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Polysubstituted Piperazinethiocarboxamides

Donald W. Kreh

Dedicated to my parents,

Donald L. and Helen W. Kreh.

Acknowledgement

The author is indebted to Dr. J. Stanton Pierce, professor of Chemistry, for direction of this research and for his generous advice and constructive criticism. Grateful acknowledgement is made to Dr. E. Emmet Reid for the use of a chapter from his forthcoming volume of Organic Chemistry of Bivalent Sulfur.

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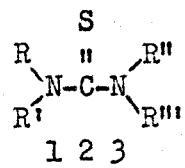
I. PURPOSE AND SCOPE OF THE RESEARCH

Thiourea and its derivatives have found wide application in dyes, photographic film, elastomers, plastics and textiles. Certain thioureas possess biological properties and considerable work has been done in this area. The historical portion of this paper is divided into biological and non-biological properties of thioureas. In the literature search, primary importance was given to the biological properties of thioureas. The objective of the experimental work was to prepare compounds having potential pharmacological activity and to determine the physical constants of these compounds.

II. NOMENCLATURE

The nomenclature used is that designated by Chemical Abstracts. The thiourea system is numbered as shown below.



S-substituted thioreas are referred to as either pseudothioureas or isothioureas. Both classifications are used in the literature.

III. HISTORY

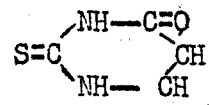
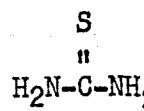
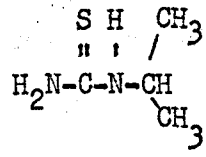
A. Biological Properties of Thioureas

1. Antithyroid Activity

An antithyroid drug is defined "as a chemical agent which lowers the basal metabolic rate by interfering with the synthesis, release, or peripheral action of the thyroid hormone."[1]

Two classes of chemical substances are known to inhibit the endocrine function of the thyroid gland. These are a number of aniline derivatives, including sulfonamides, and derivatives of thiourea. Most successful in the control of hyperthyroidism in man are thiourea and thiouracil.[2] The following table shows the comparative antithyroid effects of several compounds in the rat and in man.[3]

COMPARISON OF ANTITHYROID EFFECTS IN THE RAT AND IN MAN

Compound	Formula	Activity % Rat	Man
Thiouracil		100	100
Thiourea		10	100
Isopropylthiourea		40	100

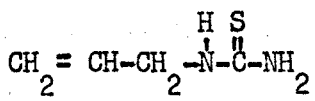
This activity has been attributed to the ability of these compounds to react with iodine.[4] Daily administration of 1-2 gm. of thiourea or 0.2-1.0 gm. of thiouracil brings about a relief of the hyperthyroidism symptoms and a return to normal of the serum cholesterol and basal metabolism.

Thiourea, even when administered with iodide or diiodotyrosine, causes thyroid hyperplasia and a decrease in both thyroxine and non-thyroxine iodine of the thyroid gland.[5] Rats given 20 mg. of allyl-thiourea daily for eight weeks developed extreme hypertrophy and hyperplasia of the thyroid.[6]

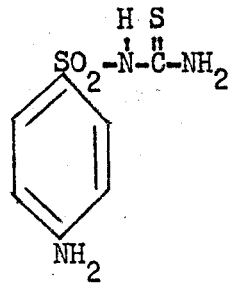
Many experimental results concerning the antithyroid activity of thioureas have been published and there are many discrepancies in the results of the different workers. These discrepancies possibly result from the different testing methods used.[7] Certain generalities, however, have been formulated.[8] Thiourea has from one-eighth to one-tenth the antithyroid activity of thiouracil. Substitution of one, two or three of the hydrogen atoms of thiourea by methyl groups does not significantly affect the activity. Replacement of all four hydrogen atoms by methyl groups increases the activity considerably. Di-ethyl, isopropyl, and diisopropyl thiourea are highly active. The activity drops or disappears as large molecular weight substituents are substituted for hydrogen atoms. Also substitution of polar groups such as NH_2, NH, and C=O in the substituents on one or both nitrogen atoms destroys the activity. Pseudothioureas are inactive but the activity is increased when the thiourea moiety is incorporated into a ring not involving the sulfur.[9]

2. Antituberculous Activity

There are numerous compounds which are able to kill tubercle bacilli *in vitro*, but the *in vivo* activity of these compounds is much less potent.[10] Thiourea and its derivatives are among the compounds which possess tuberculostatic activity. Thiourea possesses a slight but definite activity *in vitro* which is increased by appropriate substitution as in allylthiourea (I) and in p-aminobenzenesulphonylthiourea (II).[11]



(I)



(II)

Early work done by Kosuke Yamaguchi[12] during the early 1920's, led to the discovery that thioureas are active against human tuberculosis. During the early 1920's, a patent was issued for compounds described as the gold salt of the product obtained by reaction of carbon disulfide and an alkali or alkaline earth hydroxide with an amino acid or esters of amino acids.[13] These compounds, such as $(KOOC-CH_2-NHCS_2)_3Au$ were claimed to have considerable antituberculous activity. This discovery immediately caused much interest in this field and considerable work with gold compounds as chemotherapeutic agents for tuberculosis

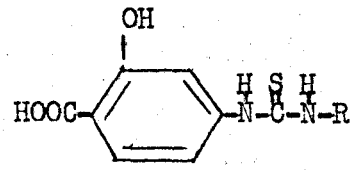
followed. It was not until many years later that thioureas, which can be prepared from carbon disulfide and an amine in the presence of an alkali hydroxide, were considered as tuberculostatic compounds.

In 1944, a patent was issued for copper compounds made from thioureidobenzoic acids. These compounds were claimed to be active against tuberculosis.[14]

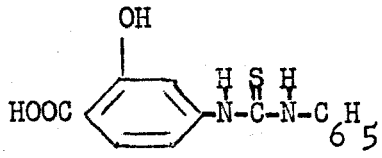
The actual suggestion of thioureas as chemotherapeutic agents for tuberculosis was made by Massie.[15] His suggestion of using long-chain alkylthioureas was based on the fact that tubercule bacilli contain large amounts of lipoidal tissue and these thioureas are lipoid soluble. The investigation of thiourea and hundreds of its derivatives followed this suggestion. In 1945, tests with rabbits injected with a suspension of human tubercule bacilli showed thiourea to be effective against tuberculosis. Improvement was noted in the test animals that received 200 mg. of thiourea.[16]

During this early work, the antituberculosis action of thiourea was believed to be due to a reduction in basal metabolism. This would reduce oxygenation of the tissues and possibly lead to an adverse effect upon the tubercle bacilli.[17]

Little success was found with the thioureas, except in the sulfonylthioureas, until 1952.[18] In that year, p-thiourea derivatives of salicylic acid were found to be effective in <u>in vitro</u> tests. Maximum activity was found in compounds of the general type

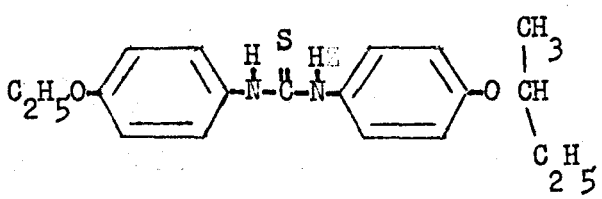


when R was aromatic. The activity decreased or disappeared completely when R was aliphatic or when o- or m-aminosalicylic acid was used. The compound giving the best results was the following,



but it did not produce a complete cure.[19]

In 1953, the discovery by Dr. R. L. Mayer that 4,4'-diethoxydiphenylthiourea had high antituberculosis activity in infected mice prompted synthesis and testing of many like compounds.[20] These compounds were tested *in vitro* against *M. tuberculosis* and *in vivo* in experimentally infected mice. The 1,3-di(4-substituted phenyl) thioureas showed considerable *in vivo* activity in mice. Exceptional activity was found in 4-ethoxy-4'-isobutoxydiphenylthiourea (III) and 4-n-butoxy-4'-dimethylaminodiphenylthiourea (IV).



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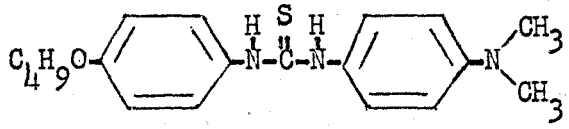
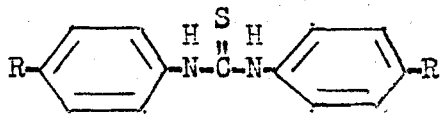


(IV)

These tests revealed specific structural requirements necessary, as indicated below, for antituberculous activity of the thioureas of the following general structure[21]



where R is an alkoxy group.

a) Shortening the 4-substituent to methoxy destroys activity.

b) Lengthening of the chain in the 4-substituent increases activity to a maximum at three to four carbon atoms. Increase beyond this causes activity to decrease and to disappear at $C_8H_{17}O$.

c) Branching of the alkyl at the carbon atom adjoining the oxygen leads to loss of activity.

d) If one of the 4-alkoxy groups is replaced by a halogen or dialkylamino substituent, activity is maintained.

e) Replacement of both 4-alkoxy groups by either halogen or dialkylamino substituent causes disappearance of activity.

f) Replacement of one alkoxy group by hydrogen causes a decrease in activity.

g) 2- and 3- position isomers are inactive.

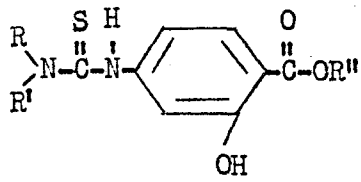
h) A second substituent in the ring destroys the activity.

i) An additional substituent on the ureido nitrogen destroys activity.

j) The thiocarbanilide moiety is necessary, since corresponding carbanilides, guanidines, guanylthiourea, dithiobuirets, and cyclohexyl-substituted thioureas are inactive.

It is believed that the metal chelating properties of the thiourea portion of the 4,4'-substituted N,N'-diarylthioureas is in part responsible for the tuberculostatic activity. To be active, the compound must have physical characteristics such that the coefficients of partition between aqueous and fatty phases are favorable to penetration into the tissues and into the bacilli themselves.[22]

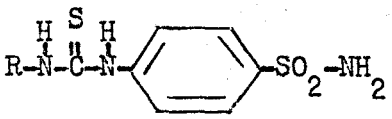
Since 1953, much investigation has been carried out in this field. Several series of compounds showing good antituberculosis activity will be mentioned. A series of derivatives of p-amino salicyclic acid have shown antituberculosis activity.[23] These compounds have the general formula



where R and R' are hydrogen, and R'' is ethyl, propyl, butyl, allyl, cyclohexyl, phenyl, o-methylphenyl, p-methylphenyl, o-chlorophenyl or m-chlorophenyl.

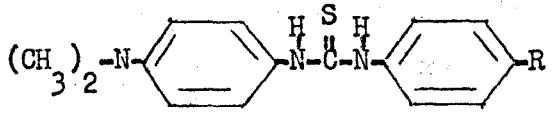
Another interesting series of compounds is the thiourea derivatives of sulfanilamide which were prepared by Viswanathan and Iyer.[24]

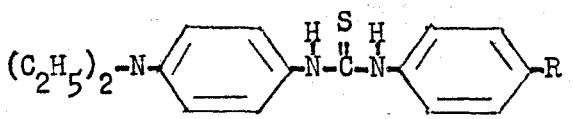
The general structure of these compounds is the following:



R is p-chloro—, bromo-, or iodophenyl; o-, m-, p-tolyl; allyl; iso-propyl, 2,4-; 2,5-dimethyl phenyl; p-methoxy phenyl, or methyl.

Huebner and Scholz[25] prepared a series of compounds having the general structure:





R is ethoxy, propoxy, butoxy, amoxy, or isoamoxy. It was found that replacement of one alkyl group on the amino nitrogen with a hydrogen atom or shortening of the R from ethoxy to methoxy caused loss of activity.

3. Anthelmintic Activity

Anthelmintics are therapeutic agents which are used to rid the body of parasitic worms known as helminths. These drugs are of great importance because helminthiasis is the most common disease in the world. It is estimated that approximately 800 million people[26] are

hosts to various types of worms. It should be emphasized that parasitic worm infestation is not restricted to tropical climates. About 40 million Americans are believed to be infected with some type of parasitic worm.[27]

Usually the helminth infections are acquired by contact with:[28] (1) infected animals, (2) ground contaminated by human or animal excrement, (3) water infested with cercariae, or (4) ingestion of infected meat.

Anthelmintics are referred to as "vermicides" if they kill the worms or as "vermifuges" if they affect the worm in such a manner that it is expelled from the intestinal tract,

An effective anthelmintic should meet the following requirements:[29]

a) The drug should reach the infested portion of the intestine with a minimal degree of absorption.

b) It should be more effective against the invading helminth than the mucous membranes of the gastrointestinal tract.

c) The drug's systemic toxicity should be minimal if absorbed from the alimentary tract.

d) The drug should be inexpensive.

e) The drug should be tolerated orally without symptoms.

Unfortunately not all of these requirements are met by the anthelmintics available at the present.

About 1916, several patents were issued for derivatives of thiourea which were claimed to be destructive against trypanosomes.[30, 31, 32]

These compounds were prepared by heating thiophosgene with amino acyl derivatives of two different aromatic amino acids. At least one of the amino acids was of the naphthalene series. In 1933, a series of compounds having the general structural formula

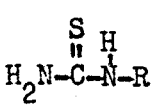
$$(Ar\text{-}NH\text{-}X'\text{-}NH\text{-}X''\text{-}NH)_2\text{-}C{=}Y$$

were claimed to have anthelmintic properties.[33] Ar is phenyl or naphthyl, X' and X'' are heterocyclic nuclei and Y is oxygen or sulfur. Closely related to the above compounds is a series having the structure:[34]

$$(Ar\text{-}NH\text{-}X''\text{-}NH)_2\text{-}C{=}Y$$

These were claimed to be effective against blood parasites.

A series of compounds showing remarkable vermicidal action was reported in 1953. The general structure was:[35]

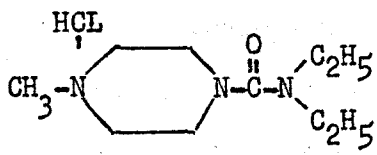


R	Vermicidal Activity	No Vermicidal Activity
C_6H_5-	x	
o-HO-C_6H_4-	x	
p-HO-C_6H_4-	x	
2,5,-HO-$(CH_3O_2C)C_6H_3$-	x	
o-CH_3O-C_6H_4-	x	
o-CH_3-C_6H_4-	x	
o-,m-CH_3O_2C-C_6H_4-	x	
o-$C_2H_5O_2C$-C_6H_4-	x	
p-$C_2H_5O_2C$-C_6H_4-		x
m-O_2N-C_6H_4-	x	
o-H_2N-C_6H_4-	x	
m-O_2N-C_6H_4-	x	
p-H_2N-C_6H_4-	x	
4,3-$CH_3(NH_2)$-C_6H_3-	x	
p-Cl-C_6H_4-	x	
p-Br-C_6H_4-	x	
$C_6H_5CH_2$-	x	

This series of compounds was examined using earthworms.

Thiourea derivatives of aromatic heterocylic compounds with a quaternary nitrogen in the nucleus are said to have anthelmintic activity.[36]

It is interesting to note that piperazine was used early in the twentieth century for the treatment of gout. During World War II when over 15,000 cases of filariasis occurred in American military personnel in the islands of the western Pacific, a derivative of piperazine was found to be an excellent antifilarial. This compound is called Hetrazane (V) (diethylcarbamazine),[37]

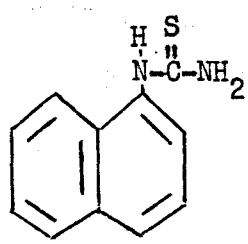


(Hetrazane)

(V)

and it is used clinically today. The piperazine derivatives are the most promising antifilarials known today.

1-Naphthylthiourea (VI) has been



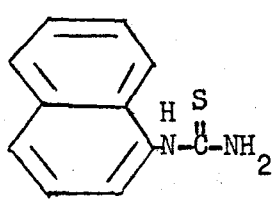
(VI)

found to be effective against intestinal parasites in man, dogs, cats, and rabbits.[38] The 2-analog and also dinaphthylthiourea are not effective.

The ultimate test of anthelmintic activity is the ability of the drug to eliminate worms from a specifically parasitized animal with a minimum toxic effect to the host. At one time, a suitable in vitro test was considered a useful screening method. At present however, in vivo screening is the method preferred and used.[39]

4. Rodenticidal Activity

Thioureas have been found to possess activity suited to the control and elimination of rodents. It is interesting to note that most of these compounds were found to have rodenticidal activity when they were being tested for other pharmacological effects on animals. 1-Naphthylthiocarbamide, previously called 1-naphthylthiourea, was discovered to be highly toxic to rats[40] when it was being tested as a possible antithyroid drug. The test rats which received this compound, even in extremely small doses, died quickly. 1-Naphthylthiourea (VI), now



ANTU

(VI)

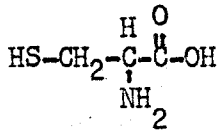
called (ANTU) is used as a rat poison and its success is due to the fact that it is much more toxic to rats than to cats and dogs. The following table shows the minimum lethal dose of ANTU for various animals:[41]

MINIMUM LD_{50} OF ANTU

Animal	LD_{50}
wild rat	15 mg./kg.
guinea pig	100 mg./kg.
mouse	120 mg./kg.
cat	150 mg./kg.
dog	500 mg./kg.
fowl	1000 mg./kg.

Rats and dogs die of pulmonary edema, caused by a selective effect on the capillaries of the lungs[42] and a resulting permeability with huge amounts of fluid in the lungs, and pleura. Cats and fowl[43] develope fatty livers. ANTU can be used effectively as a rodenticide by mixing ten grams of pulverized material with 50 gms. of powdered sugar and 400 gms. of flour.[44] A little cream or lard can be added to make a bait much more inviting than the dry powder.

Rats fed a diet high in iodine at least six hours before injection of ANTU withstood high doses of the poison.[45] Pretreatment of rats with L-cysteine (VII), DL-homocysteine (VIII), cysteamine (IX), N-methyl-,N,N-dimethyl, or N,N-diethylcysteamine (X) also prevents toxic effect of ANTU.[46]



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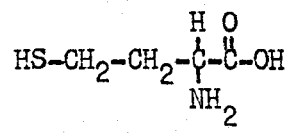

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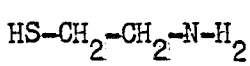

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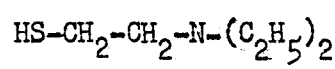
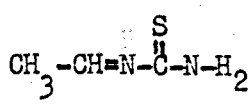


(X)

Certain thioureas with antithyroid activity also protect rats from the toxic effect of ANTU. These are thiourea, phenylallylthiourea, N-ethylidenethiourea (XI), and isopropylthiourea.

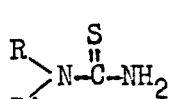


(XI)

1-Ethyl-1-phenylthiourea, ethyl-, and butylthiourea also are effective.[47]

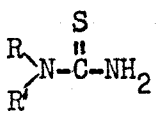
Certain specifications have been suggested for the structure of rodenticidal thioureas. A study of 196 compounds showed that a single aromatic radical attached to one nitrogen caused increase in toxicity. Two or more substituents on one or both nitrogens or a substituent on the sulfur decrease the toxicity.[48]

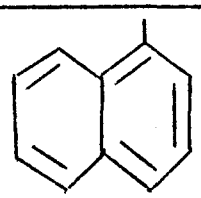
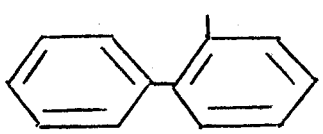
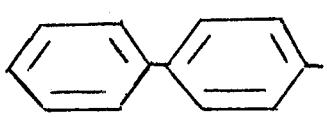
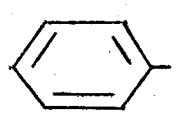
Compounds having the general structural formula



where R is hydrogen or a low aliphatic group with six or less carbon atoms, and R' is an aromatic group of molecular weight of at least 100 so that the molecular weight of the entire compound is at least 175 are claimed as rodenticides.

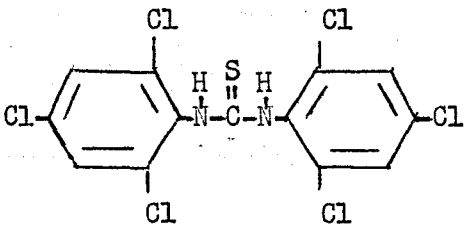
The following table shows the solubility of several of these compounds in water and also the minimum toxic dose.[49]



	R'	R	solubility gm./cc water	toxic dose mg.
1		H	12	2-4
2		H	2.8	1-2
3		H	2.8	1-3
4		H	250	1-2

Compound number 4 (phenylthiocarbamide) is unusable as a rodenticide because its taste is revolting to rats.

Several other thioureas having rodenticidal activity are 1,3 bis(2,4,6-trichlorophenyl) thiourea (XII), 1-methyl-3-phenylthiourea (XIII), and morpholinylthiocarboxamide (XIV).[50]



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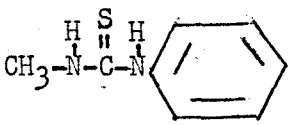
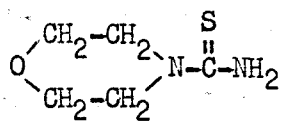


(XIII)

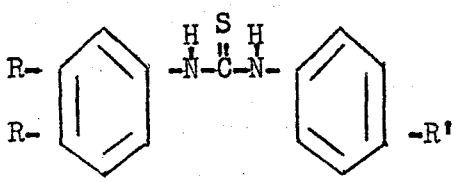


(XIV)

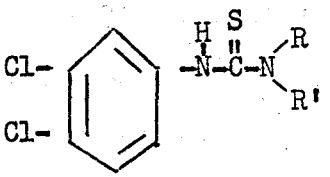
5. Antibacterial Activity

Thiourea has a definite inhibitory action on the developement and vitality of pathogenic organisms.[51] It has been found effective only at concentrations greater than 1.25%[52] when tested in milk, lactose preparations, and sucrose solutions. Reaction products of thiourea with heavy metal salts such as $HgCl_2$ or a salt of Pb, Cd, Zn, Ag, or Cu are used as disinfectants.[53] Mercurated phenylthioureas are unstable to heat and light and were not tested for bactericidal action.[54]

The following series of compounds were tested for bacteriostatic activity against Micrococcus pyogenes aureus.[55]



R	R'	Max. diln. against MPA
3,4-dichloro	3-chloro	1-10 million
3,4-dichloro	3-bromo	1-1 million



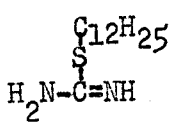
R	R'
H	3-hydroxypropyl
H	4-chlorophenyl
H	3-chlorophenyl
H	phenyl
H	3-bromophenyl
H	3,4-dichlorophenyl
H	2-Thenyl
isopropyl	allyl
isopropyl	2-propynyl

The compounds listed showed considerable activity on the (MPA) organism.

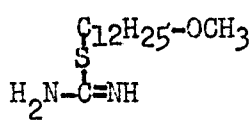
Antibacterial activity has been reported in various other types of thioureas. An aromatic, heterocyclic or aromatic-heterocyclic amine containing an aminoalkyl side chain when incorporated into a thiourea shows specific bactericidal action for the germ causing contagious abortion in cattle.[56]

From a study of twenty-three arylthioureas, it was found that $2\text{-HO-}C_6H_4NH\,CS\,NH_2$ was the best compound for preventing mold on soy sauce.[57] Some 1-aryl-3-allylthioureas have been reported to be effective against bacterial infections.[58]

Isothiourea substituted by a high molecular weight alicyclic radical on the sulfur atom make very effective disinfectants for pathogenic organisms.[59] Some guanyl and biguanyl compounds such as S-dodecylisothiourea (XV) and S-dodecyloxymethylisothiourea (XVI) have strong bactericidal activity.[60]



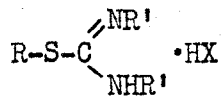
(XV)



(XVI)

These compounds also have wetting, frothing and dispersing properties which make them useful as disinfectant cleansing agents.

An extensive study of the antibacterial activity of substituted isothioureas having the general structure[61]

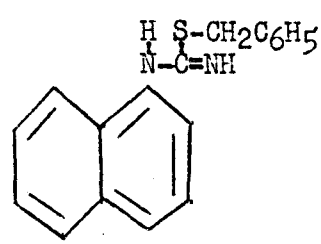


was carried out in 1952. In the above formula, R represents a straight chain alkyl group of 10-16 carbon atoms and R' ranges from hydrogen to n-butyl. It was shown that germicidal activity increased with the length of the S-alkyl chain reaching a maximum with the dodecyl derivatives. The greatest activity was obtained with the dimethyl and diethyl dodecyl derivatives.

Some thiourea derivatives possessing high antituberculous activity[62] were also found to have significant activity against some types of fungi and actinomyces.

6. Insecticidal Activity

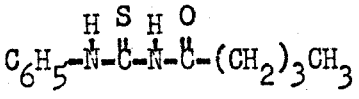
Thiourea and many of its derivatives have been found to have insecticidal activity. Thiourea, phenylthiourea, allylthiourea, and tolyl-thioureas show considerable insecticidal power on larvae and adults of various strains of Drosophila melanogaster.[63] S-Benzyl-1-(1-naphthyl) isothiourea (XVII) is effective against Altogenus picius



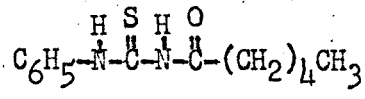
(XVII)

and Tinia pellionella.[64] 1-Dodecyl- and 1,3-didodecylthiourea are toxic to the flesh fly larva.[65]

A German patent has been issued for compounds of the general formula RNHCSNHR', where R is alkyl, cycloalkyl, aralkyl, or aryl and R' is an acid residue, for the protection of wool, furs, and hair from insects. Examples of these compounds are phenylvalerylthiourea (XVIII) and phenylcaproylthiourea (XIX).[66]

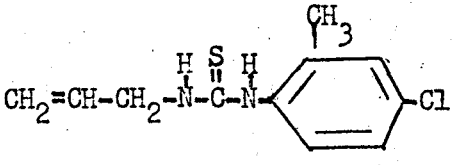


(XVIII)



(XIX)

N-allyl-N'-(4 chloro-2-methyl-phenyl) thiourea (XX) is claimed to be effective in the control of the Japanese beetle and the Mexican bean

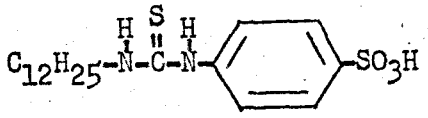


(XX)

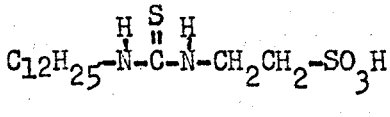
beetle.[67]

The application of thioureas to plant dusts and sprays has been investigated. A suspension of symmetrical diphenylthiourea and starch in water has been found to be an effective plant spray.[68] A mixture of symmetrical diphenylthiourea and sulfur is used to dust cotton and potato plants.[69] Thiourea plus a copper salt, with or without

arsenicals, is used as a dusting powder.[70] Rust on cereals is destroyed by treating the young grain with compounds such as thiourea and substituted thioureas.[71] Thioureas which are said to be good surface active insecticides are those N-substituted derivatives which (1) contain an open chain aliphatic group having at least eight carbon atoms, and (2) contain a radical which has a water-solublizing group attached. Examples of this group of compounds are N-dodecyl-N'-(p-sulfophenyl) thiourea (XXI) and N-dodecyl-N'-(B-sulfoethyl) thiourea (XXII).[72]



(XXI)

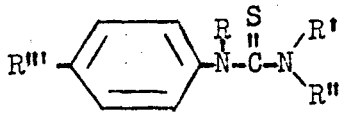


(XXII)

The dangers of cancer formation resulting from the presence of thiourea or its derivatives leads one to question the use of these compounds as dusts and sprays. Feeding tests with rabbits show that thiourea is not harmful in the concentration that would be found on fruit which had been treated with it.[73]

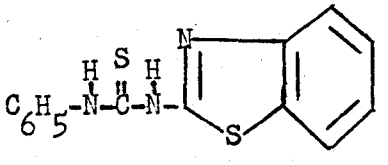
7. Hypnotic and Anesthetic Activity

Thioureas of the general formula



have been prepared and patented as hypnotics suitable for use as local or general anesthetics.[74] In this series, the patent specifies those compounds in which R represents an alkyl or alkenyl radical having less than eight carbon atoms, R' and R'' represent hydrogen or an alkyl-alkanyl radical of less than eight carbon atoms, and R''' represents an alkyl radical having from one to eight carbon atoms.

Other compounds are reported to have local anesthetic properties. These compounds are disubstituted thioureas into which a benzothiazole moiety has been introduced. Examples of this series are 1-phenyl-3-(benzothiazolyl-2-) thiourea (XXIII), 1-allyl-3-(6-nitrobenzothiazolyl-2-) thiourea (XXIV), and 1-phenyl-3-(6-chlorobenzothiazolyl-2-) thiourea (XXV). The activity of these compounds is comparable to that of procaine (novocaine).[75]

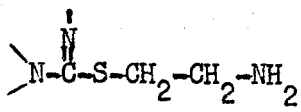


(XXIII)

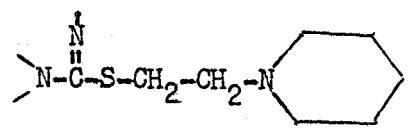
(XXIV)

(XXV)

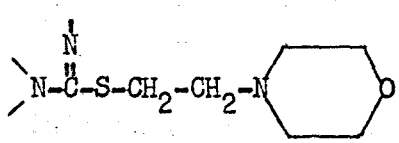
A group of pseudothiuronuim salts having high local anesthetic activity has been prepared. Sulfur substituents in these salts include 2-aminoethyl (XXVI), 2-(1-piperidylethyl) (XXVII), 2-(4-morpholinyl-ethyl) (XXVIII), and 2-dibutylaminoethyl (XXIX) groups.[76]



(XXVI)



(XXVII)



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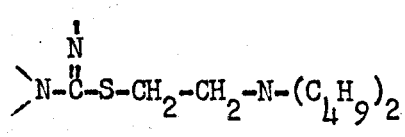


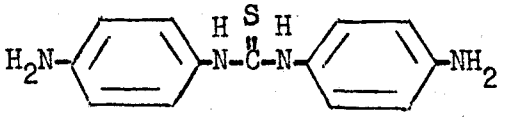
(XXIX)

In a homologous series of 1-aryl and 1-alkyl-3-arylthioureas, hypnotic effectiveness increased with increasing molecular weight.[77] Some guanylthioureas were also found to have analgesic action.[78] Some of these guanylthioureas were powerful but toxic antipyretics. Others proved to be of value and were used for muscular rheumatism during the 1930's.

8. Miscellaneous Properties

Other biological properties of thioureas have been noted and investigated. Thiourea inhibits oxygen utilization in all organs except the heart and it is a general cell antioxidant and makes less energy available for the cell for synthesis.[79] When used for a long period of time, thiourea caused thyroid tumors, some of which were malignant.[80]

Allylthiourea may be considered to act as a co-carcinogen.[81] In some specific experiments, thiourea was found to inhibit malignant growths in mice.[82, 83] 4,4'-diaminodiphenylthiourea (XXX)



(XXX)

showed inhibitory effect in mice sarcoma.[84] Thiourea affects the bone marrow of rats.[85]

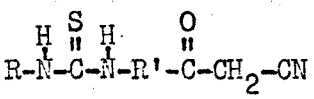
Thioureas have a definite effect on blood pressure of animals, but no generalizations can be made because the effects vary with the test animal used and compound being tested. Thiourea causes marked vasodilation in the frog.[86] Methylisothiourea has an LD_{50} of 300 mg./kg. and increases the blood pressure of dogs and cats, decreases blood pressure in rabbits, enhances histamine action, and lowers blood sugar.[87] Benzylisothiourea which has an LD_{50} of 60 mg./kg., has variable action on blood pressure depending on the dose and route of entry. It has antihistamine action and also lowers blood sugar. A study of 93 isothioureas showed that a fall in blood pressure and heart rate and inhibition of respiration[88] generally result from the use of these compounds.

The antiphenoloxidase or antityrosinase activity of thioureas is based on the fact that the thioureas form complexes with copper, the metal component of the enzyme.[89] Phenyl-, p-phenetyl-, and

p-butoxyphenylthiourea are excellent inhibitors.

Thioureas were tested as possible antimalarials,[90, 91, 92] but they have been found ineffective. Use of thioureas for protection against x-ray radiation has been tried. Thiourea protected mice from the lethal effects of Roentgen ray irradiation.[93] Allylthiourea offers no protection and it seems to hasten the lethal result of the radiation.[94]

Methylisothiourea increases the tone of smooth muscle[95] and possesses anticurare activity.[96] Compounds of the type



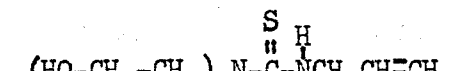
where R is an alkyl or aralkyl group and R' is an alkylene group are claimed to possess cardiovascular, diuretic, and chemotherapeutic activity.[97] Antiacetylcholine and antihistamine activity has been observed in several thioureas.[98]

B. Non-Biological Properties of Thioureas

1. Applications in Photography

Thioureas have varied usage in photography. Thiourea with potassium ferricyanide[99] has been used as a reducer. It has been used to produce blue tones on gold chloride paper, as a developer in mercury intensification, and as a fixing agent. A solution containing thiourea

and potassium carbonate[100] has been suggested as a substitute for the sulfide solution used in sepia toning. In alkaline solution, thiourea[101] is used as the "redeveloper" for direct positive paper. Low molecular weight substitution products of thiourea have been considered as substitutes for sodium thiosulfate fixing baths,[102] but have been found undesirable. Emulsions are sensitized by thiourea and allylthiourea,[103] and these plus diallylthiourea serve as suitable ripening accelerators.[104] N-diethanol-N'-allylthiourea (XXXI)[105] is used in bleaching-out layers as



(XXXI)

a "sensitizer." Thiourea or an aryl thiourea is used in wall paint or enamel for rooms in which photographic emulsions are prepared.[106]

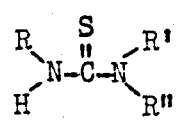
2. Applications as Inhibitors

Metals, particularly iron, and steel alloys are protected against the attack of inorganic and organic acids by thiourea or its aryl or alkyl derivatives.[107] At a concentration of 50 mg/L of 0.1 Normal hydrochloric acid, thiourea[108] shows maximum inhibitory action on steel. Methyl; ethyl; and o-, m-, and p-tolylthiourea inhibit dissolution of mild steel by sulfuric acid.[109] Thioureas have been found to both accelerate and inhibit dissolution of iron and mild steel in acid. Acceleration is attributed to hydrogen sulfide which is produced by cathodic reduction of the thioureas. Inhibition is considered to be

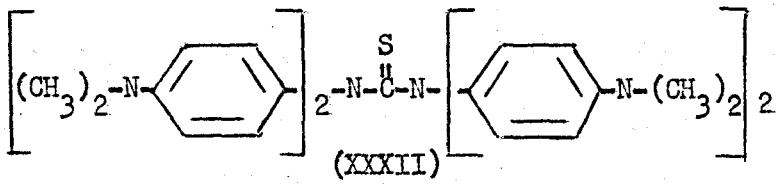
predominately the result of retardation of the anodic process.[110] The rate of solution of aluminum in acid is decreased by thiourea,[111] but thiourea has very little effect on the rate of solution of aluminum in alkalies.[112] Thiourea also retards corrosion of aluminum by potassium chloride.[113]

Considerable work has been done with thioureas and their effects on rubber. Thiourea derivatives[114] are used as vulcanization accelerators. It has been found that electropositive groups on diarylthioureas increase vulcanization activity while electronegative groups decrease the activity.[115] A mixture of 80 percent tetrabutylthiuram monosulfide, 5 percent tetrabutylthiourea, and 15 percent tetrabutylurea gives a short curing time to rubber[116] without danger of precuring.

Compounds having the general structural formula



were prepared and were found to stabilize elastomers against attack by oxygen or ozone.[117] R is alkyl, aryl, hydroxyphenyl, or aminophenyl; R' is hydroxyphenyl or aminophenyl; and R" is hydrogen, alkyl or aryl. Several compounds used as antioxidants in the aging of rubber have been prepared and found useful. N,N'-bis (p-dimethylaminophenyl) thiourea (XXXII), N-phenyl-N'-(p-dimethylaminophenyl) thiourea (XXXIII), N-phenyl-N'-(p-hydroxyphenyl) thiourea (XXXIV), and N,N'-bis (p-hydroxyphenyl) thiourea (XXXV) are useful rubber antioxidants.[118]



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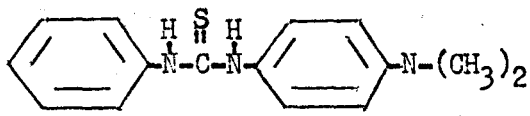

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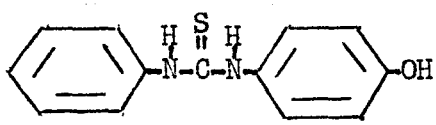

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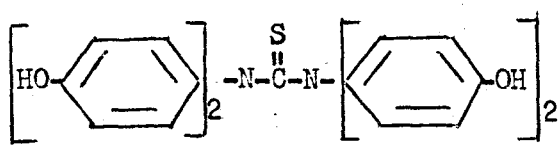
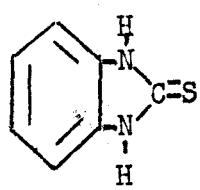


(XXXV)

Compound (XXXII) showed much better protection against oxidation of rubber than did o-phenylenethiourea (XXXVI) or 1,3-diphenylthiourea.[119]



(XXXVI)

Thiourea, in concentration of 0.01%, can be added to distillates such as gasoline or kerosene to prevent discoloration or gum formation during storage or handling.[120] Diphenyl thiourea is used as a color stabilizer of cracked hydrocarbon distillates.[121]

Thioureas protect soap against deterioration resulting from oxidation and further stabilize the soap against discoloration in light.[122] Aryl substituted thioureas are superior to the alkyl substituted compounds. Thioureas also inhibit oxidation of tung, stillingia, and linseed oils.[123]

3. Applications with Textiles and Dyes

Thiourea is used to improve the color fastness in dyeing acetate rayon.[124] It causes a swelling of cellulose fibers in water[125] and causes an increase in swelling of these fibers over that shown by sodium hydroxide alone.[126] S-Dodecylisothiourea chloride[127] or a like compound, and the condensation products of chloroacetic esters with thiourea[128] are constituents of textile assistants. These are used with other materials such as detergents and dye baths in compounds for treating animal, vegetable, and artificial fibers and serve to improve their action. The reaction product from thiourea and 2-hydroxy-5-chloromethylbenzoic acid[129] serves the same purpose. Ar-Tetrahydro-1- and -2-naphthyl thioureas are used as intermediates for the preparation of safety-paper chemicals and dyes[130] and p-fluorophenylthioureas are used as dye intermediates.[131]

Reaction products with thiourea have found wide usage in the textile industry. Reaction products of thiourea with a chloromethyl-substituted arylaminoanthraquinone,[132] a chloromethyl carboxylic acid ester, or a chloromethyl thio ether[133] are valuable aids in improving dyeing of cotton and similar cellulosic materials. Products used as

wetting, emulsifying, foam-producing, equalizing or softening agents, or for increasing the fastness of dyes to water are formed by reaction of thiourea or an alkyl, aryl, or aralkyl thiourea with a formaldehyde derivative of the general formula:[134]

$$R\text{-}CH_2\text{-}X\text{-}H$$

R is an organic radical containing at least 13 carbon atoms and X is oxygen or sulfur. The reaction product of thiourea with formaldehyde is blended with such materials as alkyl resins, varnishes, cellulose-derivative lacquers, oils, waxes, natural resins, plasticizers, pigments, dyes, and fillers to facilitate their action.[135] The reaction of thiourea with symmetrical -dichlorodimethyl ether gives a product used to prevent the shrinkage of textiles in washing. Treatment of formanilide with sym. dichloromethyl ether and subsequent reaction of this product with thiourea[136] gives a surface-active agent which increases the affinity of fibers for acid dyes. Other surface-active agents can be prepared by reacting bis-halomethyl compounds with a thiourea.[137]

Certain polythioureas prepared from diamines have valuable fiber forming properties.[138, 139]

4. Miscellaneous Applications

Thioureas have been suggested for many uses: for preparation of hardened molding resins,[140] for condensing with ligninsulfonic acid to

give products suitable for molding,[141] for binding layers in plywood preparation,[142] as a substitute for cyanide baths in silver plating,[143] as a ferroelectric,[144] and as an aid in the electrolysis of water.[145] Thiourea is used in the flotation of sulfide ores.[146, 147, 148] An increase in the viscosity of shellac varnish is caused by addition of thiourea.[149] It was hoped that this would increase the hardness, resistance to abrasion, adhesion, and elasticity of the varnish, but the films cracked and chipped off.

Thiourea is used in separation techniques in the petroleum and fat fields.[150] It forms addition products with saturated and unsaturated fatty acids and their monoalcoholic aliphatic esters, but not with triglycerides and oxidized fatty acids.[151, 152] The following separations are thus possible: 1) triglycerides from fatty acids, 2) oxidized from non-oxidized fatty acids, 3) chaulmoogric acid from straight chain acids, and 4) fatty acids from turpentine pine resinous acids. A continuous separation process of hydrocarbons makes use of thiourea,[153, 154] and thiourea is added to petroleum fractions to prevent gum formation during transfer and storage.

In the academic field thioureas are of great value in identification of organic compounds and many elements.[155] Amines readily form sharp melting substituted thioureas when reacted with an isothiocyanate. Organic acids yield crystalline pseudothiuronium salts which have sharp melting points. 2-Naphthylthiourea can be used in identification of cobalt, copper, nickel, bismuth, lead, cadmium, and mercury.[156] Thiourea or its derivatives are useful in analysis of the following elements:

selenium and tellurium,[157] ruthenium and osmium,[158] zinc,[159] phosphorus,[160] aluminum,[161] molybdenum,[162] iron,[163] and antimony.[164]

IV. METHODS FOR THE PREPARATION OF THIOUREA DERIVATIVES

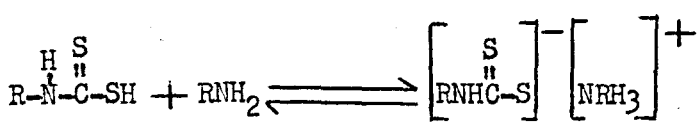
A. Carbon disulfide and an Amine

The reaction of carbon disulfide with a primary amine is the method used for preparation of symmetrical disubstituted thioureas. The overall reaction can be written in the following manner:

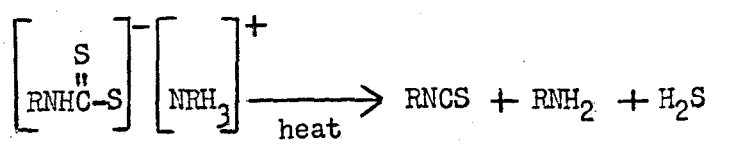
$$2RNH_2 + CS_2 \longrightarrow R\text{-}NH\text{-}C(=S)\text{-}NH\text{-}R \qquad (1)$$

This single equation however does not show the complete reaction. Schroeder[165] has studied the conflicting experimental theories of this reaction and has presented the most reasonable course for the reaction:

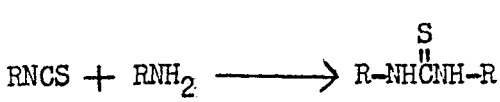
$$RNH_2 + CS_2 \longrightarrow R\text{-}NH\text{-}C(=S)\text{-}SH \qquad (2)$$



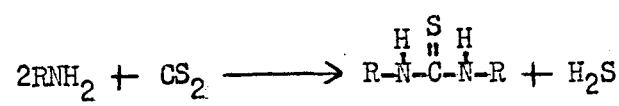
$$R\text{-}NH\text{-}C(=S)\text{-}SH + RNH_2 \rightleftharpoons [RNHC(=S)\text{-}S]^-[NRH_3]^+ \qquad (3)$$



$$[RNHC(=S)\text{-}S]^-[NRH_3]^+ \xrightarrow{\text{heat}} RNCS + RNH_2 + H_2S \qquad (4)$$



$$RNCS + RNH_2 \longrightarrow R\text{-}NHC(=S)NH\text{-}R \qquad (5)$$



$$2RNH_2 + CS_2 \longrightarrow R\text{-}NH\text{-}C(=S)\text{-}NH\text{-}R + H_2S$$

Primary amines react with carbon disulfide to give 1,3-disubstituted

thioureas, but secondary amines do not react to give the tetra-substituted thioureas. There must be an available hydrogen in the moiety $\left[RNHC(=S)-S\right]^-$ in equation (4) for the reaction to proceed. With secondary amines, this hydrogen atom is not present and the reaction will not proceed. The fact which proves the existence of the isothiocynate in equation (4) is the isolation and identification of thiourethans from the reaction mixture. when alcohols are used as solvents.

The reaction is carried out in an alcohol or benzene solvent[166] using two moles of amine and excess carbon disulfide. The reaction mixture is refluxed and the final product usually crystallizes out of the reaction mixture because of its low solubility. The reaction is slow and several ways have been found both to accelerate the reaction and improve the yield. These ways are:

1. Addition of sodium or potassium hydroxide

Sodium or potassium hydroxide is added to accelerate the removal of the hydrogen sulfide.[167, 168, 169] The overall reaction with primary arylamines is:[170]

$$2RNH_2 + CS_2 + 2NaOH \longrightarrow S{=}C(NHR)_2 + Na_2CS_3 + 2H_2O \qquad (6)$$

Either alcoholic[171] or aqueous[172] sodium hydroxide can be used. The objection to using alcoholic sodium hydroxide is the possible formation of the thiourethan.

2. Addition of Sulfur

Adding a small quantity of sulfur to the reaction of an amine with carbon disulfide has been found to accelerate the reaction.[173, 174, 175] The difficulty here, however, is the separation of the sulfur from the final product.

3. Addition of Iodine and Pyridine

In 1913, pyridine was found to accelerate the reaction of carbon disulfide with a primary amine by forming an unstable addition compound with hydrogen sulfide.[176]

$$C_5H_5N + H_2S \rightleftharpoons C_5H_5N\begin{matrix}H\\SH\end{matrix} \qquad (7)$$

Thioureas of o-, m-, and p-chloro aniline can be prepared using this procedure. Better results are obtained when the calculated amount of iodine is added to the solution of the amine, carbon disulfide and pyridine.[177] The iodine reacts with the hydrogen sulfide in the following manner:

$$H_2S + I_2 \longrightarrow 2HI + S \qquad (8)$$

The liberated hydrogen iodide reacts with the pyridine to give pyridinium iodide

$$C_5H_5N + HI \longrightarrow C_5H_5N \cdot HI \qquad (9)$$

which is insoluble in carbon disulfide and prevents reversal of equation (8). The overall reaction can be written as follows:

$$2RNH_2 + CS_2 + I_2 + 2C_5H_5N \longrightarrow (RNH)_2C{=}S + 2C_5H_5N \cdot HI + S \qquad (10)$$

The ratio of reactants giving best results is 2:1:4 with respect to amine, iodine, and pyridine. If a 1:1:2 ratio is used, there is the possibility of forming the isothiocyanate.

$$RNH_2 + CS_2 + I_2 + 2C_5H_5N \longrightarrow RNCS + 2C_5H_5N \cdot HI + S \qquad (11)$$

After reaction is complete, which is indicated by disappearance of the iodine color, the pyridine and carbon disulfide are removed by steam distillation. The pyridinium iodide is removed by washing with water. The desired product is then purified by recrystallization.

The addition of iodine and pyridine greatly promote the reaction when halo-substituted aromatic amines are used. The pyridine has an advantage of not lending itself to the formation of substituted amines or amides by interaction with halogen substituted derivatives.[178] The relative reaction rates of halo-substituted anilines were found to be o > m > p and I > Br > Cl.[179]

4. Addition of ethyl potassium xanthate

A small quantity of ethyl potassium xanthate catalyzes the reaction of carbon disulfide with a primary amine.[180, 181]

B. Thiophosgene and an Amine

The action of carbon disulfide and alcoholic alkali on a primary aromatic amine yields 1,3-disubstituted thioureas. This particular reaction, however, is not applicable if the aromatic amine is substituted in the nucleus by nitro, or hydroxyl groups. Poor yields are obtained when substituted aromatic amines are used. Separation of the desired product from the reaction mixture is difficult when substituted aromatic amines are used in the reaction.[182] To eliminate these difficulties, the reaction of the substituted aromatic amine with thiophosgene is then used.

Primary amines can react with thiophosgene to give two products. The primary product is a thiocarbamyl chloride as in equation (12).

$$RNH_2 + CSCl_2 \longrightarrow RNH \cdot CSCl + HCl \qquad (12)$$

This carbamyl chloride, in the presence of water, normally loses hydrogen chloride yielding the corresponding thiocarbimide (isothiocyanate) as in equation (13).

$$RNH \cdot CSCl \xrightarrow[H_2O]{} RNCS + HCl \qquad (13)$$

When inhibitory groups are present, the thiocarbamyl chloride loses hydrogen chloride with great difficulty and reacts with a second molecule of the amine to give the symmetrical-diarylthiocarbamide as in equation (14).

$$RNH \cdot CSCl + RNH_2 \longrightarrow (RNH)_2C{=}S + HCl \qquad (14)$$

With 2,4,6-tribromoaniline, inhibition of equation (12) occurs. If 2,6-dichloroaniline is used, no reaction whatever takes place. Methoxy and ethoxy groups inhibit equation (12) slightly and nitro groups completely inhibit equation (12).[183]

Secondary amines give only symmetrical thioureas. The mechanism of these reactions has been explained as follows:[184]

$$RR'NH + CSCl_2 \longrightarrow \left[RR'NHClCSCl\right] \longrightarrow \underset{\text{(XXXVII)}}{RR'NCSCl} + HCl \qquad (15)$$

Compound (XXXVII) reacts in the following manner if R' is not hydrogen or if R' is hydrogen and (XXXVII) is stable:

$$RR'NCSCl + RR'NH \longrightarrow RR'\text{-}N\text{-}\overset{\overset{S}{\|}}{C}\text{-}N\text{-}RR' + HCl \qquad (16)$$

When R' is hydrogen and (XXXVII) is unstable, the following reaction occurs:

$$RNHCSCl \longrightarrow RNCS + HCl \qquad (17)$$

$$RNCS + RNH_2 \longrightarrow RNHCSNHR \qquad (18)$$

Proof of this mechanism lies in the fact that compound (XXXVII) have been isloated and identified in many reactions even when R' is hydrogen. If a 1:1 ratio of secondary amine to thiophosgene is used, the reaction stops at the thiocarbamyl chloride stage and (XXXVII) is often stable.

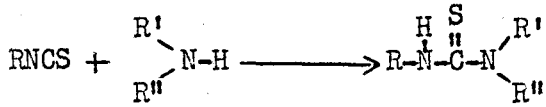
Preparation of the thioureas is best carried out by refluxing two moles of amine with one mole of thiophosgene. This reaction can be carried out in an aqueous acetone medium,[185] in chloroform-aqueous medium,[186] or in aqueous medium.[187]

After complete reaction of the thiophosgene, a mole of potassium carbonate is added and the reaction mixture is heated for several additional hours. Separation and purification of the final product is carried out in a manner appropriate to the particular compound.[188]

As was stated in the first paragraph of this section, thiophosgene is used only when other methods of preparation fail. The dangers of using thiophosgene limit the use of this method.

C. Organic Isothiocyanate and an Amine

The reaction of an organic isothiocyanate and an amine in a suitable solvent is the most common method for preparing unsymmetrical thioureas. The reaction follows the general equation:



(19)

Ammonia, primary amines, or secondary amines may be used, and R, R', and R'' may be aliphatic, aromatic, alicyclic, or heterocyclic. R may also be an acyl group.[189] Mono-,[190, 191, 192] di-,[193, 194, 195], or tri-substituted thioureas are produced when ammonia, a primary amine, or a secondary amine respectively are used. The amine is usually added to the isothiocyanate in a solvent such as alcohol or an inert solvent. Cooling may be necessary to control the reaction and refluxing may be needed in some cases to facilitate the reaction. The thioureas obtained are usually sharp melting solids, and for this reason the reaction is used in the characterizing of amines.[196, 197, 198, 199, 200, 201, 202, 203] The characterizing of isothiocyanates by conversion to a thiourea with an amine is also practiced.[204]

The speed of reaction of aryl isothiocyanates with an amine varies depending on the nuclear substituent in the ring. Halogen, nitro, m-methoxy, and m-ethoxy groups on the aryl ring accelerate the reaction. Alkyl, o- and p-alkoxy groups retard the reaction. The nitro group is the most active accelerator and the isopropyl group is the most active inhibitor.[205]

The reaction of an organic isothiocyanate with an amine can be reversed by boiling with concentrated hydrochloric acid or 40% sulfuric acid.

$$RNCS + R'NH_2 \longrightarrow R'\text{-}\overset{H}{\underset{|}{N}}\text{-}\overset{S}{\underset{\|}{C}}\text{-}\overset{H}{\underset{|}{N}}\text{-}R \qquad (20)$$

$$R'\text{-}\overset{H}{\underset{|}{N}}\text{-}\overset{S}{\underset{\|}{C}}\text{-}\overset{H}{\underset{|}{N}}\text{-}R \longrightarrow \begin{cases} \xrightarrow{HCl} RNCS + R'NH_2 \cdot HCl \\ \xrightarrow{H_2SO_4} RNCS + [R'NH_2]_2 \cdot H_2SO_4 \end{cases} \qquad (21)$$

The hydrolysis products are actually mixtures of the two isothiocyanates and amine salts.[206]

Several undesirable reactions may take place, but these can be partially eliminated. Thiourethan formation, according to the following equation, results when alcohols are used as solvents when long reflux periods are required.[207]

$$RNCS + R'OH \longrightarrow RNC\begin{matrix} SH \\ OR' \end{matrix} \rightleftharpoons R\overset{H}{\underset{|}{N}}\text{-}\overset{S}{\underset{\|}{C}}\text{-}OR' \qquad (22)$$

This undesirable reaction may be eliminated by using inert solvents such as benzene, chlorobenzene, or toluene. Pyridine has also been used as a solvent.[208]

In addition to the thiourethan formation, the following exchange reactions may take place.[209, 210]

$$2RNCS + R'NH_2 \longrightarrow R'NCS + (RNH)_2C{=}S \qquad (23)$$

$$2RNCS + (R'NH)_2C{=}S \longrightarrow R'NCS + (RNH)_2C{=}S \qquad (24)$$

D. Alkali Thiocyanate and an Amine Hydrochloride

Heating ammonium thiocyanate at 160°C for several hours causes it to rearrange to thiourea.[211]

$$NH_4SCN \xrightarrow[160^{\circ}C]{2\ hrs.} NH_2\overset{\overset{S}{\|}}{C}-NH_2 \qquad (25)$$

Substituted ammonium thiocyanates likewise rearrange on heating to the corresponding thioureas.[212]

$$RNH_3SCN \xrightarrow{heat} R-NH-\overset{\overset{S}{\|}}{C}-NH_2 \qquad (26)$$

The reaction will proceed with the mono- or disubstituted ammonium ion, but not with tri- or tetrasubstitution.

The reaction involves addition of hydrochloric acid or hydrogen chloride gas to form the amine salt and then heating with ammonium or potassium thiocyanate.[213]

$$\begin{matrix} R \\ \diagdown \\ R' \diagup \end{matrix}NH + HCl + NH_4SCN \longrightarrow NH_4Cl + \begin{matrix} R \\ \diagdown \\ R' \diagup \end{matrix}NH_2SCN \qquad (27)$$

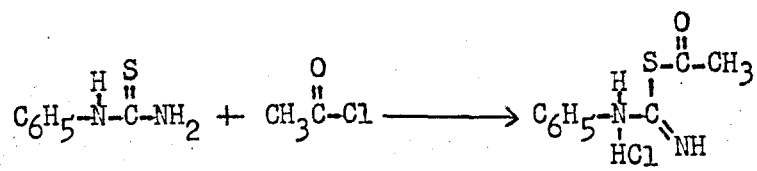
$$\begin{matrix} R \\ \diagdown \\ R' \diagup \end{matrix}NH_2SCN \xrightarrow{heat} \begin{matrix} R \\ \diagdown \\ R' \diagup \end{matrix}NH-\overset{\overset{S}{\|}}{C}-NH_2 \qquad (28)$$

Use is made of this reaction to prepare 1-mono-substituted[214, 215, 216, 217] and 1,1-disubstituted[218, 219] thioureas. The reaction can be carried out in an aqueous medium[220] or in an inert organic solvent.[221] Chlorobenzene

is usually the organic solvent used and both methods are applicable to aliphatic or aromatic amines.

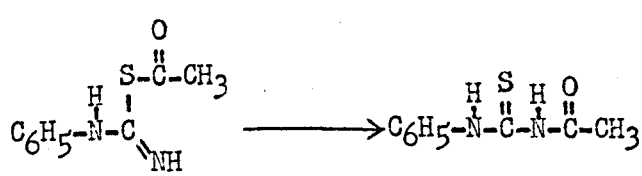
E. Thioureas and Organic Halides

Thioureas react with alkyl, acyl, aralkyl, and heterocyclic halides to give thiourea derivatives. When acyl halides react with a thiourea, S-acylation occurs first[222] as in the following reaction of acetyl chloride with 1-phenylthiourea:

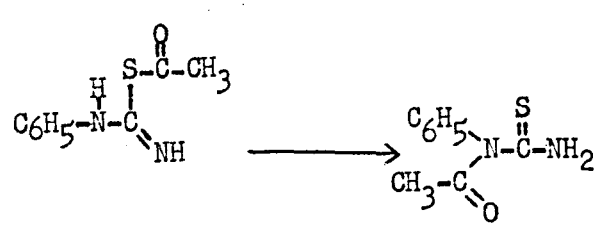


(29)

The free base of the reaction product on standing at room temperature or on being heated, rearranges to the N-substituted derivative as in equation (30) or (31).



(30)

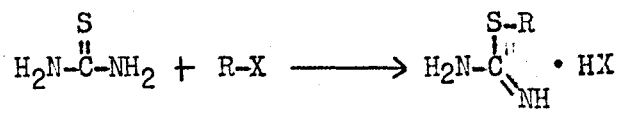


(31)

In some reactions, the rearrangement from the S-substituted derivative

to the N-substituted derivative is spontaneous and requires no heat or period of standing. When S- alkylisothioureas are heated with an acyl halide, an N-acyl-S-alkylisothiourea results.[223, 224]

Reaction of alkyl, aralkyl and heterocyclic halides with a thiourea give a stable S-substituted isothiourea.[225, 226, 227]

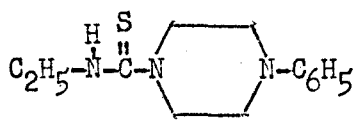


(32)

R is an alkyl, aralkyl or heterocyclic group and X is either iodide or bromide. Alkyl chlorides are less reactive and the reaction does not give good yields when chlorides are used.[228] The reaction of alkyl, aralkyl, or heterocyclic iodides or bromides with a thiourea is the common method for preparation of isothioureas.

V. EXPERIMENTAL

4-Phenyl-1-piperazine-N-ethylthiocarboxamide



A solution of 5.0 g. (0.054 mole) of ethylisothiocyanate in 20 ml. ethanol was added slowly to a solution of 8.1 g. (0.050 mole) of N-phenylpiperazine in 35 ml. ethanol and the resulting mixture was refluxed for 15 minutes. On cooling and filtering, 10.0 g. of crude product, m. p. 130-133°, was obtained. This product was recrystallized from 30 ml. of hot ethanol and 8.2 g. (66%) of crystalline title product, m. p. 130-133°, was obtained. Calculated for $C_{13}H_{19}N_3S$: titratable N, 5.61%. Found 5.69%.

4-Phenyl-1-piperazine-N-butylthiocarboxamide

A solution of 5.1 g. (0.044 mole) of butylisothiocyanate in 20 ml. of ethanol was added slowly to a solution of 6.5 g. (0.040 mole) of N-butylisothiocyanate in 30 ml. of ethanol and the resulting mixture was refluxed for 15 minutes. On cooling and filtering, 9.5 g. of crude product, m. p. 108-110°, was obtained. This product was recrystallized from 55 ml. of hot ethanol and 7.3 g. (65%) of crystalline product, m. p. 112-114°, was obtained. This product was recrystallized from a minimum amount of hot ethanol and 6.5 g. (58%) of crystalline title product, m. p. 112-114°, was obtained. Calculated for $C_{15}H_{23}N_3S$: titratable N, 5.04%. Found 5.05%.

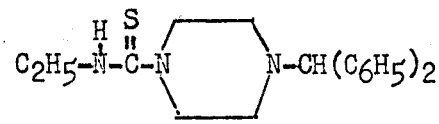
4-Phenyl-1-piperazine-N-allylthiocarboxamide

A solution of 5.4 g. (0.054 mole) of allylisothiocyanate in 5 ml. of ethanol was added slowly to a solution of 8.1 g. (0.050 mole) of N-phenylpiperazine in 20 ml. ethanol and refluxed for 15 minutes. On cooling, the reaction mixture remained liquid. A 50:50 solution of ether and petroleum ether was added to the reaction mixture and a crystalline product separated. This product was filtered off using suction and 7.8 g. of crude product, m. p. 75-78°, was obtained. This product was recrystallized from 35 ml. of hot absolute ethanol by adding 75 ml. of hot petroleum ether and cooling. Thus 5.5 g. (42%) of crystalline title product, m. p. 77-79°, was obtained. Calculated for $C_{14}H_{19}N_3S$: titratable N, 5.35%. Found 5.32%.

4-Phenyl-1-piperazine-N-phenylthiocarboxamide

A solution of 8.5 g. (0.064 mole) of phenylisothiocyanate in 10 ml. of ethanol was added slowly to 9.7 g. (0.060 mole) of N-phenylpiperazine in 20 ml. of ethanol and the resulting mixture was refluxed for 15 minutes. On cooling and filtering, 9.0 g. of crude product, m. p. 157-159°, was obtained. This product was recrystallized from 300 ml. of hot ethanol and 8.3 g. (46%) of crystalline product, m. p. 157-159°, was obtained. Calculated for $C_{17}H_{19}N_3S$: titratable N, 4.70%. Found 4.68%.

4-Benzhydryl-1-piperazine-N-ethylthiocarboxamide



A solution of 3.0 g. (0.034 mole) of ethylisothiocyanate in 5 ml. ethanol was added slowly to a solution of 7.6 g. (0.030 mole) of N-benzhydrylpiperazine in 25 ml. of ethanol and the resulting mixture was refluxed for 15 minutes. On cooling and filtering the reaction mixture, 9.5 g. of crude product, m. p. 171-175°, was obtained. This product was recrystallized from 200 ml. of hot ethanol and 6.7 g. (66%) of crystalline title product, m. p. 172-175°, was obtained. Calculated for $C_{20}H_{25}N_3S$: titratable N, 4.12%. Found 4.10%.

4-Benzhydryl-1-piperazine-N-butylthiocarboxamide

A solution of 3.3 g. (0.029 mole) of butylisothiocyanate in 10 ml. ethanol was added slowly to a solution of 6.3 g. (0.025 mole) of N-benzhydrylpiperazine in 20 ml. of ethanol and the resulting mixture was refluxed for 15 minutes. On cooling and filtering with suction, the reaction mixture yielded 7.0 g. of crude product, m. p. 132-136°. This product was recrystallized from a minimum amount of hot ethanol and 5.6 g. (61%) of crystalline title product, m. p. 132-135°, was obtained. Calculated for $C_{22}H_{29}N_3S$: titratable N, 3.81%. Found 3.80%.

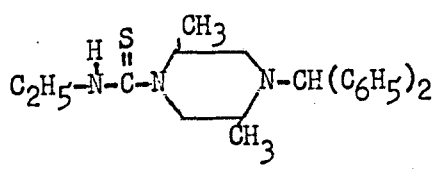
4-Benzhydryl-1-piperazine-N-allylthiocarboxamide

A solution of 3.3 g. (0.034 mole) of allylisothiocyanate in 5 ml. ethanol was added slowly to a solution of 7.6 g. (0.030 mole) of N-benzhydrylpiperazine in 20 ml. of ethanol and the resulting mixture was refluxed for 15 minutes. On cooling and filtering, 9.9 of crude product, m. p. 151-153°, was obtained. This product was recrystallized from 50 ml. of hot ethanol and 7.0 g. (69%) of crystalline title product, m. p. 151-153°, was obtained. Calculated for $C_{21}H_{25}N_3S$: titratable N, 3.98%. Found 4.04%.

4-Benzhydryl-1-piperazine-N-phenylthiocarboxamide.

A solution of 3.9 g. (0.029 mole) of phenylisothiocyanate in 5 ml. ethanol was added slowly to a solution of 6.3 g. (0.025 mole) of N-benzhydrylpiperazine in 20 ml. ethanol and the resulting mixture was refluxed for 15 minutes. On cooling and filtering, 9.5 g. of crude product, m. p. 204-207°, was obtained. This product was recrystallized from a minimum amount of hot ethanol and 8.0 g. (82%) of crystalline title product, m. p. 204-206°, was obtained. Calculated for $C_{24}H_{25}N_3S$: titratable N, 3.61%. Found 3.52%.

4-Benzhydryl-2,5-dimethyl-1-piperazine-N-ethylthiocarboxamide



A solution of 3.8 g. (0.044 mole) of ethylisothiocyanate in 5 ml. ethanol was added slowly to a solution of 11.2 g. (0.040 mole) of N-benzhydryl-2,5-dimethylpiperazine in 30 ml. of ethanol. The reaction mixture was then refluxed for 15 minutes. On cooling and filtering, 11.5 g. of crude product, m. p. 134-138°, was obtained. This product was recrystallized from 130 ml. of hot ethanol and 7.0 g. (47%) of crystalline title product, m. p. 136-138°, was obtained. Calculated for $C_{22}H_{29}N_3S$: titratable N, 3.81%. Found 3.79%.

4-Benzhydryl-2,5-dimethyl-1-piperazine-N-butylthiocarboxamide

A solution of 3.3 g. (0.029 mole) of butylisothiocyanate in 25 ml. absolute ether was added to a mechanically stirred solution of 7.0 g. (0.025 mole) of N-benzhydryl-2,5-dimethylpiperazine in 50 ml. of absolute ether over a 2 hour period. On filtering the reaction mixture using suction filtration, 6.0 g. of crude product, m. p. 129-132°, was obtained. This product was recrystallized from a minimum amount of hot ethanol and 5.2 g. (53%) of crystalline title product, m. p. 131-132°, was obtained. Calculated for $C_{24}H_{33}N_3S$: titratable N, 3.54%. Found 3.51%.

4-Benzhydryl-2,5-dimethyl-1-piperazine-N-allylthiocarboxamide

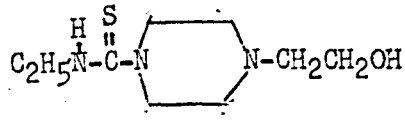
A solution of 3.3 g. (0.034 mole) of allylisothiocyanate in 25 ml. of absolute ether was added to a mechanically stirred solution of 8.4 g. (0.030 mole) of N-benzhydryl-2,5-dimethylpiperazine in 50 ml. of absolute ether over a 1.5 hour period. The reaction mixture was

filtered using suction and 7.2 g. of crude product, m. p. 127-130°, was obtained. This product was recrystallized from a minimum amount of hot ethanol and 5.6 g. (49%) of crystalline title product, m. p. 128-130°, was obtained. Calculated for $C_{23}H_{29}N_3S$: titratable N, 3.69%. Found 3.70%.

4-Benzhydryl-2,5-dimethyl-1-piperazine-N-phenylthiocarboxamide

A solution of 3.8 g. (0.029 mole) of phenylisothiocyanate in 5 ml. of ethanol was added slowly to a solution of 7.0 g. (0.025 mole) of N-benzhydryl-2,5-dimethylpiperazine in 30 ml. of ethanol and was refluxed for 15 minutes. On cooling and filtering, 9.3 g. of crude product, m. p. 138-143°, was obtained. This product was recrystallized from a minimum amount of hot ethanol and 5.3 g. (51%) of crystalline title product, m. p. 140-143°, was obtained. Calculated for $C_{26}H_{29}N_3S$: titratable N, 3.37%. Found 3.43%.

4-Hydroxyethyl-1-piperazine-N-ethylthiocarboxamide



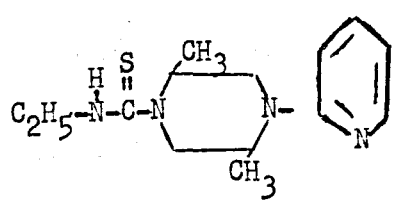
A solution of 6.1 g. (0.074 mole) of ethylisothiocyanate in 5 ml. of ethanol was added slowly to 9.0 g. (0.070 mole) of N-hydroxyethyl-piperazine in 15 ml. ethanol and the resulting mixture was refluxed for 15 minutes. On cooling and filtering, 8.7 g. of crude product, m. p. 78-83°, was obtained. This product was recrystallized from a minimum

amount of hot ethanol by adding petroleum ether until the solution became cloudy. The solution was cooled and 8.0 g. (53%) of crystalline title product, m. p. 79-82°, was obtained. Calculated for $C_9H_{19}ON_3S$: titratable N, 6.44%. Found 6.44%.

4-Hydroxyethyl-1-piperazine-N-phenylthiocarboxamide

A solution of 17 g. (0.128 mole) of phenylisothiocyanate in 10 ml. of ethanol was added slowly to a solution of 15.4 g. (0.120 mole) of N-hydroxyethylpiperazine in 20 ml. of ethanol and the resulting mixture was refluxed for 15 minutes. On cooling, the reaction mixture remained liquid. Petroleum ether was added to cause precipitation of the desired product. This product was filtered using suction and 26 g. of crude product, m. p. 119-122°, was obtained. This product was recrystallized from a minimum amount of hot ethanol by addition of a minimum amount of hot petroleum ether. The petroleum ether was added until the solution just became cloudy and 13.8 g. (43%) of crystalline title product, m. p. 119-122°, was obtained on filtration of the cold solution. Calculated for $C_{13}H_{19}ON_3S$: titratable N, 5.27%. Found 4.82%.

4-(2-Pyridyl)-2,5-dimethyl-1-piperazine-N-ethylthiocarboxamide



A solution of 4.7 g. (0.054 mole) of ethylisothiocyanate in 5 ml.

of ethanol was added slowly to a solution of 9.6 g. (0.050 mole) of N-(2-pyridyl)-2,5-dimethylpiperazine in 15 ml. ethanol and the resulting solution was refluxed for 15 minutes. On cooling and filtering, 9.5 g. of crude product, m. p. 159-164°, was obtained. This product was recrystallized from 105 ml. of hot ethanol and 8.0 g. of crystalline product, m. p. 164-166°, was obtained. This product was recrystallized from a minimum amount of hot ethanol and 7.2 g. (51%) of crystalline title product, m. p. 164-166°, was obtained. Calculated for $C_{14}H_{22}N_4S$: titratable N, 5.03%. Found 4.86%.

4-(2-Pyridyl)-2,5-dimethyl-1-piperazine-N-butylthiocarboxamide

A solution of 6.2 g. (0.054 mole) of butylisothiocyanate in 25 ml. of absolute ether was added slowly with shaking to a solution of 9.6 g. of N-(2-pyridyl)-2,5-dimethylpiperazine in 50 ml. absolute ether. The reaction mixture was shaken for 10-15 minutes and then set aside for 2 hours. Filtration of the reaction mixture yielded 6.2 g. of crude product, m. p. 196-199°. This product was recrystallized from 30 ml. absolute ethanol and 2.0 g. (13%) of crystalline title product, m. p. 196-199°, was obtained. Calculated for $C_{16}H_{26}N_4S$: titratable N, 4.57%. Found 4.69%.

4-(2-Pyridyl)-2,5-dimethyl-1-piperazine-N-allylthiocarboxamide

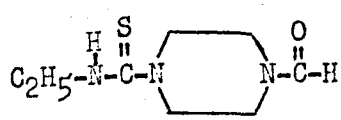
A solution of 5.4 g. (0.054 mole) of allylisothiocyanate in 5 ml. ethanol was added slowly to 9.6 g. (0.050 mole) of N-(2-pyridyl)-2,5-dimethylpiperazine in 15 ml. of ethanol and the resulting solution was

refluxed for 15 minutes. On cooling and filtering, 7.0 g. of crude product, m. p. 134-140°, was obtained. This product was recrystallized from 20 ml. of hot ethanol and 5.2 g. (35%) of crystalline title product, m. p. 138-140°, was obtained. Calculated for $C_{15}H_{22}N_4S$: titratable N, 3.82%. Found 3.78%.

4-(2-Pyridyl)-2,5-dimethyl-1-piperazine-N-phenylthiocarboxamide

A solution of 11.3 g. (0.084 mole) of phenylisothiocyanate in 10 ml. ethanol was added slowly to a solution of 15.3 g. (0.080 mole) of N-(2-pyridyl)-2,5-dimethylpiperazine in 20 ml. ethanol and the resulting solution was refluxed for 15 minutes. Petroleum ether was added to the cooled reaction mixture to cause crystallization of the desired product. Filtration of the reaction mixture yielded 23.0 g. of crude product, m. p. 151-154°. This product was recrystallized from 500 ml. of hot ethanol and 7.5 g. (28%) of crystalline title product, m. p. 151-154°, was obtained. Calculated for $C_{18}H_{22}N_4S$: titratable N, 4.27%. Found 4.25%.

4-Formyl-1-piperazine-N-ethylthiocarboxamide



A solution of 7.3 g. (0.084 mole) of ethylisothiocyanate in 5 ml. ethanol was added slowly to 9.1 g. (0.080 mole) of N-formylpiperazine in 15 ml. of ethanol and the resulting mixture was refluxed for 15 minutes. On cooling and filtering, 15.5 g. of crude product, m. p. 142-146°, was

obtained. This product was recrystallized from 80 ml. of hot ethanol and 9.3 g. (58%) of crystalline title product, m. p. 144-146°, was obtained. Calculated for $C_8H_{15}ON_3S$: total N, 20.87%. Found 20.84%.*

4-Formyl-1-piperazine-N-butylthiocarboxamide

A solution of 7.3 g. (0.064 mole) of butylisothiocyanate in 5 ml. of ethanol was added slowly to a solution of 6.8 g. (0.060 mole) of N-formylpiperazine in 15 ml. of ethanol and was refluxed for 15 minutes. Addition of absolute ether to the cooled reaction mixture caused crystallization. These crystals were filtered using suction and a yield of 7.2 g. of crude product, m. p. 60-72°, was obtained. This product was recrystallized from 30 ml. of hot ethanol by adding 30 ml. hot petroleum ether. A yield of 3.2 g. of crystalline product, m. p. 70-75°, was obtained. This product was recrystallized from 9 ml. of hot absolute ethanol by adding 40 ml. hot petroleum ether, and 1.9 g. (14%) of crystalline title product, m. p. 73-75°, was obtained. Calculated for $C_{10}H_{19}ON_3S$: total N, 18.32%. Found 18.34%.*

4-Formyl-1-piperazine-N-allylthiocarboxamide

A solution of 7.3 g. (0.074 mole) of allylisothiocyanate in 5 ml. of ethanol was added slowly to a solution of 8.0 g. (0.070 mole) of N-formylpiperazine in 15 ml. of ethanol and the resulting mixture was refluxed for 15 minutes. Addition of absolute ether to the cooled

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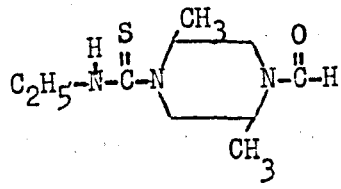
* Analysis by Galbraith Laboratories, Inc., Knoxville, Tennessee.

reaction mixture caused crystallization and this product was filtered using suction. A yield of 9.1 g. of crude product, m. p. 95-97°, was obtained. This product was recrystallized from a solution of 42 ml. of hot absolute ethanol and 100 ml. of hot petroleum ether. On filtering, 8.2 g. of crystalline product, m. p. 98-101°, was obtained. This product was recrystallized from a solution of 25 ml. of absolute hot ethanol and 18 ml. of hot petroleum ether. A yield of 5.7 g. (38%) of crystalline title product, m. p. 99-101°, was obtained. Calculated for $C_9H_{15}ON_3S$: total N, 19.69%. Found 19.71%.*

4-Formyl-1-piperazine-N-phenylthiocarboxamide

A solution of 18.9 g. (0.140 mole) of phenylisothiocyanate in 10 ml. of ethanol was added slowly to a solution of 11.4 g. (0.10 mole) of N-formylpiperazine in 20 ml. of ethanol and the resulting mixture was refluxed for 15 minutes. On cooling and filtering, 17.0 g. of crude product, m. p. 162-166°, was obtained. This product was recrystallized from 500 ml. of hot ethanol and 11.3 g. (45%) of crystalline title product, m. p. 163-166°, was obtained. Calculated for $C_{12}H_{15}ON_3S$: total N, 17.00%. Found 16.80%.*

4-Formyl-2,5-dimethyl-1-piperazine-N-ethylthiocarboxamide



A solution of 5.6 g. (0.064 mole) of ethylisothiocyanate in 5 ml. of ethanol was added slowly to a solution of 8.5 g. (0.060 mole) of N-formyl-2,5-dimethylpiperazine in 15 ml. of ethanol and the resulting solution was refluxed for 15 minutes. On cooling and filtering, 11.9 g. of crude product, m. p. 129-134°, was obtained from the reaction mixture. This product was recrystallized from 67 ml. of hot ethanol by addition of 350 ml. of hot petroleum ether, and 7.1 g. (51%) of crystalline title product, m. p. 133-135°, was obtained. Calculated for $C_{10}H_{19}ON_3S$: total N, 18.32%. Found 18.16%.*

4-Formyl-2,5-dimethyl-1-piperazine-N-butylthiocarboxamide

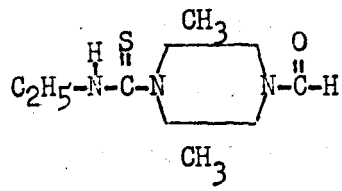
A solution of 7.3 g. (0.064 mole) of butylisothiocyanate in 5 ml. of ethanol was added slowly to a solution of 8.5 g. (0.060 mole) of N-formyl-2,5-dimethylpiperazine in 15 ml. of ethanol and the solution was refluxed for 15 minutes. Absolute ether was added to the cooled reaction mixture to cause crystallization. Filtration yielded 8.7 g. of crude product, m. p. 78-87°. This product was recrystallized from a minimum amount of hot ethanol by addition of a minimum amount of hot petroleum ether and 5.0 g. (32%) of crystalline title product, m. p. 85-88°, was obtained. Calculated for $C_{12}H_{23}ON_3S$: total N, 16.32%. Found 16.08%.*

4-Formyl-2,5-dimethyl-1-piperazine-N-phenylthiocarboxamide

A solution of 18.9 g. (0.13 mole) of phenylisothiocyanate in 10 ml. of ethanol was added slowly to a solution of 14.2 g. (0.10 mole) of

N-formyl-2,5-dimethylpiperazine in 20 ml. of ethanol and this mixture was refluxed for 15 minutes. On cooling and filtering, 23 g. of crude product, m. p. 155-157°, was obtained. This product was recrystallized from 300 ml. of hot ethanol and 11.5 g. (41%) of crystalline title product, m. p. 155-157°, was obtained. Calculated for $C_{14}H_{19}ON_3S$: total N, 15.14%. Found 14.91%.*

4-Formyl-2,6-dimethyl-1-piperazine-N-ethylthiocarboxamide



A solution of 5.0 g. (0.054 mole) of ethylisothiocyanate in 5 ml. of ethanol was added slowly to 7.0 g. (0.050 mole) of N-formyl-3,5-dimethylpiperazine in 15 ml. of ethanol and the resulting solution was refluxed for 15 minutes. On cooling and filtering, 7.5 g. of crude product, m. p. 133-136°, was obtained. This product was recrystallized from 27 ml. of hot ethanol and 4.0 g. (35%) of crystalline title product, m. p. 133-135°, was obtained. Calculated for $C_{10}H_{19}ON_3S$: total N, 18.32%. Found 18.34%.*

4-Formyl-2,6-dimethyl-1-piperazine-N-butylthiocarboxamide

A solution of 7.3 g. (0.064 mole) of butylisothiocyanate in 20 ml. of absolute ether was added over a 1.5 hour period to a mechanically stirred solution of 8.5 g. (0.060 mole) of N-formyl-3,5-dimethylpiperazine

in 30 ml. of absolute ether. The reaction mixture was then filtered and 13.2 g. of crude product, m. p. 121-123°, was obtained. This product was recrystallized from a minimum amount of hot ethanol and 7.5 g. (49%) of crystalline title product, m. p. 121-123°, was obtained. Calculated for $C_{12}H_{23}ON_3S$: total N, 16.32%. Found 16.21%.*

4-Formyl-2,6-dimethyl-1-piperazine-N-allylthiocarboxamide

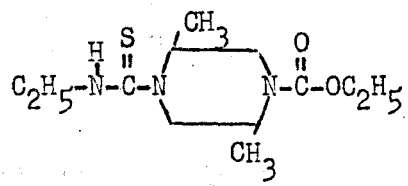
A solution of 5.4 g. (0.054 mole) of allylisothiocyanate in 5 ml. of ethanol was added slowly to a solution of 7.1 g. (0.050 mole) of N-formyl-3,5-dimethylpiperazine in 15 ml. of ethanol and the resulting solution was refluxed for 15 minutes. Absolute ether was added to the cooled reaction mixture to cause crystallization. The solution was filtered and 9.4 g. of crude product, m. p. 122-128°, was obtained. This product was recrystallized from 35 ml. of hot ethanol by the addition of a minimum amount of hot petroleum ether and 7.4 g. (61%) of crystalline title product, m. p. 126-128°, was obtained. Calculated for $C_{11}H_{19}ON_3S$: total N, 17.41%. Found 17.09%.*

4-Formyl-2,6-dimethyl-1-piperazine-N-phenylthiocarboxamide

A solution of 7.3 g. (0.054 mole) of phenylisothiocyanate in 5 ml. of ethanol was added slowly to a solution of 7.0 g. (0.050 mole) of N-formyl-3,5-dimethylpiperazine in 15 ml. of ethanol and the resulting mixture was refluxed for 15 minutes. On cooling and filtering, 12.5 g. of crude product, m. p. 149-152°, was obtained. This product was recrystallized from 150 ml. of hot ethanol and 8.1 g. (59%) of crystal-

line title product, m. p. 149-151°, was obtained. Calculated for $C_{14}H_{19}ON_3S$: total N, 15.14%. Found 15.36%.*

4-Carbethoxy-2,5-dimethyl-1-piperazine-N-ethylthiocarboxamide



A solution of 5.0 g. (0.054 mole) of ethylisothiocyanate in 5 ml. of ethanol was added slowly to a solution of 9.3 g. (0.050 mole) of N-carbethoxy-2,5-dimethylpiperazine in 15 ml. of ethanol and this solution was refluxed for 15 minutes. On cooling and filtering, 9.7 g. of crude product, m. p. 136-139°, was obtained. This product was recrystallized from 25 ml. of hot ethanol and 6.8 g. of crystalline product, m. p. 139-141°, was obtained. This product was recrystallized from 20 ml. of hot ethanol and 4.9 g. (36%) of crystalline title product, m. p. 139-141°, was obtained. Calculated for $C_{12}H_{23}O_2N_3S$: total N, 15.37%. Found 15.63%.*

4-Carbethoxy-2,5-dimethyl-1-piperazine-N-butylthiocarboxamide

A solution of 5.1 g. (0.044 mole) of butylisothiocyanate in 5 ml. of ethanol was added slowly to a solution of 7.4 g. (0.040 mole) of N-carbethoxy-2,5-dimethylpiperazine in 15 ml. of ethanol and the resulting solution was refluxed for 15 minutes. On cooling and filtering, 8.0 g. of crude product, m. p. 134-136°, was obtained. This product was

recrystallized from 20 ml. of hot ethanol and 5.3 g. (44%) of crystalline title product, m. p. 134-136°, was obtained. Calculated for $C_{14}H_{27}O_2N_3S$: total N, 13.94%. Found 14.09%.*

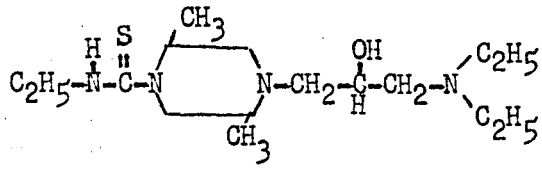
4-Carbethoxy-2,5-dimethyl-1-piperazine-N-allylthiocarboxamide

A solution of 5.4 g. (0.054 mole) of allylisothiocyanate in 5 ml. of ethanol was added slowly to a solution of 9.3 g. (0.050 mole) of N-carbethoxy-2,5-dimethylpiperazine in 15 ml. of ethanol and the resulting solution was refluxed for 15 minutes. On cooling and filtering, 10.4 g. of crude product, m. p. 139-142°, was obtained. This product was recrystallized from 35 ml. of hot ethanol and 9.0 g. (62%) of crystalline product, m. p. 140-142°, was obtained. Calculated for $C_{13}H_{23}O_2N_3S$: total N, 14.72%. Found 14.73%.*

4-Carbethoxy-2,5-dimethyl-1-piperazine-N-phenylthiocarboxamide

A solution of 8.5 g. (0.064 mole) of phenylisothiocyanate in 5 ml. ethanol was added slowly to a solution of 11.2 g. (0.060 mole) of N-carbethoxy-2,5-dimethylpiperazine in 15 ml. of ethanol and the resulting solution was refluxed for 15 minutes. On cooling and filtering, 12 g. of crude product, m. p. 151-153°, was obtained. This product was recrystallized from 400 ml. of hot ethanol and 8.0 g. of crystalline product, m. p. 156-157°, was obtained. This product was recrystallized from a minimum amount of hot ethanol and 7.5 g. (39%) of crystalline title product, m. p. 155-157°, was obtained. Calculated for $C_{16}H_{23}O_2N_3S$: total N, 13.07%. Found 12.92%.*

4-(3-Diethylamino-2-hydroxypropyl)-2,5-dimethyl-1-piperazine-N-ethyl-thiocarboxamide



A solution of 3.8 g. (0.044 mole) of ethylisothiocyanate in 25 ml. absolute ether was added over a 20 minute period to a mechanically stirred solution of 9.7 g. (0.040 mole) of 1-(3-diethylamino-2-hydroxypropyl)-2,5-dimethylpiperazine in 35 ml. of absolute ether. The solution was then stirred for 2.5 hours. The reaction mixture was poured into a separatory funnel and 100 ml. of 1N HCl was added. The acid layer was made basic to pH=11 with 6N NaOH. This mixture was extracted with 50 ml. of ether and the ether layer was filtered and dried for 24 hours over K_2CO_3. Evaporation of the ether yielded 7.5 g. (57%) of oily title product. Calculated for $C_{16}H_{34}ON_4S$: titratable N, 8.47%. Found 8.50%.

4-(3-Diethylamino-2-hydroxypropyl)-2,5-dimethyl-1-piperazine-N-butyl-thiocarboxamide

A solution of 5.1 g. (0.044 mole) of butylisothiocyanate in 5 ml. ethanol was added slowly to a solution of 9.7 g. (0.040 mole) of 1-(3-diethylamino-2-hydroxypropyl)-2,5-dimethylpiperazine in 15 ml. of ethanol and the resulting solution was refluxed for 15 minutes. The cooled reaction mixture was poured into a separatory funnel and 150 ml. of 1N HCl and 60 ml. of ether were added. The aqueous layer was made

basic to pH=11 with 6N NaOH and extracted with 90 ml. of ether. The ether layer was filtered and dried for 24 hours over K_2CO_3. Evaporation of the ether yielded 4.5 g. (31%) of oily title product. Calculated for $C_{18}H_{38}ON_4S$: titratable N, 7.81%. Found 7.61%.

4-(3-Diethylamino-2-hydroxypropyl)-2,5-dimethyl-1-piperazine-N-allyl-thiocarboxamide

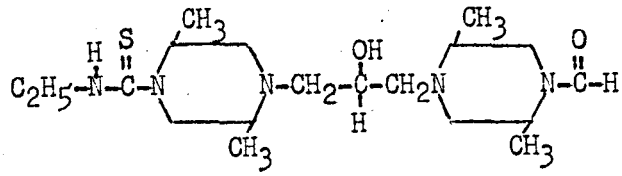
A solution of 3.3 g. (0.034 mole) of allylisothiocyanate in 10 ml. of ethanol was added slowly to a solution of 7.3 g. (0.030 mole) of 1-(3-diethylamino-2-hydroxypropyl)-2,5-dimethylpiperazine in 20 ml. of ethanol and the resulting solution was refluxed for 15 minutes. The cooled reaction mixture was poured into a separatory funnel and 100 ml. of 1N HCl and 75 ml. of ether were added. The aqueous layer was made basic to pH=11 with 6N NaOH and extracted with 100 ml. of ether. The ether layer was filtered and dried over K_2CO_3 for 24 hours. Evaporation of the ether yielded 5.0 g. (49%) of oily title product. Calculated for $C_{17}H_{34}ON_4S$: titratable N, 8.18%. Found 7.93%.

4-(3-Diethylamino-2-hydroxypropyl)-2,5-dimethyl-1-piperazine-N-phenyl-thiocarboxamide

A solution of 5.9 g. (0.044 mole) of phenylisothiocyanate in 5 ml. of ethanol was added to a solution of 9.7 g. (0.040 mole) of 1-(3-dimethylamino-2-hydroxypropyl)-2,5-dimethylpiperazine and the resulting solution was refluxed for 15 minutes. The cooled reaction mixture was placed in a separatory funnel and 300 ml. 1N HCl and 70 ml. of ether

were added. The aqueous layer was made basic to pH=11 with 6N NaOH and extracted with 100 ml. of ether. The ether layer was filtered and dried for 24 hours over K_2CO_3. Evaporation of the ether yielded 2.5 g. (17%) of oily title product. Calculated for $C_{20}H_{34}ON_4S$: titratable N, 7.40%. Found 7.30%.

4-[3-(4-Formylpiperazyl)-2-hydroxypropyl]-2,5-dimethyl-1-piperazine-N-ethylthiocarboxamide



A solution of 2.0 g. (0.024 mole) of ethylisothiocyanate in 25 ml. of benzene was added to a solution of 6.14 1-[3-(4-formylpiperazyl)-2-hydroxypropyl]-2,5-dimethylpiperazine in 50 ml. of benzene and the resulting solution was refluxed for 15 minutes. The cooled reaction mixture was placed in a separatory funnel and 60 ml. of 1N HCl, 40 ml. of H_2O, and 30 ml. of ether were added. The aqueous layer was made basic to pH=11 and extracted with 70 ml. of ether. The ether layer was filtered and dried over K_2CO_3. Evaporation of the ether yielded 3.0 g. (37%) of oily product. Calculated for $C_{19}H_{37}O_2N_5S$: titratable N, 7.01%. Found 5.34%.

The above procedure was repeated and 1.5 g. (18%) of oily title product was obtained. Calculated for $C_{19}H_{32}O_2N_5S$: titratable N, 7.01%. Found 6.56%.

4-[3-(4-Formylpiperazyl)-2-hydroxypropyl]-2,5-dimethyl-1-piperazine-N-butylthiocarboxamide

A solution of 2.7 g. (0.024 mole) of butylisothiocyanate in 25 ml. benzene was added to a solution of 6.2 g. (0.020 mole) of 1-[3-(4-formylpiperazyl)-2-hydroxypropyl]-2,5-dimethylpiperazine in 50 ml. of benzene and refluxed for 15 minutes. Sixty ml. of 1N HCl, 40 ml. of H_2O, and 20 ml. of ether were added to the reaction mixture in a separatory funnel. The aqueous layer was made basic to pH=11 and extracted with three 150 ml. portions of ether. The combined ether layers were extracted with acid, made basic, and extracted with ether as before. The ether layer was filtered and dried over K_2CO_3 for 24 hours. Evaporation of the ether yielded 2.5 g. (29%) of oily title product. Calculated for $C_{21}H_{41}O_2N_5S$: titratable N, 6.55%. Found 5.69%. The sample was warmed under a heat lamp for 2 hours and analyzed again. Found 6.14%.

4-[3-(4-Formylpiperazyl)-2-hydroxypropyl]-2,5-dimethyl-1-piperazine-N-allylthiocarboxamide

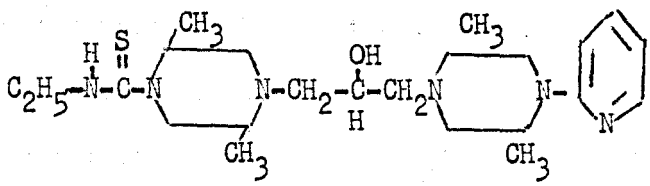
A solution of 2.4 g. (0.024 mole) of allylisothiocyanate in 25 ml. benzene was added to 6.2 g. (0.020 mole) of 1-[3-(4-formylpiperazyl)-2-hydroxypropyl]-2,5-dimethylpiperazine in 50 ml. of benzene and refluxed for 15 minutes. Forty ml. of 1N HCl, 60 ml. of water, and 30 ml. of ether were added to the reaction mixture in a separatory funnel. The aqueous layer was extracted with 50 ml. of ether and then made basic

to pH=11 and extracted with three 150 ml. portions of ether. The combined ether layers were then extracted with acid and the above procedure was repeated. The final ether layer was filtered and dried for 24 hours over K_2CO_3. Evaporation of the ether yielded 3.0 g. (37%) of oily title product. Calculated for $C_{20}H_{37}O_2N_5S$: titratable N, 6.80%. Found 6.03%. The sample was warmed under a heat lamp for 2 hours and analyzed again. Found 6.29%.

4-[3-(4-Formylpiperazyl)-2-hydroxypropyl]-2,5-dimethyl-1-piperazine-N-phenylthiocarboxamide

A solution of 3.1 g. (0.023 mole) of phenylisothiocyanate in 25 ml. of benzene was added to a solution of 6.2 g. (0.020 mole) of 1- 3-(4-formylpiperazyl)-2-hydroxypropyl -2,5-dimethylpiperazine in 50 ml. of benzene and refluxed for 15 minutes. Forty ml. of 1N HCl, 60 ml. of water, and 30 ml. of ether were added to the reaction mixture in a separatory funnel. The aqueous layer was extracted with 50 ml. of ether and then made basic to pH=11 and extracted with three 150 ml. portions of ether. The above procedure was repeated on the combined ether layers and 3.0 g. (34%) of oily title product was obtained on evaporation of the final ether layer. Calculated for $C_{23}H_{37}O_2N_5S$: titratable N, 6.25%. Found 5.64%. The sample was warmed under a heat lamp for 2 hours and analyzed again. Found 6.08%.

4-{3-[4-(2-Pyridyl)-2,5-dimethylpiperazyl]-2-hydroxypropyl}-2,5-dimethyl-1-piperazine-N-ethylthiocarboxamide



A solution of 2.0 g. (0.024 mole) of ethylisothiocyanate in 10 ml. of ethanol was added to a solution of 1-{3-[4-(2-Pyridyl)-2,5-dimethylpiperazyl]-2-hydroxypropyl}-2,5-dimethylpiperazine in 20 ml. of ethanol and was refluxed for 15 minutes. The cooled reaction mixture was placed in a separatory funnel and 200 ml. of 1N HCl and 70 ml. of ether were added. The aqueous layer was made basic with 6N NaOH to pH=11 and extracted with 70 ml. of ether. The ether layer was filtered and dried over K_2CO_3 for 24 hours. Evaporation of the ether yielded 6.2 g. (69%) of oily product. Calculated for $C_{23}H_{40}ON_6S$: titratable N, 9.36%. Found 8.66%. The above procedure was repeated on the oily product and 3.5 g. (39%) of oily title product was obtained. Found 9.08%.

4-{3-[4-(2-Pyridyl)-2,5-dimethylpiperazyl]-2-hydroxypropyl}-2,5-dimethyl-1-piperazine-N-butylthiocarboxamide

A solution of 2.7 g. (0.024 mole) of butylisothiocyanate in 10 ml. of ethanol was added to 7.2 g. (0.020 mole) of 1-{3-[4-(2-Pyridyl)-2,5-dimethylpiperazyl]-2-hydroxypropyl}-2,5-dimethylpiperazine in 20 ml.

of ethanol and the resulting solution was refluxed for 15 minutes. The reaction mixture was placed in a separatory funnel and 90 ml. of 1N HCl and 50 ml. of ether were added. The aqueous layer was made basic to pH=11 and extracted with 90 ml. of ether. The ether layer was filtered and dried over K_2CO_3. Evaporation of the ether yielded 1.0 g. (10%) of oily title product. Calculated for $C_{25}H_{44}ON_6S$: titratable N, 8.81%. Found 8.59%.

4-{3-[4-(2-Pyridyl)-2,5-dimethylpiperazyl]-2-hydroxypropyl}-2,5-dimethyl-1-piperazine-N-allylthiocarboxamide

A solution of 2.4 g. (0.024 mole) of allylisothiocyanate in 10 ml. ethanol was added to a solution of 7.2 g. 1-{3-[4-(2-Pyridyl)-2,5-dimethylpiperazyl]-2-hydroxypropyl}-2,5-dimethylpiperazine in 20 ml. of ethanol and the resulting solution was refluxed for 15 minutes. The cooled reaction mixture was placed in a separatory funnel and 100 ml. of 1N HCl and 25 ml. of ether were added. The aqueous layer was made basic to pH=11 with 6N NaOH and extracted with 70 ml. of ether. The ether layer was filtered and dried for 24 hours over K_2CO_3. Evaporation of the ether yielded 1.5 g. (16%) of oily title product. Calculated for $C_{24}H_{40}ON_6S$: titratable N, 9.12%. Found 9.23%.

4-{3-[4-(2-Pyridyl)-2,5-dimethylpiperazyl]-2-hydroxypropyl}-2,5-dimethyl-1-piperazine-N-phenylthiocarboxamide

A solution of 3.2 g. (0.024 mole) of phenylisothiocyanate in 25 ml. benzene was added to a solution of 7.2 g. (0.020 mole) of

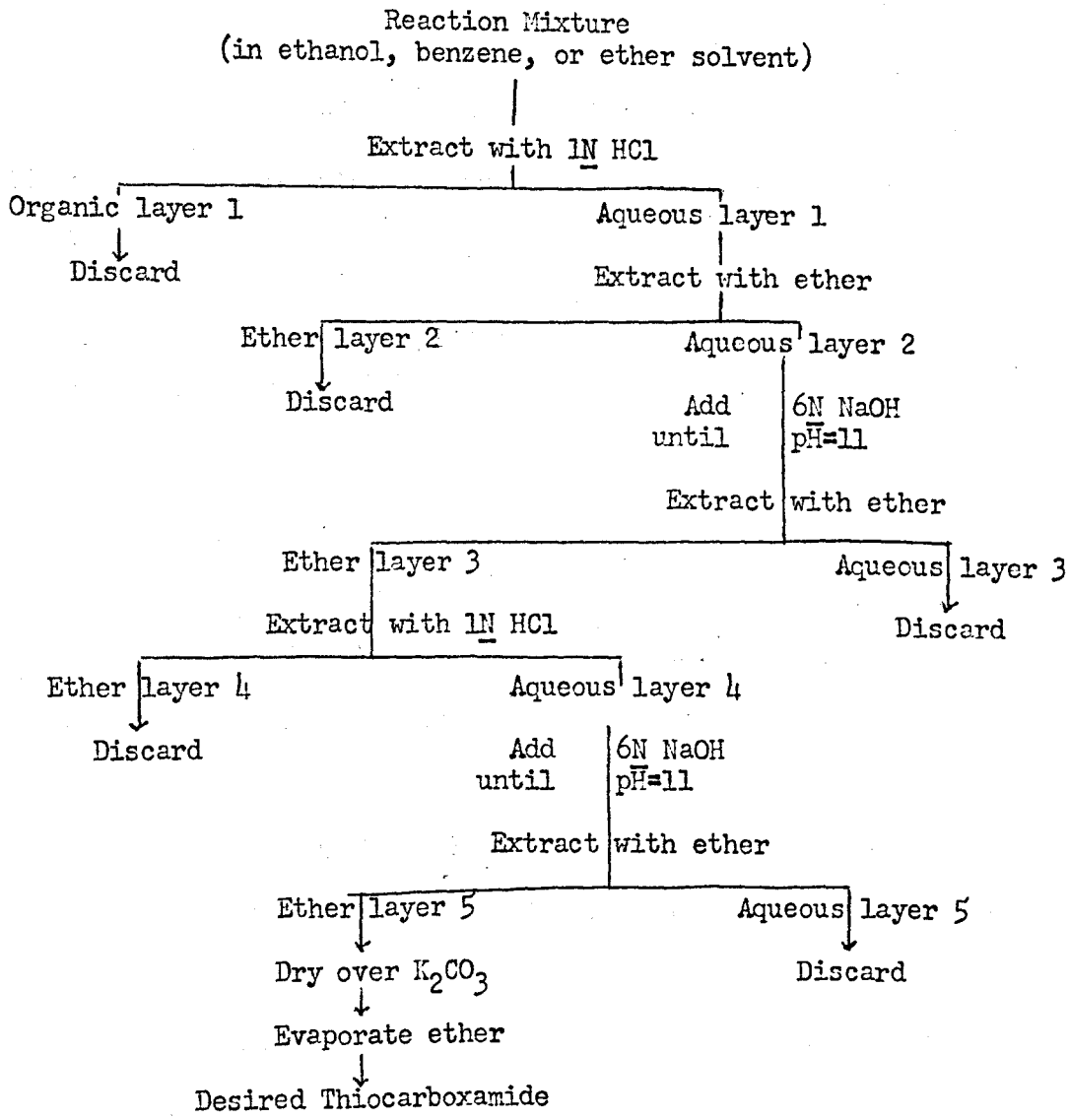
1-{3-[4-(2-Pyridyl)-2,5-dimethylpiperazyl]-2-hydroxypropyl}-2,5-dimethylpiperazine in 25 ml. of benzene and the resulting solution was refluxed for 15 minutes. Ninety ml. of 1N HCl, 40 ml. of water, and 30 ml. of ether were added to the cooled reaction in a separatory funnel. The aqueous layer was made basic with 6N NaOH to pH=11 and was extracted with 200 ml. of ether. The ether layer was washed with 100 ml. of water, filtered, and dried over K_2CO_3 for 2 hours. Evaporation of the ether yielded 4.5 g. (45%) of oily title product. Calculated for $C_{27}H_{40}ON_6S$: titratable N, 8.46%. Found 8.42%.

The 2,5-dimethylpiperazine used in the preparation of the preceding compounds was the cis form.

SCHEMATIC DIAGRAM FOR THE PURIFICATION

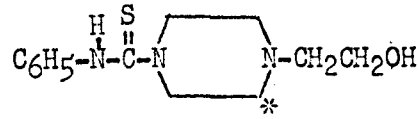
OF THE

NON-CRYSTALLINE POLYSUBSTITUTED PIPERAZINETHIOCARBOXAMIDES

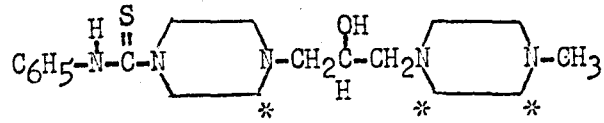


VI. ANALYTICAL

The purity of the compounds prepared in this work was determined by titration of the basic nitrogen atom(s) using glacial acetic acid as solvent and o.1 N perchloric acid in glacial acetic acid as the titrant.[229] Under the conditions of the determinations, the nitrogen atoms adjacent to the thiocarbanyl group, the formyl group, or the carbethoxy group are not titrated. The following compounds, for example, would contain:



one titratable nitrogen atom



three titratable nitrogen atoms

Equipment: Beckman Glass Electrode pH meter, Model H-2.

Reagents: Reagent grade glacial acetic acid, o.1 N perchloric acid in glacial acetic acid.

Procedure: A sample ranging from 0.05 g. - 0.1 g. is weighed into a 250 ml. beaker. The sample is dissolved in 25-35 ml. of glacial acetic acid. Using a pH meter to follow the change in potential of the solution, the sample is titrated with 0.1 N perchloric acid in acetic acid. Increments of 0.10 ml. are added to the solution and the endpoint

is indicated by the greatest change in potential per 0.10 ml. increment of acid.

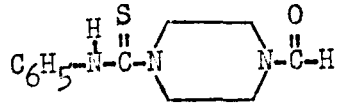
Calculations:

$$\frac{A \times \text{Wt. sample} \times 1000}{\text{ml. Acid} \times \text{N acid}} = \text{Molecular Weight}$$

A = Number of titratable nitrogen atoms

$$\frac{14.0 \times A \times 100}{\text{Molecular Weight}} = \% \text{ Nitrogen}$$

The compounds prepared which contained no basic nitrogen atom, for example,

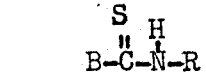


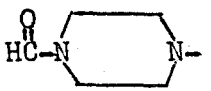
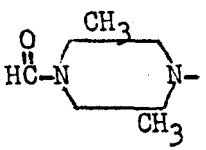
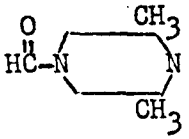
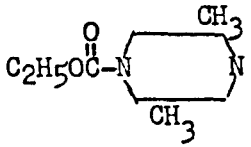
were analyzed for total nitrogen by Galbraith Laboratories, Inc., Knoxville, Tennessee.

VII. TABLES

TABLE I

CRYSTALLINE POLYSUBSTITUTED PIPERAZINETHIOCARBOXAMIDES



B	R	Method	Recryst. Solvent	No. of Recryst.	Yield %	m. p. °C	Formula	% N Calcd.	% N Found
	C_2H_5	#1	A	1	58	144-146	$C_8H_{15}ON_3S$	20.87	20.84*
	C_4H_9	#1	AAPE	2	14	73-75	$C_{10}H_{19}ON_3S$	18.32	18.34*
	$CH_2-CH=CH_2$	#1	AAPE	2	38	99-101	$C_9H_{15}ON_3S$	19.69	19.71*
	C_6H_5	#1	A	1	45	163-166	$C_{12}H_{15}ON_3S$	17.00	16.80*
	C_2H_5	#1	APE	1	51	133-135	$C_{10}H_{19}ON_3S$	18.32	18.16*
	C_4H_9	#1	APE	1	32	85-88	$C_{12}H_{23}ON_3S$	16.32	16.08*
	C_6H_5	#1	A	1	41	155-157	$C_{14}H_{19}ON_3S$	15.14	14.91*
	C_2H_5	#1	A	1	35	133-135	$C_{10}H_{19}ON_3S$	18.32	18.34*
	C_4H_9	#2	A	1	49	121-123	$C_{12}H_{23}ON_3S$	16.32	16.21*
	$CH_2-CH=CH_2$	#1	APE	1	61	126-128	$C_{11}H_{19}ON_3S$	17.41	17.09*
	C_6H_5	#1	A	1	59	149-151	$C_{14}H_{19}ON_3S$	15.14	15.36*
	C_2H_5	#1	A	2	36	139-141	$C_{12}H_{23}O_2N_3S$	15.37	15.63*
	C_4H_9	#1	A	1	44	134-136	$C_{14}H_{27}O_2N_3S$	13.94	14.09*
	$CH_2-CH=CH_2$	#1	A	1	62	140-142	$C_{13}H_{23}O_2N_3S$	14.72	14.73*
	C_6H_5	#1	A	2	39	155-157	$C_{16}H_{23}O_2N_3S$	13.07	12.92*

* Analysis by Galbraith Microanalytical Laboratories, Inc., Knoxville, Tennessee.

Method: #1 Refluxed reactants using ethanol as solvent.
#2 Absolute ether used as solvent and reaction carried out at room temperature.

Recrystallization solvents: A= ethanol; AA= absolute ethanol; PE= petroleum ether.

TABLE II

CRYSTALLINE POLYSUBSTITUTED PIPERAZINETHIOCARBOXAMIDES

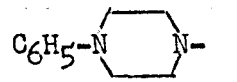
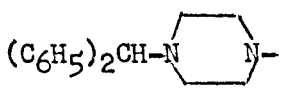
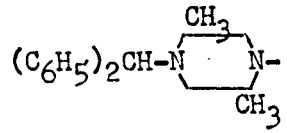
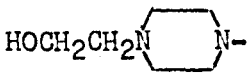
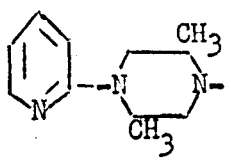
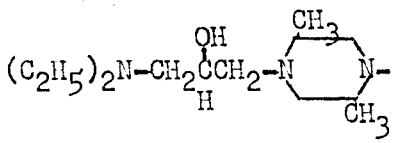
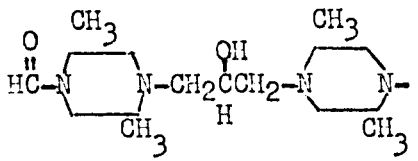
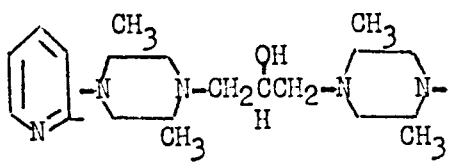
B	R	Method	Recryst. Solvent	No.of Recryst.	Yield %	m. p. °C	Formula	%Titratable Nitrogen Calcd.	Found
	C_2H_5	#1	A	1	66	130-133	$C_{13}H_{19}N_3S$	5.61	5.69
	C_4H_9	#1	A	2	58	112-114	$C_{15}H_{23}N_3S$	5.04	5.05
	$CH_2-CH=CH_2$	#1	AAPE	1	42	77-79	$C_{14}H_{19}N_3S$	5.35	5.32
	C_6H_5	#1	A	1	46	157-159	$C_{17}H_{19}N_3S$	4.70	4.68
	C_2H_5	#1	A	1	66	172-175	$C_{20}H_{25}N_3S$	4.12	4.10
	C_4H_9	#1	A	1	61	132-135	$C_{22}H_{29}N_3S$	3.81	3.80
	$CH_2-CH=CH_2$	#1	A	1	69	151-153	$C_{21}H_{25}N_3S$	3.98	4.04
	C_6H_5	#1	A	1	82	204-206	$C_{24}H_{25}N_3S$	3.61	3.52
	C_2H_5	#1	A	1	47	136-138	$C_{22}H_{29}N_3S$	3.81	3.79
	C_4H_9	#2	A	1	53	131-132	$C_{24}H_{33}N_3S$	3.54	3.51
	$CH_2-CH=CH_2$	#2	A	1	49	128-130	$C_{23}H_{29}N_3S$	3.69	3.70
	C_6H_5	#1	A	1	51	140-143	$C_{26}H_{29}N_3S$	3.37	3.43
	C_2H_5	#1	APE	1	53	79-82	$C_9H_{19}ON_3S$	6.44	6.44
	C_6H_5	#1	APE	1	43	119-122	$C_{13}H_{19}ON_3S$	5.27	4.82
	C_2H_5	#1	A	2	51	164-166	$C_{14}H_{22}N_4S$	5.03	4.86
	C_4H_9	#2	A	1	13	196-199	$C_{16}H_{26}N_4S$	4.57	4.69
	$CH_2-CH=CH_2$	#1	A	1	35	138-140	$C_{15}H_{22}N_4S$	3.82	3.78
	C_6H_5	#1	A	1	28	151-154	$C_{18}H_{22}N_4S$	4.27	4.25

TABLE III

NON-CRYSTALLINE POLYSUBSTITUTED PIPERAZINETHIOCARBOXAMIDES

B	R	Method	Yield %	Formula	% Titratable Nitrogen Calcd.	Found
	C_2H_5	#2	57	$C_{16}H_{34}ON_4S$	8.47	8.50
	C_4H_9	#1	31	$C_{18}H_{38}ON_4S$	7.81	7.61
	$CH_2-CH=CH_2$	#1	49	$C_{17}H_{34}ON_4S$	8.18	7.93
	C_6H_5	#1	17	$C_{20}H_{34}ON_4S$	7.40	7.30
	C_2H_5	#3	37	$C_{19}H_{37}O_2N_5S$	7.01	6.56
	C_4H_9	#3	29	$C_{21}H_{41}O_2N_5S$	6.55	6.14
	$CH_2-CH=CH_2$	#3	37	$C_{20}H_{37}O_2N_5S$	6.80	6.29
	C_6H_5	#3	34	$C_{23}H_{37}O_2N_5S$	6.25	5.64
	C_2H_5	#1	69	$C_{23}H_{40}ON_6S$	9.36	9.08
	C_4H_9	#1	10	$C_{25}H_{44}ON_6S$	8.81	8.59
	$CH_2-CH=CH_2$	#1	16	$C_{24}H_{40}ON_6S$	9.12	9.23
	C_6H_5	#3	45	$C_{27}H_{40}ON_6S$	8.46	8.42

Method: #3 Refluxed reactants using benzene solvent.

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VIII. BIBLIOGRAPHY

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AUTOBIOGRAPHY

I, Donald W. Kreh, was born in Frederick, Maryland, on March 17, 1937. In June of 1955, I was graduated from Hagerstown High School in Hagerstown, Maryland. In September of 1955, I entered Mars Hill Junior College at Mars Hill, North Carolina. I received the Associate in Arts degree in June of 1957 and then entered the University of Richmond. In June of 1959, I received the Bachelor of Science degree from the University of Richmond.

I entered the Graduate School of the University of Richmond in September of 1959 and was Puryear Fellow in Chemistry for the school terms of 1959-1960 and 1960-1961. During these two years and during the summers of 1960 and 1961, I have carried on research with Dr. J. Stanton Pierce.