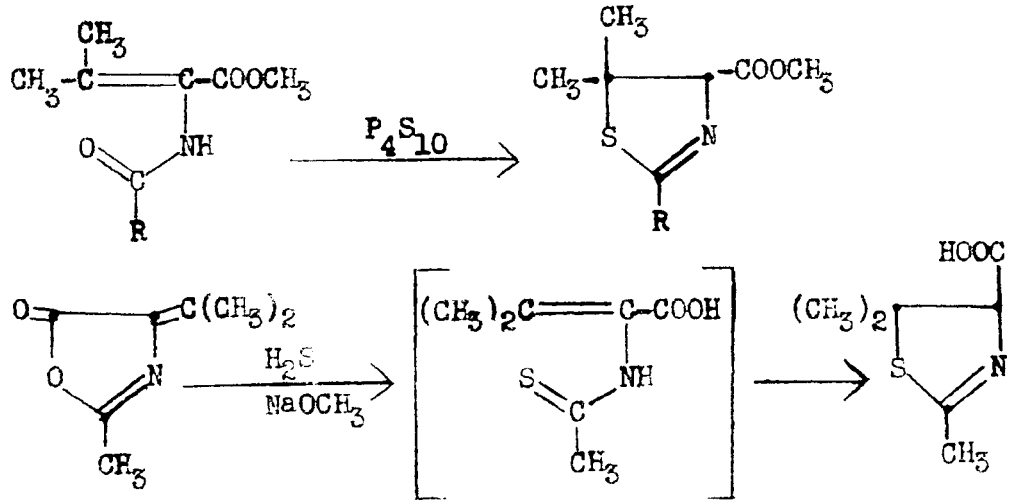


When allyl isothiocyanates containing an alkyl group on the beta carbon atom are treated with sulfuric acid in the cold, 2-mercapto-2-thiazolines are formed. The reaction is believed to proceed through a dithiocarbamic acid intermediate[65].

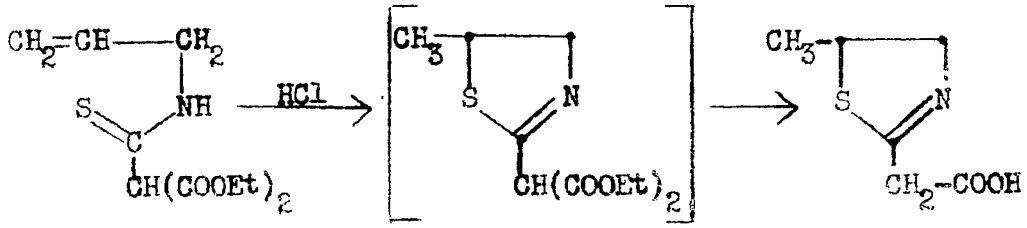


Yields are always less than 50%, indicating that the second sulfur atom comes from the breakdown of one equivalent of the isothiocyanate.

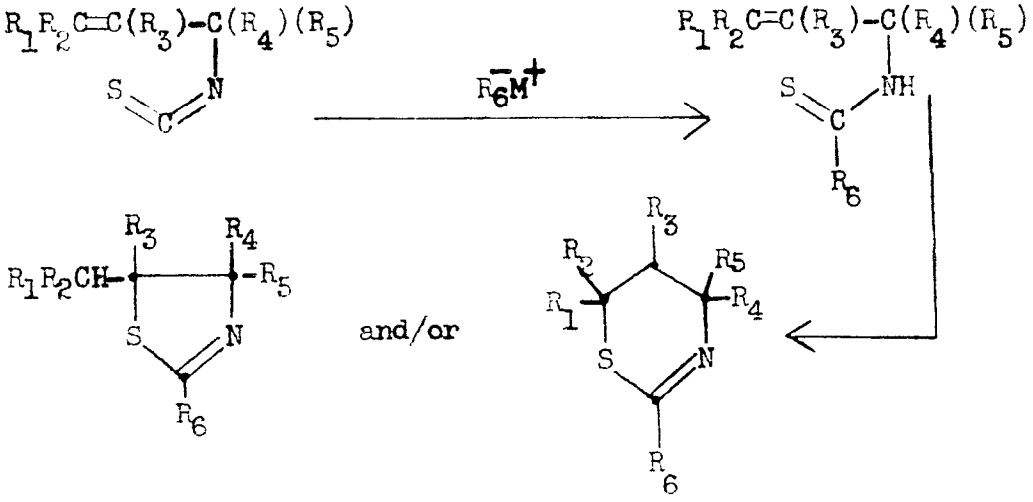
3) 2-Methyl- and 2-phenyl-5,5-dimethyl-2-thiazoline-4-carboxylic acids and their esters have been prepared by the following reactions[66, 67].



4) In the O. S. R. D. penicillin project conducted at the University of Michigan during World War II, it was discovered that N-allyldicarbethoxythioacetamide could be cyclized by treatment with dry hydrogen chloride in ether. During the workup, hydrolysis and decarboxylation of the initial product took place to give 5-methyl-2-thiazoline-2-acetic acid.



With the exception of the last two reactions shown, the cyclization of N-allylthioamides is limited to examples which produce a thiazoline which contains a sulfur, oxygen, or nitrogen function at the 2-position. Since N-allylthioamides of the type $R_1R_2C{=}C(R_3){-}C(R_4)(R_5){-}NH{-}\overset{\overset{S}{\|}}{C}{-}R_6$ are readily obtainable by the addition of organometallic compounds, such as Grignard reagents or the sodio derivatives of β-dicarbonyl compounds, to isothiocyanates; it is evident that if these cyclizations can be brought about generally, a route will be available for the synthesis of alkyl-substituted 2-thiazolines or 5,6-dihydro-1,3,4-thiazines, depending upon which carbon atom of the allylic double bond is the site of ring closure.



The fact that the size of the ring depends upon the point of attack on a carbon-carbon double bond raises some question as to the validity of the structures previously indicated as arising from this type of reaction. In general, it can be said that those reactions which reportedly give rise to thiazolines with oxygen, sulfur, or nitrogen functions at the 2-position have been correctly interpreted, since these thiazolines have also been made by unequivocal routes. The fact that a thiazoline rather than a dihydrothiazine was formed is not surprising, because in all cases tried, formation of a thiazoline results from ring closure at

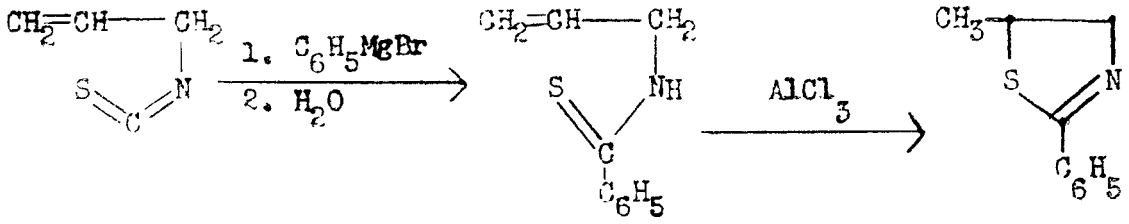
the more substituted carbon atom of the double bond.

No structure proof was carried out on the cyclization product of N-allyldicarbethoxythioacetamide, although the thiazoline is the likely product since it would have arisen from ring closure at the more substituted carbon atom.

It is the purpose of this research first to determine if the cyclization of N-allylthioamides and their homologs can be brought about generally, and secondly to determine which carbon atom of the allylic double bond is the point of ring closure for a variety of cases.

DISCUSSION AND RESULTS

Cyclization of N-allylthiobenzamide, prepared by the reaction of allyl isothiocyanate with phenylmagnesium bromide, was brought about by heating the thioamide with one equivalent of aluminum chloride. A single, pure product, 2-phenyl-5-methyl-2-thiazoline, was obtained in 50% yield.

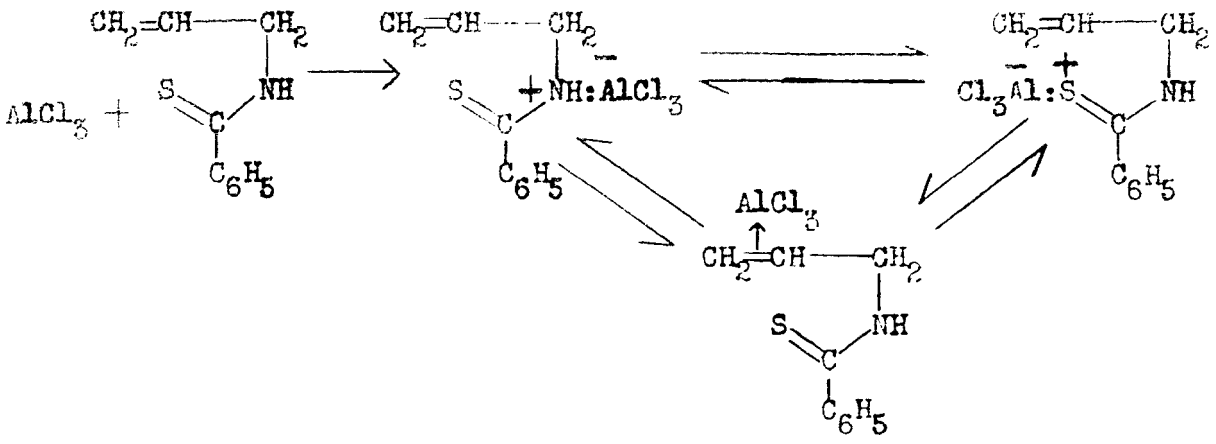


Since both 2-phenyl-5-methyl-2-thiazoline (which would be formed if ring closure took place at the more substituted carbon atom of the double bond) and 2-phenyl-5,6-dihydro-1,3,4-thiazine (which would be formed if ring closure took place at the less substituted carbon atom of the double bond) are known compounds, no difficulty was encountered in establishing the identity of the product.

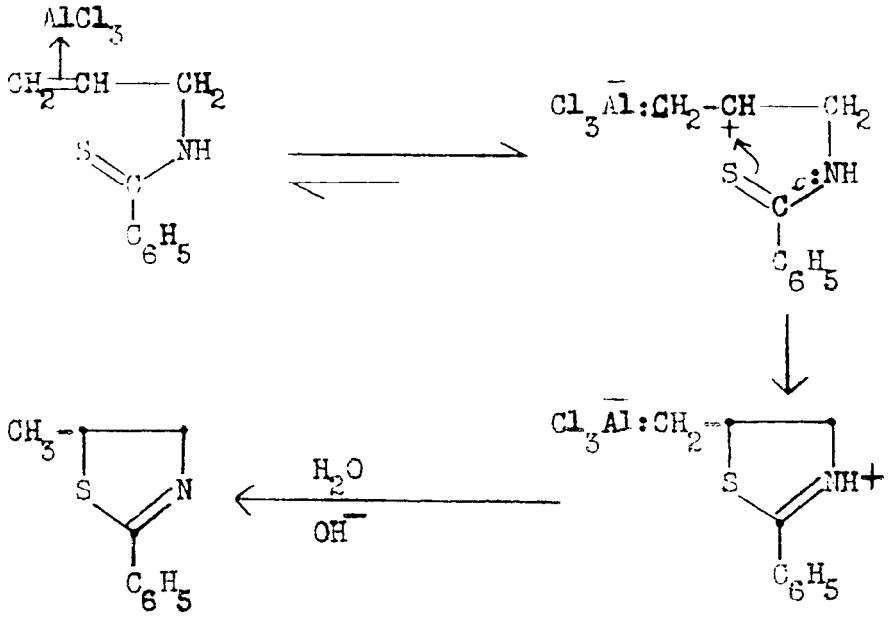
Other Lewis acids (zinc chloride, boron fluoride, sulfuric acid) also brought about the cyclization, but yields were lower. Free radical initiators, such as benzoyl peroxide, did not bring about the cyclization.

The fact that ring closure occurred exclusively at the more substituted carbon atom of the double bond and was brought about by Lewis acids indicated an ionic mechanism, with nucleophilic attack on the allylic double bond by the sulfur atom. It is proposed that the Lewis acid would attack the various basic sites in the N-allylthiobenzamide molecule, viz. the nitrogen atom, the sulfur atom, and the allylic double bond, the extent of attack on any given site being proportional

to the basic strenght of that site.



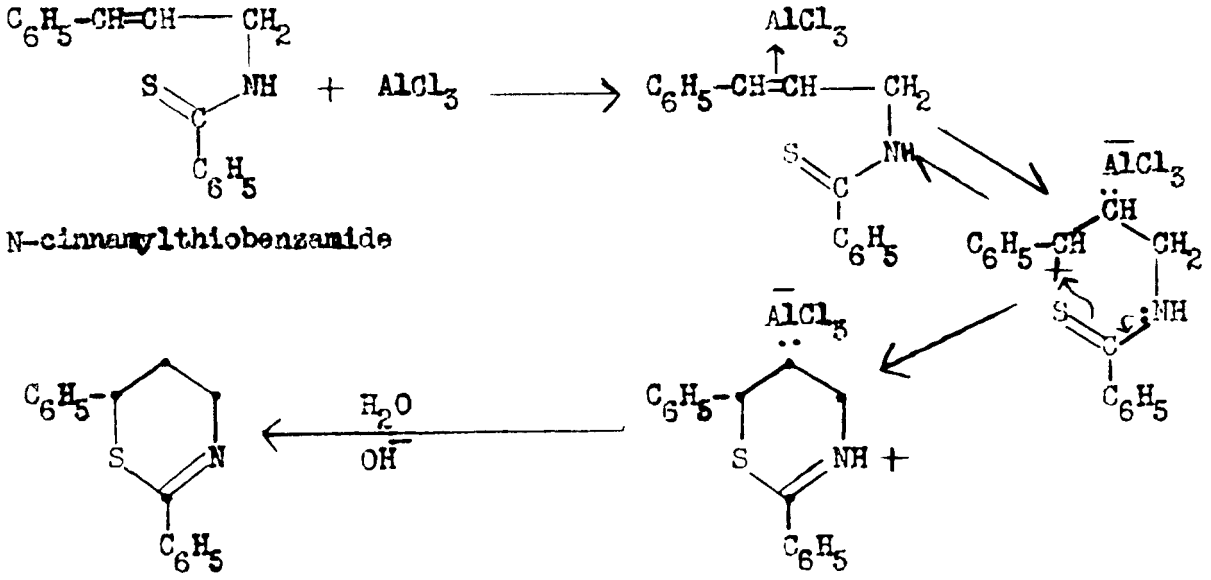
The species containing the Lewis acid on the allylic double bond would shift into the more stable secondary carbonium ion, and nucleophilic attack by the sulfur atom on this site could bring about the observed ring closure. Basic hydrolysis would liberate the free base, 2-phenyl-5-methyl-2-thiazoline.



2-phenyl-5-methyl-
2-thiazoline

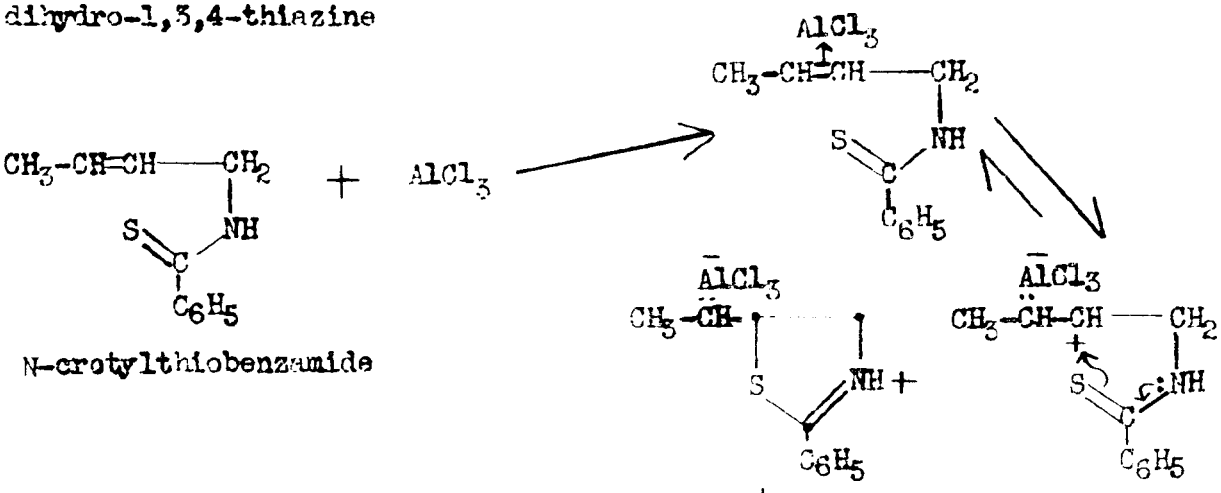
In order to substantiate this mechanism, it was decided to carry out ring closures on N-cinnamylthiobenzamide and N-crotylthiobenzamide. According to the proposed mechanism, the former should proceed through

the highly stabilized benzyl carbonium ion to give 2,6-diphenyl-5,6-dihydro-1,3,4-thiazine, while the latter should give a mixture of 2-phenyl-5-ethyl-2-thiazoline and 2-phenyl-6-methyl-5,6-dihydro-1,3,4-thiazine, since the two possible carbonium ions are of comparable stability.

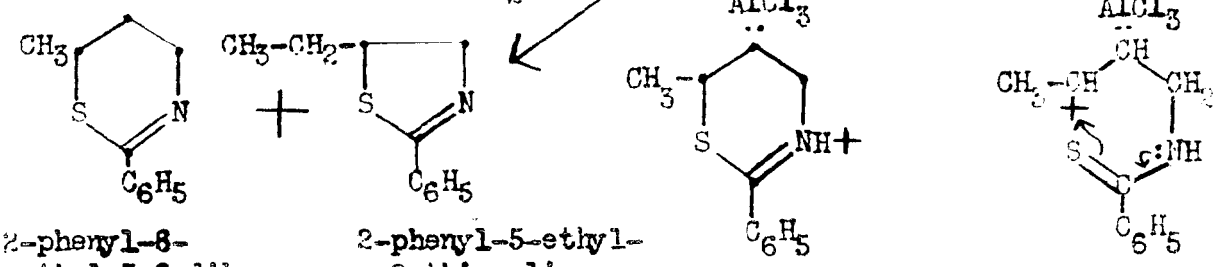


N-cinnamylthiobenzamide

2,6-diphenyl-5,6-dihydro-1,3,4-thiazine



N-crotylthiobenzamide



2-phenyl-6-methyl-5,6-dihydro-1,3,4-thiazine

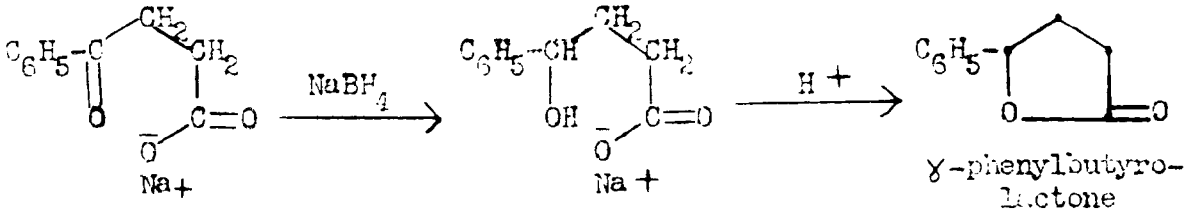
2-phenyl-5-ethyl-2-thiazoline

The results of the cyclizations just outlined were in complete agreement with those predicted. The structures of the products were proven by comparing them and their derivatives with authentic samples prepared by unequivocal routes.

An authentic sample of 2,6-diphenyl-5,6-dihydro-1,3,4-thiazine was prepared in the following manner.

The sodium salt of β-benzoylpropionic acid was reduced with sodium borohydride to the sodium salt of δ-hydroxy-γ-phenylbutyric acid, and acidification brought about lactonization to δ-phenylbutyrolactone. Hydrazinolysis of the lactone produced δ-hydroxy-δ-phenylbutyric acid hydrazide. Diazotization of the hydrazide gave the corresponding azide, which was allowed to undergo the Curtius rearrangement to the isocyanate. The isocyanate could not be isolated since it underwent internal attack by the hydroxy group to produce 6-phenyltetrahydro-1,3-oxazone-2. Treatment of the oxazone with alcoholic potassium hydroxide gave 3-hydroxy-3-phenylpropylamine, which was monobenzoylated to give N-(3-hydroxy-3-phenylpropyl)benzamide. Heating the amide with phosphorus pentasulfide brought about cyclization to 2,6-diphenyl-5,6-dihydro-1,3,4-thiazine.

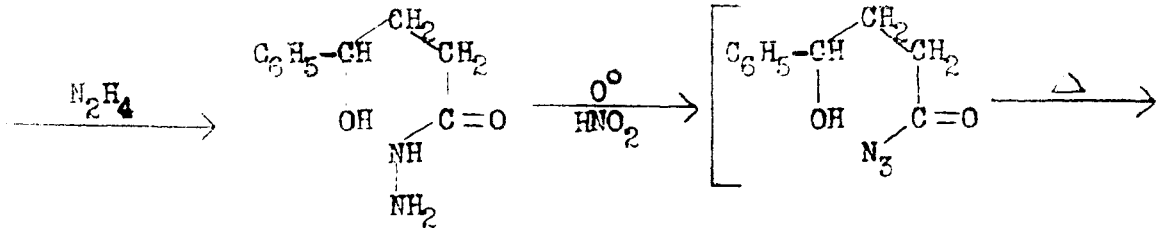
The following is an outline of the series of reactions just described.



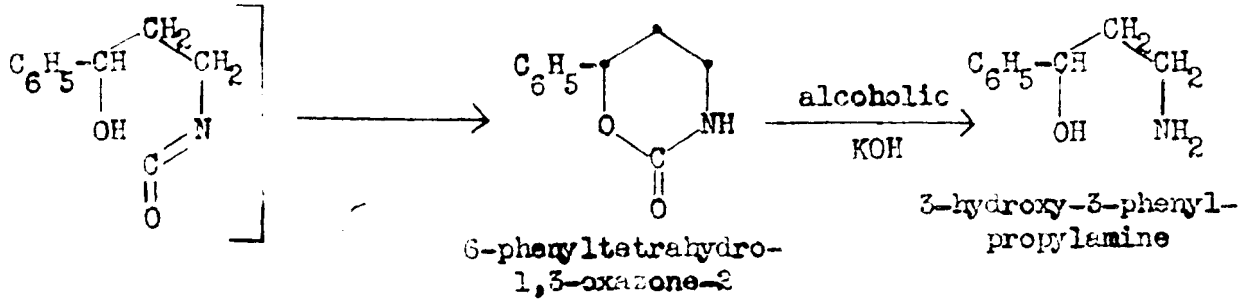
sodium β-benzoyl-propionate

sodium δ-hydroxy-δ-phenylbutyrate

δ-phenylbutyro-lactone

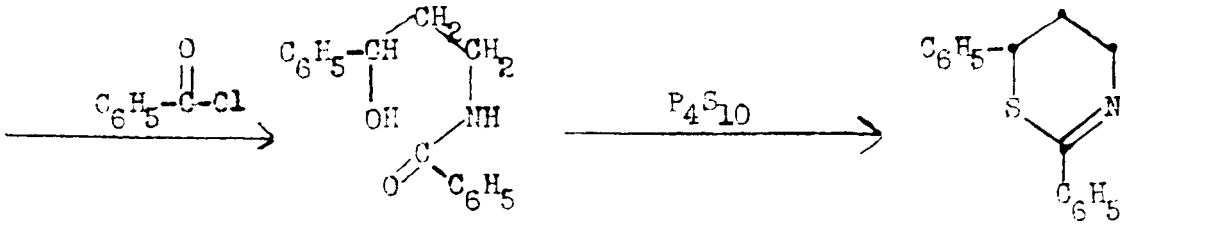


γ-hydroxy-γ-phenylbutyric acid hydrazide



6-phenyltetrahydro-1,3-oxazone-2

3-hydroxy-3-phenylpropylamine



N-(3-hydroxy-3-phenylpropyl)benzamide

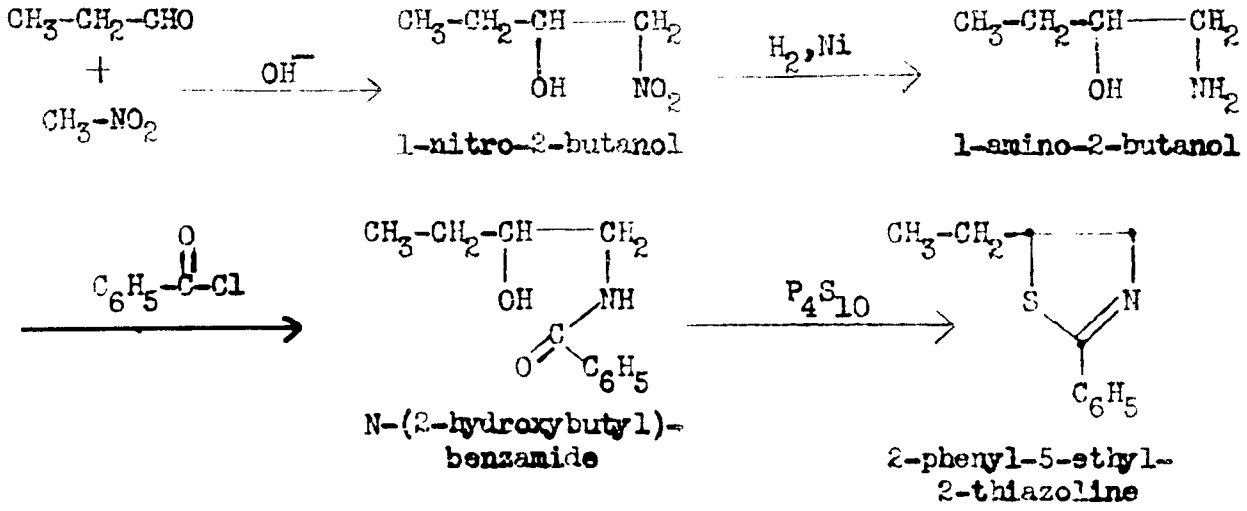
2,6-diphenyl-5,6-dihydro-1,3,4-thiazine

The authentic sample of 2,6-diphenyl-5,6-dihydro-1,3,4-thiazine and its picrate were compared with the N-cinnamylthiobenzamide cyclization product and its picrate. Mixed melting points showed no depression and the infra-red spectra were superposable.

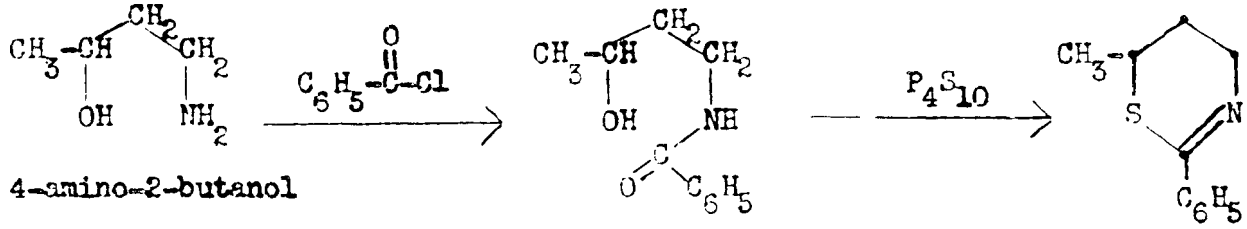
An authentic sample of 2-phenyl-5-ethyl-2-thiazoline was prepared in the following manner.

Propionaldehyde was reacted with nitromethane in the presence of base to produce 1-nitro-2-butanol, which was reduced with hydrogen and nickel catalyst to 1-amino-2-butanol. Monobenzoylation converted the amino alcohol to N-(2-hydroxybutyl)benzamide, and heating of the amide with phosphorus pentasulfide brought about cyclization to 2-phenyl-5-ethyl-2-thiazoline.

The following is an outline of the series of reactions just described.



An authentic sample of 2-phenyl-6-methyl-5,6-dihydro-1,3,4-thiazine was prepared from 4-amino-2-butanol. The amino alcohol was monobenzoylated to give N-(3-hydroxybutyl)benzamide, which was heated with phosphorus pentasulfide to bring about ring closure to the desired product.

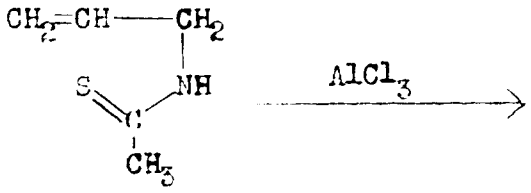


The liquid mixture obtained in the cyclization of N-crotylthiobenzamide was partially separated by fractional distillation. The lower boiling fraction gave a picrate whose melting point was identical with that of the picrate of the authentic sample of 2-phenyl-5-ethyl-2-thiazoline; a mixed melting point showed no depression. The higher boiling fraction gave a picrate whose melting point coincided with that of the picrate of the authentic sample of 2-phenyl-6-methyl-5,6-dihydro-

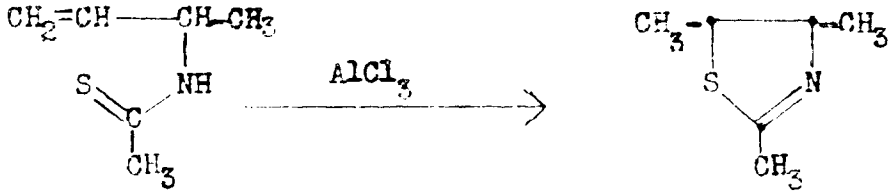
1,3,4-thiazine; a mixed melting point showed no depression. The melting points of the picrates of the two authentic samples differed by thirty degrees.

The mixture obtained in the cyclization of N-crotylthiobenzamide favored the thiazoline over the dihydrothiazine by a ratio of approximately three to one.

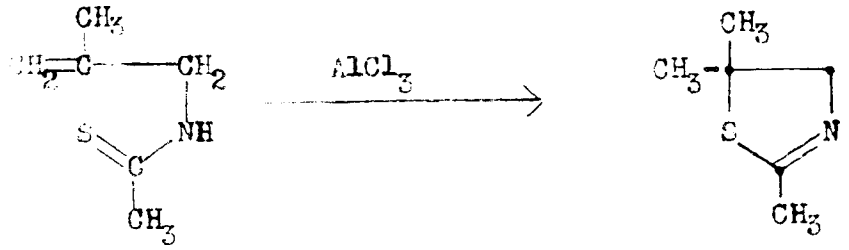
Cyclizations were also carried out on N-allylthioacetamide, N-(α-methallyl)thioacetamide, and N-(β-methallyl)thioacetamide to give 2,5-dimethyl-2-thiazoline, 2,4,5-trimethyl-2-thiazoline, and 2,5,5-trimethyl-2-thiazoline, respectively.



N-allylthioacetamide 2,5-dimethyl-2-thiazoline



N-(α-methallyl)thioacetamide 2,4,5-trimethyl-2-thiazoline

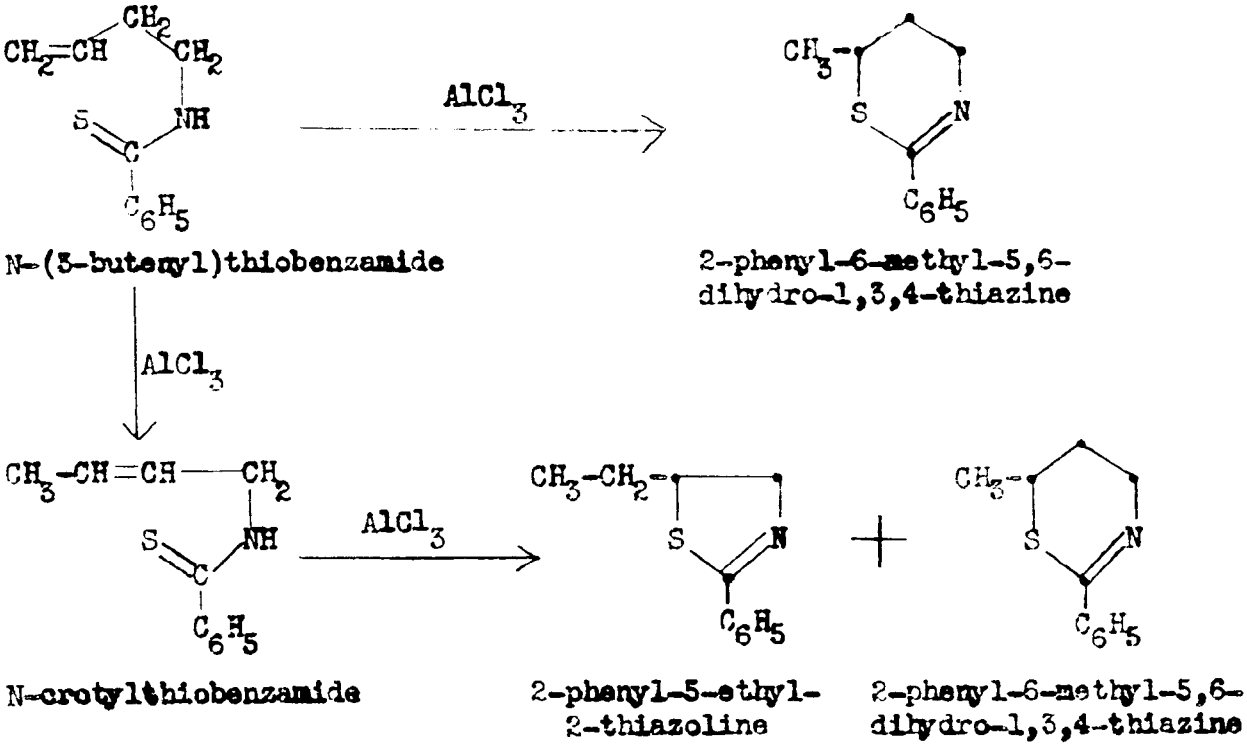


N-(β-methallyl)thioacetamide 2,5,5-trimethyl-2-thiazoline

These cyclizations are analagous to the cyclization of N-allylthiobenzamide in that the formation of the five-membered thiazoline ring results from attack by the sulfur atom on the more substituted carbon atom of the double bond. The formation of the six-membered

dihydrothiazine ring would result from attack by the sulfur atom on the less substituted carbon atom of the double bond. Since the single product isolated in the cyclization of N-allylthiobenzamide was proven to be the thiazoline, and since each of the above cyclizations gave a single, pure product; that product was in each case considered to be the thiazoline rather than the dihydrothiazine, although no structure proofs were carried out.

The cyclization of N-(3-butenyl)thiobenzamide was attempted, but only a trace of product was obtained, from which was isolated the picrate of 2-phenyl-6-methyl-5,6-dihydro-1,3,4-thiazine. It is not known whether the dihydrothiazine was the exclusive product or part of a mixture with 2-phenyl-5-ethyl-2-thiazoline, which could result from double bond migration to form N-crotylthiobenzamide from N-(3-butenyl)thiobenzamide.



N-(3-butenyl)thiobenzamide

2-phenyl-6-methyl-5,6-dihydro-1,3,4-thiazine

N-crotylthiobenzamide

2-phenyl-5-ethyl-2-thiazoline

2-phenyl-6-methyl-5,6-dihydro-1,3,4-thiazine

EXPERIMENTAL

Preparations of Thiazolines and Dihydrothiazines by Cyclization of N-Alkenylthioamides.

Preparation of N-allylthiobenzamide.—N-Allylthiobenzamide was prepared in 60% yield by the method of Sachs and Loevy[68]. It boiled at 153-160°/ 1.5 mm. (reported[68] b.p. 214-215°/ 17 mm.).

The bromine addition product was prepared by dissolving 3 drops of N-allylthiobenzamide in carbon tetrachloride and adding a 5% solution of bromine in the same solvent until the red color persisted. A yellowish solid was formed which was collected and recrystallized from glacial acetic acid; m.p. 205.5-206.5°(reported[68] m.p. 208-209°).

Cyclization of N-allylthiobenzamide.—Anhydrous aluminum chloride (33 g., 0.25 mole) was added directly to 44.3 g. (0.25 mole) of N-allylthiobenzamide and the mixture was stirred. Much heat was evolved and a solid cake soon formed. Nitrobenzene was added to dissolve the cake and the mixture was held at 125° for 2 hours. Excess 25% sodium hydroxide solution was added to the cooled mixture and it was stirred for 0.5 hour to break up the aluminum complex. The mixture was extracted with ether and the ether layer was extracted with 10% hydrochloric acid. The acid layer was neutralized by adding excess 10% sodium hydroxide solution and was extracted with ether. After removal of solvent from the dried ether extracts and distillation of the residue, 21 g. (47%) of 2-phenyl-5-methyl-2-thiazoline was obtained, b.p. 148-150°/ 18 mm.

Anal. Calcd. for $C_{10}H_{11}NS$: C, 67.75; H, 6.26; N, 7.90. Found: C, 67.76; H, 6.31; N, 7.94.

The picrate was prepared by dissolving a few drops of the thiazoline

in 95% ethanol and adding several drops of a saturated ethanol solution of picric acid. After recrystallization from 95% ethanol, it melted at 158-160° (reported[37] m.p. 155-157°).

The chloroplatinate was prepared by adding a drop of the thiazoline to a solution of chloroplatinic acid and collecting the resulting solid. It melted at 184-186° (dec.) (reported[37] m.p. 179°).

The nitro derivative was prepared by dissolving 3 drops of the thiazoline in a few milliliters of concentrated sulfuric acid and adding a few drops of concentrated nitric acid while cooling under the tap. The mixture was poured into water and neutralized with excess 10% sodium hydroxide solution. The precipitated nitro derivative, after filtration, drying, and recrystallization twice from ethanol, melted at 67-69° (reported[36] m.p. 70.5-71.5°, corrected).

Hydrolysis of 2-phenyl-5-methyl-2-thiazoline.--A solution of 5.5 g. of 2-phenyl-5-methyl-2-thiazoline in 75 ml. of concentrated hydrochloric acid was heated at 175° for 5 hours in a sealed tube. The cooled reaction mixture deposited 2.4 g. (58%) of benzoic acid, which was removed by filtration. The filtrate was extracted with ether to remove the last traces of benzoic acid. The aqueous layer was made strongly basic with 10% sodium hydroxide and extracted with ether in order to remove unreacted thiazoline. The aqueous layer was then acidified and the amino mercaptan salt was converted to the amino disulfide salt by adding iodine-potassium iodide solution until the iodine color persisted. Then the mixture was made basic and the amino disulfide was separated by continuous ether extraction for 2 hours. The ether was dried and saturated with dry hydrogen chloride to precipitate 1-amino-2-propyldisulfide dihydrochloride. This was filtered and after 2 recrystallizations from

absolute alcohol it melted at 222-222.5° (reported[69] m.p. 213-214°).

Anal. Calcd. for $C_6H_{18}N_2S_2Cl_2$: C, 28.45; H, 7.16; N, 11.06; S, 25.32; Cl, 28.00. Found: C, 28.53; H, 7.25; N, 10.94; S, 25.21; Cl, 27.84.

Preparation of cinnamyl chloride.--Cinnamyl chloride was prepared in 66% yield by reacting cinnamyl alcohol with thionyl chloride according to the procedure of Gilman and Harris[70]; b.p. 66-72°/ 0.8 mm., m.p. 10-12°, n_D^{21} 1.5830.

Preparation of cinnamylamine.--Cinnamylamine was prepared by the Gabriel reaction on cinnamyl chloride according to the procedure used by Roberts and Mazur[71] to convert crotyl chloride to crotylamine. From 48.7 g. (0.32 mole) of cinnamyl chloride there was obtained 16 g. (40%) of cinnamylamine, b.p. 71-77°/ 0.1 mm. (reported[72] b.p. 235-237°/ 775 mm.).

Preparation of cinnamyl isothiocyanate.--The Kaluza reaction was used to convert cinnamylamine to cinnamyl isothiocyanate. The experimental procedure was that described by Moore and Crossley[73] for the conversion of free amines to isothiocyanates. From 21.7 g. (0.16 mole) of cinnamylamine there was obtained 15 g. (54%) of cinnamyl isothiocyanate, b.p. 120-127°/ 1 mm. (reported[74] b.p. 162°/ 12 mm.).

N-Cinnamyl-N'-phenylthiourea was prepared by warming 1 g. of cinnamyl isothiocyanate with 3 g. of aniline for 1 hour on a steam bath. Ether was added to dissolve the cooled mixture and the solution was freed of excess aniline by extraction with dilute hydrochloric acid. After removal of solvent from the dried solution, the residue was recrystallized from absolute alcohol; m.p. 116-119°(reported[74] m.p. 119°).

Preparation of N-cinnamylthiobenzamide.--Cinnamyl isothiocyanate (14 g., 0.08 mole) was added dropwise to a stirred ethereal solution of

0.1 mole of phenylmagnesium bromide (prepared as described in the preparation of N-allylthiobenzamide). After the addition, the mixture was refluxed for 1 hour, and the crude product was isolated by the same procedure used in the preparation of N-allylthiobenzamide; 19.8 g. of crude, yellow solid was obtained; m.p. 58-78°. Recrystallization from petroleum ether (b.p. 60-75°), with a trace of ethanol to bring the last undissolved material into solution, gave 12.5 g. of yellow solid, m.p. 82-88°. A small amount was recrystallized 3 more times for an analytical sample, m.p. 88-89°.

Anal. Calcd. for $C_{16}H_{15}NS$: C, 75.84; H, 5.97; N, 5.53. Found; C, 75.54; H, 6.26; N, 5.38.

Cyclization of N-cinnamylthiobenzamide.—A solution of 6.2 g. (0.025 mole) of N-cinnamylthiobenzamide and 3.3 g. (0.025 mole) of powdered anhydrous aluminum chloride in 30 ml. of nitrobenzene was stirred at 135° for 3 hours. After cooling, excess 10% sodium hydroxide solution was added and the thiazoline was isolated by the same procedure used in the cyclization of N-allylthiobenzamide. The crude product was an oily yellow solid, which was triturated with ice-cold absolute alcohol to give 1.2 g. (19%) of 2,6-diphenyl-5,6-dihydro-1,3,4-thiazine, m.p. 79-85°. A small amount recrystallized from ether melted at 86-88°. This was compared with the analyzed sample prepared by the multi-step *in situ* synthesis from cinnamyl thiocyanate*. A mixed melting point showed no depression and the infrared spectra were superimposable.

The picrate was prepared by heating a small amount of the crude solid with 5 ml. of a saturated ethanol-picric acid solution. After 2 recrystallizations from aqueous ethanol, the m.p. was 158-160.5°, undepressed

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* This Dissertation, p. 41.

when mixed with the analyzed picrate prepared by the multi-step in situ synthesis from cinnamyl thiocyanate*; the infrared spectra were superimposable.

Preparation of trans-crotyl alcohol.—A solution of 150 g. (2.14 moles) of trans-crotonaldehyde was slowly added to a stirred solution of 25 g. (0.66 mole) of lithium aluminum hydride. The excess hydride was destroyed by slowly adding 22 g. (0.25 mole) of ethyl acetate. The complex was broken up by the addition of 55 g. (3 moles) of water and the ether solution was filtered to remove the inorganic salts. The ether solution was dried and after removal of the solvent and distillation of the residue, 87 g. (72%) of trans-crotyl alcohol, b.p. 113-123°/ 740 mm., was obtained (reported[75] b.p. 121.2°/ 745 mm.).

Preparation of trans-crotyl chloride.—trans-Crotyl chloride was prepared by the reaction of trans-crotyl alcohol with phosphorus trichloride in the presence of pyridine according to the method of Hatch and Nesbitt[75]; from 87 g. (1.53 moles) of trans-crotyl alcohol there was obtained 73 g. (53%) of trans-crotyl chloride, b.p. 80-85°.

Conversion of trans-crotyl chloride to trans-crotylamine.—The Gabriel reaction was used to convert trans-crotyl chloride to trans-crotylamine according to the procedure of Roberts and Mazur[71]; from 81.5 g. (0.89 mole) of the chloride there was obtained 18.2 g. (28%) of trans-crotylamine, b.p. 80-81.5°/ 742 mm.

Preparation of trans-crotyl isothiocyanate.—The method of Ettlinger and Hodgkins[76] was used to convert 18 g. (0.254 mole) of trans-crotylamine to 17.4 g. (59%) of trans-crotyl isothiocyanate, b.p. 61-64°/15 mm., n_D^{25} 1.5231.

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* This Dissertation, p. 41.

Preparation of N-crotylthiobenzamide.--trans-Crotyl isothiocyanate (17 g., 0.15 mole) was added dropwise to a stirred ether solution of 0.2 mole of phenylmagnesium bromide (prepared as in the preparation of N-allylthiobenzamide). When the reaction subsided, reflux was maintained for 0.5 hour. The Grignard complex was broken up by the slow addition of 30 ml. of saturated aqueous ammonium chloride. The ether solution was decanted from the magnesium salts, which were washed once with ether by decantation. Removal of solvent from the combined ether portions and distillation of the residue gave 21 g. (73%) of N-crotylthiobenzamide, b.p. 156-157°/ 0.9 mm.

Anal. Calcd. for $C_{11}H_{13}NS$: C, 69.07; H, 6.85; N, 7.32. Found: C, 69.31; H, 7.06; N, 7.19.

Cyclization of N-crotylthiobenzamide.--N-Crotylthiobenzamide (21 g., 0.11 mole) was dissolved in 65 ml. of nitrobenzene and 7.34 g. (0.055 mole) of powdered, anhydrous aluminum chloride was added. The resulting solution was stirred at 145° for 2 hours. The basic products were isolated by the same procedure used in the cyclization of N-allylthiobenzamide. Fractional distillation of the crude product gave 8.46 g. of 2-phenyl-5-ethyl-2-thiazoline, b.p. 88-90°/ 0.2 mm., an intermediate fraction (1.47 g.), b.p. 90-112°/ 0.2 mm., and 0.2 g. of 2-phenyl-6-methyl-5,6-dihydro-1,3,4-thiazine, b.p. 112-119°/0.3 mm. The products were identified by comparing their picrates with authentic samples prepared by unequivocal routes. Their melting points were the same as those of the authentic samples and showed no depression on mixing.

Assuming the intermediate fraction to consist of half of each isomer, it was concluded that the cyclization of N-crotylthiobenzamide gave an approximately 3:1 mixture of 2-phenyl-5-ethyl-2-thiazoline and

2-phenyl-6-methyl-5,6-dihydro-1,3,4-thiazine, respectively.

Preparation of allyl cyanide.--Allyl bromide (131 g., 1.08 moles) was converted to allyl cyanide by the method of Supinewski and Salzberg[77]. The product, obtained in 77% yield, boiled at 112-122°.

Preparation of 3-butenylamine hydrochloride.--Allyl cyanide (40 g., 0.6 mole) was reduced with lithium aluminum hydride to 3-butenylamine by the method of Kjaer et al.[78] The crude product was isolated by distillation of the base into aqueous hydrochloric acid followed by removal of water. The yield was 9 g. (14%).

Preparation of 3-butenyl isothiocyanate.--Crude 3-butenylamine hydrochloride (9 g., 0.084 mole) was converted to 3-butenyl isothiocyanate by the general method of Moore and Crossley[73]. The product, obtained in 18% yield, boiled at 37-46°/ 3 mm. (reported[76] b.p. 77.5°/ 28 mm.).

Preparation of N-(3-butenyl)thiobenzamide.--3-Butenyl isothiocyanate (1.7 g., 0.015 mole) was added to an ether solution of 0.05 mole of phenylmagnesium bromide (prepared as described in the preparation of N-allylthiobenzamide); 1.2 g. (42%) of N-(3-butenyl)thiobenzamide, b.p. 137-145°/ 0.4 mm., was isolated by the method described in the preparation of N-allylthiobenzamide.

Cyclization of N-(3-butenyl)thiobenzamide.--N-(3-Butenyl)thiobenzamide (1.2 g., 0.0063 mole) was cyclized by the procedure employed in the cyclization of N-allylthiobenzamide. Since the product was obtained in too small an amount to distill, it was converted to its picrate. After recrystallization from aqueous ethanol it melted at 164-165.5°.

Anal. Calcd. for $C_{17}H_{16}N_4O_7S$: C, 48.57; H, 3.84; N, 13.33. Found: C, 48.98, 48.91; H, 3.68, 3.60; N, 12.89, 12.81.

The picrate was compared 1 year later with an authentic sample of the picrate of 2-phenyl-6-methyl-5,6-dihydro-1,3,4-thiazine. Both samples melted at 162-164°; a mixed melting point showed no depression.

Preparation of N-allylthioacetamide.--N-Allylthioacetamide was prepared by the method used to prepare N-crotylthiobenzamide, substituting methylmagnesium iodide for phenylmagnesium bromide. The product, obtained in 52% yield, boiled at 87°/ 0.4 mm. (reported[68] b.p. 135-136°/ 17 mm.).

Preparation of 2,5-dimethyl-2-thiazoline.--N-Allylthioacetamide (11 g., 0.096 mole) was stirred with 3.3 g. (0.025 mole) of powdered, anhydrous aluminum chloride. As the mixture was gradually heated to 150°, 4.2 g. of 2,5-dimethyl-2-thiazoline was distilled directly from the reaction mixture under slightly reduced pressure. The residue, a reddish looking gum, was dissolved in dilute hydrochloric acid, made basic, and extracted with ether. After drying the ether solution, removal of the solvent, and distillation of the residue, an additional 1.1 g. of 2,5-dimethyl-2-thiazoline was obtained; b.p. 48°/ 22 mm. (reported[9] b.p. 152°). The total yield was 48%.

Preparation of α-methallyl isothiocyanate.-- α-Methallyl isothiocyanate was prepared by the reaction of crotyl chloride and sodium thiocyanate according to the method used by Bruson and Eastes[65] to convert β-methallyl chloride to β-methallyl isothiocyanate; from 20 g. (0.22 mole) of crotyl chloride there was obtained 6.6 g. (26%) of α-methallyl isothiocyanate, b.p. 51-57°/ 22 mm. (reported[78] b.p. 70-72°/ 34 mm.).

Derivatives were prepared by treating the isothiocyanate with ammonia and with aniline according to the procedures of Kjaer et al.[78] The N-(α-methallyl)thiourea, after recrystallization from water, melted

at 104-108° (reported[78] m.p. 109-110°). The N-(α-methallyl)-N'-phenylthiourea, after recrystallization from 50% aqueous ethanol, melted at 106-108° (reported[78] m.p. 109-110°).

Preparation of N-(α-methallyl)thioacetamide.—α-Methallyl isothiocyanate (7.9 g., 0.07 mole) was converted to 4.15 g. (46%) of N-(α-methallyl)thioacetamide, b.p. 90-98°/ 1 mm., by the general procedure used to prepare N-crotylthiobenzamide, substituting methylmagnesium iodide for phenylmagnesium bromide.

Anal. Calcd. for $C_6H_{11}NS$: C, 55.77; H, 8.58; N, 10.84. Found: C, 55.78; H, 8.58; N, 10,93.

Cyclization of N-(α-methallyl)thioacetamide.—A mixture of 4.15 g. (0.032 mole) of N-(α-methallyl)thioacetamide and 1 g. (0.0075 mole) of powdered, anhydrous aluminum chloride was heated in a three-necked flask equipped with a mechanical stirrer, thermometer, and a distillation head with a condenser attached. When the temperature reached 180-200°, 1.9 g. (46%) of 2,4,5-trimethyl-2-thiazoline distilled directly from the reaction mixture; b.p. 144-148° under slightly reduced pressure. The product was redistilled in order to obtain an analytical sample, b.p. 55-56°/ 25 mm.

Anal. Calcd. for $C_6H_{11}NS$: C, 55.77; H, 8.58; N, 10.84. Found: C, 55.95; H, 8.79; N, 10.70.

The picrate was prepared in the same manner as 2-phenyl-5-methyl-2-thiazoline picrate, and after 4 recrystallizations from ethanol, it melted at 170-172°.

Anal. Calcd. for $C_{12}H_{14}N_4O_7S$: C, 40.22; H, 3.94; N, 15.63. Found: C, 40.21; H, 4.09; N, 15.77.

Preparation of β-methallyl isothiocyanate.—β-Methallyl isothio-

cyanate was prepared by treating β-methallyl chloride with sodium thiocyanate according to the method of Bruson and Eastes[65]. The product boiled at 75-85°/ 30 mm.

Preparation of N-(β-methallyl)thioacetamide.—β-Methallyl isothiocyanate (56 g., 0.5 mole) was converted to N-(β-methallyl)thioacetamide, b.p. 98-103°/ 0.5 mm., by the general procedure used to prepare N-crotylthiobenzamide, substituting methylmagnesium iodide for phenylmagnesium bromide. The yield was 67%.

Anal. Calcd. for $C_6H_{11}NS$: C, 55.77; H, 8.58; N, 10.84. Found: C, 55.54; H, 8.34; N, 11.02.

Cyclization of N-(β-methallyl)thioacetamide.—N-(β-Methallyl)thioacetamide (26.5 g., 0.2 mole) was heated with 6.7 g. (0.05 mole) of powdered, anhydrous aluminum chloride in a three-necked flask equipped with a mechanical stirrer, a thermometer, and a distillation head attached to a condenser. When the temperature of the reaction mixture reached 150-170°, the product distilled at 64-80° at slightly reduced pressure. Toward the end of the distillation, a solid, believed to be an aluminum chloride complex, formed in the condenser. The distillate was purified by shaking it in a separatory funnel with 10% sodium hydroxide solution and separating and drying the organic layer. Distillation gave 12.1 g. (46%) of 2,5,5-trimethyl-2-thiazoline, b.p. 49-50°/ 25 mm., 152°/ 760 mm. A small amount was redistilled for an analytical sample, b.p. 52°/ 25 mm.

Anal. Calcd. for $C_6H_{11}NS$: C, 55.77; H, 8.58; N, 10.84. Found: C, 55.64; H, 8.42; N, 10.86.

The picrate was prepared in the same manner as 2-phenyl-5-methyl-2-thiazoline picrate and melted at 150-154° after 2 recrystallizations

from ethanol.

Anal. Calcd. for $C_{12}H_{14}N_4O_7S$: C, 40.22; H, 3.94; N, 15.63. Found: C, 40.28; H, 4.06; N, 15.74.

Preparation of Thiazolines and Dihydrothiazines by Cyclization of N-Hydroxyalkylbenzamides

Preparation of N-(2-hydroxypropyl)benzamide.--To a stirred mixture of 15 g. (0.2 mole) of 1-amino-2-propanol, 25 ml. of chloroform, and 50 ml. of a saturated solution of potassium carbonate in water, there was slowly added 28 g. (0.2 mole) of benzoyl chloride. The addition required 1 hour, after which the reaction mixture was allowed to remain at room temperature for 12 hours. Water was added to assure that all inorganic salts were in solution and a white solid was removed by filtration. After 2 recrystallizations from benezene, 16 g. (45%) of N-(2-hydroxypropyl)-benzamide was obtained; m.p. 87-93° (reported[20] m.p. 92-93°).

Cyclization of N-(2-hydroxypropyl)benzamide.--A mixture of 16 g. (0.089 mole) of N-(2-hydroxypropyl)benzamide, 10 g. of phosphorus pentasulfide, and 250 ml. of toluene was refluxed for 12 hours. The toluene was decanted from a gummy residue which remained in the flask. The residue was warmed on a steam bath with 10% sodium hydroxide solution. The basic solution was extracted with ether and the ether layer was combined with the toluene and extracted with 10% hydrochloric acid. The acid extracts were neutralized and extracted with ether. After drying of the ether solution, removal of solvent, and distillation of the residual oil, 4.8 g. (30%) of 2-phenyl-5-methyl-2-thiazoline was obtained; b.p. 146-149°/18 mm. (reported* b.p. 148-150°/ 18 mm.). The picrate was prepared and recrystallized from 95% ethanol; m.p. 153-155° (reported[37] m.p. 156-157°).

Preparation of N-(3-hydroxypropyl)benzamide.--3-Amino-1-propanol (15 g., 0.2 mole) was benzoylated in the same manner as 1-amino-2-propanol.

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Since no solid appeared, the chloroform layer was separated and dried. After removal of solvent, distillation of the residual oil gave an impure product which would not crystallize; b.p. 168-184°/ 0.5 mm. The infrared spectrum was consistant with that of an hydroxyamide structure, so the cyclization reaction reaction was carried out on the crude material.

Cyclization of crude N-(3-hydroxypropyl)benzamide.—The crude N-(3-hydroxypropyl)benzamide was added to 250 ml. of toluene which contained 10 g. of phosphorus pentasulfide, and the mixture was refluxed for 3 hours. The isolation of the product, 2-phenyl-5,6-dihydro-1,3,4-thiazine, was carried out by the same procedure described in the cyclization of N-(2-hydroxypropyl)benzamide. Three grams of product, b.p. 124°/ 1.5 mm., was obtained; it solidified upon standing and melted at 44-46° (reported[5] m.p. 44-45°).

The picrate was prepared and recrystallized from 95% ethanol; m.p. 181-182.5°.

Anal. Calcd. for $C_{16}H_{14}O_7N_4S$: C, 47.29; H, 3.47; N, 13.79. Found: C, 47.39; H, 3.65; N, 13.88.

Conversion of β-benzoylpropionic acid to γ-phenyl-γ-butyrolactone.—β-Benzoylpropionic acid (35.6 g., 0.2 mole) was converted to its sodium salt by dissolving it in 200 ml. of water which contained 12 g. (0.3 mole) of sodium hydroxide. To this stirred solution there was added a solution of 8.4 g. (0.22 mole) of sodium borohydride in 100 ml. of water which contained a small amount of sodium hydroxide. The reaction mixture became warm during the addition; it was heated on a steam bath for 2 hours after the addition was completed.

Lactonization was brought about by slowly acidifying the cooled

reaction mixture with 10% hydrochloric acid, and then heating for 45 minutes on a steam bath. The lactone, which settled out as an oil, was separated and the aqueous portion was extracted with ether, which was combined with the oil. The ether solution was dried and after removal of solvent and distillation of the residual oil, 27.5 g. (85%) of γ-phenyl-γ-butyrolactone was obtained; b.p. 121-127°/ 1 mm. (reported[79] b.p. 126-126.5°/ 0.8 mm.).

Preparation of γ-hydroxy-γ-phenylbutyric acid hydrazide.—γ-Phenyl-γ-butyrolactone (16.2 g. , 0.1 mole) was dissolved in 100 ml. of absolute alcohol and refluxed for 12 hours with 3.2 g. (0.1 mole) of hydrazine. Upon cooling, the hydrazide precipitated; the yield of crude material, m.p. 118-128°, was 85%. A small amount was recrystallized 3 times from a mixture of benzene and ethanol for an analytical sample, m.p. 124.5-126°.

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.27; N, 14.42. Found: C, 61.84; H, 7.30; N, 14.59.

Preparation of 6-phenyltetrahydro-1,3-oxazone-4.—γ-Hydroxy-γ-phenylbutyric acid hydrazide (5.2 g., 0.027 mole) was dissolved in 200 ml. of water which contained 1.4 ml. (0.025 mole) of concentrated sulfuric acid. This solution was stirred at -5° with 70 ml. of ether while 1.83 g. (0.027 mole) of sodium nitrite dissolved in 75 ml. of water was added over a 0.5 hour period. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether layers were dried and then refluxed in an attempt to rearrange the azide. No gas evolution was observed, so an equal amount of benzene was added to raise the boiling temperature. Again no gas evolution was observed, so the solution was allowed to reflux for 12 hours. During this time,

6-phenyltetrahydro-1,3-oxazone-2 precipitated in a ring of beautiful, white, analytically pure crystals around the surface of the liquid; weight 2.4 g. (50%), m.p. 180-181°.

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.89; H, 6.30; N, 7.77.

An additional 0.7 g. of crude product, m.p. 170-178°, was obtained by evaporation of the benzene-ether solution.

Hydrolysis of 6-phenyltetrahydro-1,3-oxazone-2 to 3-hydroxy-3-phenylpropylamine.--6-Phenyltetrahydro-1,3-oxazone-2 (2.4 g., 0.0135 mole) was dissolved in 20 ml. of ethanol which contained 7 g. of 85% potassium hydroxide and the mixture was refluxed for 20 hours. The reaction mixture was then poured into water and carefully acidified to pH 2. Carbon dioxide was evolved during the acidification. The acidified solution was extracted with ether to remove non-basic impurities and was then made basic and extracted successively with ether and benzene. The combined extracts were dried and after removal of solvent, 1.2 g. of yellowish oil with an amine-like odor was obtained. Davies and Powell[80] report 3-hydroxy-3-phenylpropylamine to be a solid, m.p. 63.5-64.5°. The impure amino alcohol was converted to its oxalate by dissolving it in ether and adding excess saturated ethereal oxalic acid. The salt precipitated immediately and was collected and recrystallized from aqueous ethanol; weight 0.6 g., m.p. 190-194°. After a second recrystallization it melted at 194-195°.

Anal. Calcd. for $C_{20}H_{28}N_2O_6$: C, 61.21; H, 7.19; N, 7.14. Found: C, 61.27; H, 7.22; N, 7.09.

The amine oxalate can also be obtained with m.p. 148-150°. It is probably either the acid oxalate or a crystalline modification of the

full oxalate.

Preparation of N-(3-hydroxy-3-phenylpropyl)benzamide.--3-Hydroxy-3-phenylpropylammonium oxalate (0.6 g., 0.0015 mole) was dissolved in 20 ml. of 10% sodium hydroxide solution and 10 ml. of benzene was added. The mixture was stirred while 0.35 g. (0.0025 mole) of benzoyl chloride, dissolved in 10 ml. of benzene, was added over a 15 minute period. The mixture was stirred for 12 hours; the benzene layer was separated and the aqueous layer was extracted with ether. The combined organic layers were dried and after removal of solvent, 0.5 g. of impure N-(3-hydroxy-3-phenylpropyl)benzamide was obtained; m.p. 64-85°. Trituration under petroleum ether (b.p. 60-75°) gave 0.35 g. (90%) of product, m.p. 84-86.5° (reported[80] m.p. 85-86°).

Cyclization of N-(3-hydroxy-3-phenylpropyl)benzamide.--N-(3-Hydroxy-3-phenylpropyl)benzamide (0.35 g., 0.0014 mole) was dissolved in 25 ml. of toluene and refluxed for 3 hours with 0.25 g. of phosphorus pentasulfide. The isolation of the product, 2,6-diphenyl-5,6-dihydro-1,3,4-thiazine, was carried out by the same procedure described in the cyclization of N-(2-hydroxypropyl)benzamide. The crude product weighed 0.2 g. (40%); m.p. 81-85°. After 2 recrystallizations from ether, it melted at 86-88°. Comparison of this sample with the cyclization product of N-cinnamylthiobenzamide proved the products to be identical. A mixed melting point showed no depression and the infrared spectra were superimposable.

The picrate was prepared by dissolving a small amount of the thiazine in ethanol and adding a small amount of a saturated solution of picric acid in ethanol. After recrystallization from aqueous ethanol, it melted at 157.5-159.5°. Comparison of this salt with the picrate of

the cyclization product of N-cinnamylthiobenzamide proved them to be identical. A mixed melting point showed no depression and the infrared spectra were superimposable.

Preparation of 1-nitro-2-butanol.--1-Nitro-2-butanol was prepared in 48% yield by the reaction of 61 g. (1 mole) of nitromethane with 64 g. (1.1 moles) of freshly distilled propionaldehyde. The procedure was that of de Montmollin and Ackermann[81]. The product boiled at 101-105°/ 25 mm.

Preparation of 1-amino-2-butanol.--1-Nitro-2-butanol (52 g., 0.44 mole) was dissolved in 25 ml. of ethanol and was shaken with 5 g. of spongy nickel catalyst (Davison Chemical Company, Cincinnati, Ohio) under 950 p.s.i. of hydrogen for 12 hours. After filtration of the nickel and removal of the solvent, the product was distilled, yielding 16.5 g. (41%) of 1-amino-2-butanol, b.p. 75-81°/ 20 mm. (reported[81] b.p. 75-77°/ 12 mm.).

Preparation of N-(2-hydroxybutyl)benzamide.--1-Amino-2-butanol (13.5 g., 0.15 mole) was benzoylated by the same general procedure used to benzoylate 1-amino-2-propanol, yielding 14.7 g. (50%) of crude product, m.p. 97-104°. A small amount was recrystallized 4 times from benzene for an analytical sample, m.p. 106.5-108°.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.34; H, 7.80; N, 7.53.

Cyclization of N-(2-hydroxybutyl)benzamide.--N-(2-Hydroxybutyl)-benzamide (14 g., 0.072 mole) was cyclized with phosphorus pentasulfide by the procedure employed in the cyclization of N-(2-hydroxypropyl) benzamide, to give 8.3 g. (60%) of 2-phenyl-5-ethyl-2-thiazoline, b.p. 106-109°/ 1 mm. An analytical sample was prepared by redistillation;

b.p. 109°/ 1 mm.

Anal. Calcd. for $C_{11}H_{13}NS$: C, 69.06; H, 6.85; N, 7.32. Found: C, 68.86; H, 6.72; N, 7.40.

The picrate was prepared and after 3 recrystallizations from ethanol it melted at 131-132°.

Anal. Calcd. for $C_{17}H_{16}N_4O_7S$: C, 48.57; H, 3.84; N, 13.33. Found: C, 48.72; H, 3.89; N, 13.52.

Preparation of N-(3-hydroxybutyl)benzamide.—4-Amino-2-butanol (9.9 g., 0.11 mole) was benzoylated by the procedure used to benzoylate 1-amino-2-propanol. No solid appeared, so the chloroform layer was separated and dried; after removal of solvent and distillation of the residual oil, 11.7 g. (55%) of N-(3-hydroxybutyl)benzamide was obtained; b.p. 174-180°/ 0.5 mm. The product was very viscous, and could not be induced to crystallize. The infrared spectrum was consistant with the N-hydroxyalkylbenzamide structure.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.35; H, 7.90; N, 7.34.

Cyclization of N-(3-hydroxybutyl)benzamide.—N-(3-Hydroxybutyl)-benzamide (11.7 g., 0.061 mole) was cyclized with phosphorus pentasulfide by the procedure employed in the cyclization of N-(2-hydroxypropyl)benzamide to give 5.2 g. (44%) of 2-phenyl-6-methyl-5,6-dihydro-1,3,4-thiazine, b.p. 122-123°/ 1.5 mm.

Anal. Calcd. for $C_{11}H_{13}NS$: C, 69.06; H, 6.85; N, 7.32. Found: C, 68.88; H, 6.80; N, 7.52.

The picrate was prepared and after 4 recrystallizations from ethanol it melted at 162.5-164.5°.

Anal. Calcd. for $C_{17}H_{16}N_4O_7S$: C, 48.57; H, 3.84; N, 13.33.

Found: C, 48.64; H, 3.86; N, 13.46.

APPENDIX

Cyclization of N-allylthiobenzamide with zinc chloride.--A mixture of 44.2 g. (0.25 mole) of N-allylthiobenzamide and 34 g. (0.25 mole) of zinc chloride was stirred for 12 hours at 125°. The zinc chloride formed hard lumps at first, but softened and settled to the bottom of the flask as the temperature was raised. After cooling, the mixture was stirred with excess 20% sodium hydroxide solution for 3 hours and extracted with ether. The ether solution was extracted with 10% hydrochloric acid; the aqueous layer was separated and neutralized with 20% sodium hydroxide solution, whereupon an oil separated. The oil was dissolved in anhydrous ether, which was then saturated with dry hydrogen chloride. A yellow oil separated which would not crystallize; it was treated with 10% sodium hydroxide solution and extracted with ether. The ether solution was dried, and after removal of solvent and distillation of the residual oil, 13.5 g. (31%) of 2-phenyl-5-methyl-2-thiazoline was obtained; b.p. 150-155°/ 25 mm. (reported* b.p. 148-150°/ 18 mm.).

The picrate, m.p. 158.5-160°, was prepared by adding a few drops of the thiazoline to a saturated solution of picric acid in ethanol and recrystallizing the precipitate from ethanol.

Cyclization of N-allylthiobenzamide with boron trifluoride.--A mixture of 4 g. (0.023 mole) of N-allylthiobenzamide and 10 ml. of boron trifluoride etherate was heated for 12 hours at 105° in a sealed tube. The reaction mixture was poured into excess 10% sodium hydroxide solution and extracted with ether. The ether solution was extracted with 10% hydrochloric acid, and the acidic aqueous layer was neutralized with

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dilute sodium hydroxide and extracted with ether. The ethereal extracts were dried and after removal of solvent, distillation of the residue gave 1.4 g. (35%) of 2-phenyl-5-methyl-2-thiazoline, b.p. 86-91°/ 1 mm.

The picrate, prepared by adding a few drops of the thiazoline to a saturated solution of picric acid in ethanol, melted at 156-161°.

C-Methyl determination on 2-phenyl-5-methyl-2-thiazoline.--The Kuhn-Roth[82] C-methyl determination was used. A 0.558 g. sample (0.00315 mole) of 2-phenyl-5-methyl-2-thiazoline gave 0.00226 mole of acetic acid, determined by titration to the phenolphthalein end point with 0.098 M sodium hydroxide. This is 72% of the theoretical amount of acetic acid from 1 methyl group.

Preparation of 1-amino-2-bromopropane hydrobromide.--1-Amino-2-propanol (75 g., 1 mole) was treated with 48% hydrobromic acid according to the procedure used by Desseigne[83] to convert ethanolamine to 2-bromoethylamine hydrobromide; 48 g. (22%) of 1-amino-2-bromopropane hydrobromide was obtained; m.p. 159-164° (reported[84] m.p. 157-159°).

Preparation of N-(2-bromopropyl)benzamide.--1-Amino-2-bromopropane hydrobromide (28.5 g., 0.13 mole) was converted to N-(2-bromopropyl)-benzamide in 86% yield by reaction with benzoyl chloride according to the procedure of Leffler and Adams[84]. The product melted at 76.5-79°.

Attempted conversion of N-(2-bromopropyl)benzamide to N-(2-mercapto-propyl)benzamide.--A solution of 12.1 g. (0.05 mole) of N-(2-bromopropyl)benzamide and 3.8 g. (0.05 mole) of thiourea in 25 ml. of 95% ethanol was refluxed for 6 hours. Then a solution of 3 g. of sodium hydroxide in 30 ml. of water was added and the mixture was refluxed for 2 hours. The mixture was extracted with three 50 ml. portions of benzene and the aqueous portion was acidified with dilute hydrochloric acid and

extracted with ether. The ether extracts were dried, and removal of solvent left a small amount of yellow oil. In an attempt to cyclize the mercaptoamide, if present, the oil was dissolved in 50 ml. of benzene and refluxed for 30 minutes with 2 g. of phosphorus pentoxide. The benzene solution was filtered, and removal of solvent left a small amount of oil which failed to give a picrate when treated with a saturated solution of picric acid in ethanol.

Conversion of N-(2-bromopropyl)benzamide to 2-phenyl-5-methyl-2-oxazoline hydrobromide.-When an attempt was made to purify a crude sample of N-(2-bromopropyl)benzamide by recrystallization from benzene, the solution appeared cloudy, as if wet, and was poured through a filter cone of magnesium sulfate. Upon cooling the solution, beautiful colorless crystals, m.p. 122-125°, formed in the filtrate. This compound was very water-soluble and produced an acidic solution, which gave a positive test for ionizable halogen. When dissolved in a saturated solution of picric acid in ethanol and warmed, it gave a picrate, m.p. 161-163°. 2-Phenyl-5-methyl-2-oxazoline picrate is reported to melt at 167° [85].

Preparation of 2-mercapto-5-methyl-2-thiazoline.—2-Mercapto-5-methyl-2-thiazoline was prepared by the reaction of 1-amino-2-bromopropane hydrobromide with carbon disulfide in basic solution according to the procedure of Hirsch[20]. The product melted at 93-95°, although Hirsch reported 82°.

Anal. Calcd. for $C_4H_7NS_2$: C, 36.06; H, 5.30; N, 10.51. Found: C, 36.34, 36.25; H, 5.22, 5.28; N, 10.56, 10.47.

Hydrolysis of 2-mercapto-5-methyl-2-thiazoline.—The hydrolysis procedure was the same as that used in the hydrolysis of 2-phenyl-5-methyl-2-thiazoline except that removal of benzoic acid was not necessary.

A 3.4 g. sample (0.26 mole) of 2-mercapto-5-methyl-2-thiazoline gave 1.1 g. (53%) of crude 1-amino-2-propyldisulfide dihydrochloride, m.p. 202-210°. After recrystallization from ethanol, it melted at 223.5-226° (reported[69] m.p. 213-214°).

Preparation of cinnamyl thiocyanate.—Cinnamyl chloride was converted to cinnamyl thiocyanate by treating it with an alcoholic solution of potassium thiocyanate. The crude product, m.p. 58-66°, was obtained in 65% yield. Recrystallization from petroleum ether (b.p. 60-75°) gave a purer product, m.p. 68-70° (reported[74] m.p. 68°).

Attempted rearrangements of cinnamyl thiocyanate to cinnamyl isothiocyanate.—Attempts to rearrange cinnamyl thiocyanate to the isothiocyanate by heating it alone and with aluminum chloride gave unreacted starting material as the only isolatable product. Attempts to prepare isothiocyanate derivatives by reaction with various amines failed. The existence of the isothiocyanate in the reaction mixture having been proven by the work of Smith and Emerson[86], it was decided to attempt to react the isothiocyanate in situ with phenylmagnesium bromide, and isolate the N-cinnamylthiobenzamide. The product, however, was an oil which decomposed when distillation was attempted, so the cyclization of N-cinnamylthiobenzamide was also carried out in situ.

Conversion of cinnamyl thiocyanate to 2,6-diphenyl-5,6-dihydro-1,3,4-thiazine.—A mixture of 22.5 g. (0.13 mole) of cinnamyl thiocyanate and 100 ml. of diphenylmethane was heated at 140-145° for 5 hours. The mixture was cooled and added to 250 ml. of anhydrous ether. This solution was slowly added to a stirred solution of 0.15 mole of phenylmagnesium bromide in 100 ml. of ether. The mixture, which became cloudy during the addition, was refluxed for 2 hours after the addition was

complete. It was then poured onto ice, and dilute hydrochloric acid was added to dissolve the magnesium salts. The mixture was then extracted with ether and the ether portion was dried and the ether was removed. The reaction product was separated from the resulting diphenylmethane solution by addition of 100 ml. of petroleum ether (b.p. 60-75°) and removal of the 17 g. of oil which separated. The oil was dissolved in 30 ml. of nitrobenzene and heated for 12 hours at 85° with 7.5 g. (0.056 mole) of powdered, anhydrous aluminum chloride. The cooled mixture was then stirred with excess 10% sodium hydroxide solution and extracted with ether. The ether layer was extracted with 10% hydrochloric acid, the acid layer was made basic, and the basic mixture was extracted with ether. Drying of the ether extracts and removal of solvent left 1.2 g. (0.0048 mole) of crude 2,6-diphenyl-5,6-dihydro-1,3,4-thiazine, m.p. 77-81°. After grinding under petroleum ether (b.p. 60-75°) and recrystallizing twice from ether, it melted at 86.5-87.5°.

Anal. Calcd. for $C_{16}H_{15}NS$: C, 75.84; H, 5.97; N, 5.53. Found: C, 75.67; H, 5.86; N, 5.47.

The picrate was prepared from the crude product by adding a small amount of the base to a saturated solution of picric acid in ethanol, warming the mixture on a steam bath, and allowing it to remain at room temperature for 12 hours. After 3 recrystallizations from aqueous ethanol, it melted at 160-162°.

Anal. Calcd. for $C_{22}H_{18}N_4O_7S$: C, 54.77; H, 3.76; N, 11.61; S, 6.65. Found: C, 54.67; H, 3.92; N, 11.71; S, 6.54.

The thiazine and the picrate were identical with those prepared by the cyclization of pure N-cinnamylthiobenzamide.

Preparation of 1-phenyl-2,3-dibromopropane.—To a solution of 23.7 g.

(0.2 mole) of allylbenzene in 150 ml. of chloroform, there was added 32 g. (0.2 mole) of bromine, dropwise, with cooling and stirring. Removal of solvent and distillation of the residue gave 37 g. (67%) of 1-phenyl-2,3-dibromopropane, b.p. 85-90°/ 0.5 mm. (reported[87] b.p. 114-115°/ 5 mm.).

Attempted reactions of 1-phenyl-2,3-dibromopropane with thiobenzamide.- 1-Phenyl-2,3-dibromopropane (3 g., 0.011 mole) was dissolved in 25 ml. of chlorobenzene and refluxed for 3 hours with 1.5 g. (0.011 mole) of thiobenzamide. Hydrogen sulfide and hydrogen bromide were evolved. The mixture was extracted with 10% hydrochloric acid, the acid layer was neutralized with 10% sodium hydroxide solution, and the basic solution was extracted with ether. After drying of the ether extract and removal of solvent, only a small amount of unreacted thiobenzamide was obtained.

Similar attempts using xylene and alcoholic potassium hydroxide as solvents also gave only unreacted thiobenzamide.

Attempted reaction of 1,2-dibromobutane with thiobenzamide.—Thiobenzamide (1.4 g., 0.01 mole) was refluxed for 1 hour with 25 g. of 1,2-dibromobutane. Hydrogen sulfide and hydrogen bromide were evolved. The reaction mixture was steam-distilled to remove excess 1,2-dibromobutane and the residue was made basic with 10% sodium hydroxide solution and extracted with ether. After drying of the ether solution and removal of solvent, only a slight trace of oil remained. A small amount of a saturated solution of picric acid in ethanol was added to the oil; after several minutes, a trace of picrate formed; m.p. 134-147°. After 2 recrystallizations from ethanol, it melted at 151-154°. There was too little material for further purification. The picrate of the expected

product, 2-phenyl-5-ethyl-2-thiazoline, melts at 131-132°*.

Preparation of allylcarbinol.--Allylcarbinol was prepared by treating allylmagnesium chloride with the gaseous depolymerizate of paraformaldehyde, according to the procedure of Ettlinger and Hodgkins[76]; from 307 g. (4 moles) of allyl chloride there was obtained 65 g. (23%) of allylcarbinol, b.p. 42-44.5°/ 20 mm.

Preparation of 3-butenyl chloride.--Allylcarbinol (58.7 g., 0.8 mole) was converted to 50.2 g. (69%) of 3-butenyl chloride by reaction with thionyl chloride according to the procedure of Roberts and Mazur[71]. It boiled at 71-75°.

Preparation of 3-butenylamine.--The Gabriel reaction was used to convert 3-butenyl chloride to 3-butenylamine. The procedure of Roberts and Mazur[71] was followed; from 50.2 g. (0.55 mole) of 3-butenyl chloride there was obtained 6.2 g. (11%) of 3-butenylamine, b.p. 71-76°. The picrate, prepared by adding a drop of the amine to a saturated ethereal solution of picric acid, melted at 136-139° (reported[76] m.p. 139.5-140.5°).

Preparation of 3-butenyl isothiocyanate.--3-Butenylamine was converted to 3-butenyl isothiocyanate by the Kaluza reaction as described by Moore and Crossley[73]; from 6 g. (0.085 mole) of 3-butenylamine there was obtained 5.5 g. (57%) of 3-butenyl isothiocyanate, b.p. 80-90°/ 30 mm. (reported[76] b.p 77.5°/ 28 mm.).

Preparation of N-(3-butenyl)thiobenzamide.--3-Butenyl isothiocyanate (5.5 g., 0.049 mole) was treated with phenylmagnesium bromide, and gave 6.4 g. (68%) of N-(3-butenyl)thiobenzamide, b.p. 142-145°/ 0.1 mm. The procedure was the same as that used to prepare N-allylthiobenzamide.

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* This dissertation, p. 35.

Cyclization of N-(3-butenyl)thiobenzamide.--N-(3-butenyl)thiobenzamide (6.4 g., 0.034 mole) was dissolved in 30 ml. of nitrobenzene and heated at 120° for 2.5 hours with 4.6 g. (0.034 mole) of zinc chloride. The crude product was isolated by the procedure used in other thioamide cyclizations and on distillation gave 0.22 g. of dark colored liquid, b.p. 93-103°/ 0.8 mm. The crude product was converted to its picrate, m.p. 155-164°, by adding a drop of it to a saturated solution of picric acid in ethanol. After 4 recrystallizations from ethanol, it melted at 166-170°. This melting point is too high for the picrate of the expected product, 2-phenyl-6-methyl-5,6-dihydro-1,3,4-thiazine, which melts at 162.5-164.5°. It is possible that the product contained 2-phenyl-4,5-dimethyl-2-thiazoline, which could have arisen if the 3-butenyl chloride were partially rearranged to α-methallyl chloride during its preparation.

Preparation of α-bromobutyryl chloride.--A mixture of 62 g. (0.37 mole) of α-bromobutyric acid and 78 g. (0.655 mole) of thionyl chloride was refluxed for 2 hours. The mixture was distilled, giving 49 g. (72%) of α-bromobutyryl chloride, b.p. 144-149°.

Preparation of α-bromobutyramide.--α-Bromobutyryl chloride (80 g., 0.43 mole) was added with stirring and cooling to 500 ml. of concentrated ammonium hydroxide. The precipitated α-bromobutyramide was filtered, washed with water, and recrystallized from a mixture of chloroform and petroleum ether (b.p. 60-75°). The yield was 42.3 g. (60%), m.p. 108-112° (reported[88] m.p. 112-115°).

Preparation of α-mercaptobutyramide.--α-Mercaptobutyramide was prepared by the reaction of potassium hydrogen sulfide on α-bromobutyramide according to the procedure of Pennington, et al.[89]; from 30 g.

(0.15 mole) of α-bromobutyramide there was obtained 6.5 g. (36%) of α-mercaptobutyramide, m.p. 78-86°.

Attempted reduction of α-mercaptobutyramide with lithium aluminum hydride.—The reaction was carried out in tetrahydrofuran because the α-mercaptobutyramide was not sufficiently soluble in ether. A solution of 1.0 g. (0.0084 mole) of α-mercaptobutyramide in 20 ml. of tetrahydrofuran was slowly added to a stirred solution of 1.0 g. (0.026 mole) of lithium aluminum hydride in 50 ml. of tetrahydrofuran. After the addition, the reaction mixture was refluxed for 12 hours. Aqueous sodium hydroxide was cautiously added to hydrolyze the complex; the inorganic salts were removed by filtration and washed with tetrahydrofuran. After removal of solvent from the combined filtrate and washings, only a trace of oil remained which failed to give a picrate. Attempts to isolate the expected amino mercaptan from the solid which was previously removed by filtration failed.

Attempted reaction of 1-amino-2-butanol with thiobenzoylmercaptoacetic acid.—1-Amino-2-butanol (1.0 g., 0.011 mole) was added to a solution of 2.4 g. (0.011 mole) of thiobenzoylmercaptoacetic acid in 12 ml. of 0.1 M sodium hydroxide. The mixture was placed in an ice bath for 30 minutes and then 1 ml. of glacial acetic acid was added. The product separated as a red oil which gradually turned to a sticky solid. Attempts to crystallize the product failed. In an attempt to convert any N-(2-hydroxybutyl)thiobenzamide which may have been present to its tosylate, 2.1 g. (0.011 mole) of p-toluenesulfonyl chloride, 1.2 g. (0.011 mole) of 2,6-lutidine, and 10 ml. of benzene were added. After warming the mixture for 1 hour on a steam bath, an oil separated which solidified after some time. The solid was removed by filtration;

it gave a positive test for ionizable chloride and was considered to be 2,6-lutidine hydrochloride. Evaporation of the solvent from the filtrate left a solid, m.p. 62-155° (dec.), which could not be recrystallized. The solid was partially soluble in water and gave a brown precipitate when silver nitrate solution was added. The solid which had been previously removed by filtration exhibited the same behavior. Water was added to all the solids obtained from the reaction and the aqueous mixture was extracted with ether. The ether layer was dried, and after removal of solvent, a small amount of gum remained. In an attempt to cyclize the tosylate of N-(2-hydroxybutyl)thiobenzamide, if present, the gum was refluxed for 2 hours with 25 ml. of xylene. The xylene solution was then extracted successively with dilute sodium carbonate solution and 10% hydrochloric acid. The acid extracts were neutralized with 10% sodium hydroxide solution and extracted with ether. The ether solution was dried, and after removal of solvent, a trace of oil remained. A picrate, m.p. 100-135°, was prepared by adding a small amount of a saturated solution of picric acid in ethanol to the oil. After recrystallization from ethanol, it melted at 130-137°. It was evidently not the picrate of the expected 2-phenyl-5-ethyl-2-thiazoline, which melts at 131-132°*.

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* This dissertation, p. 35.

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