Derivatives of Piperazine. XI. Addition of 1-Arylpiperazines to *alpha, beta*-Unsaturated Nitriles and Esters

BY

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PREFACE

The presentation of this dissertation material is purposely given in detail to facilitate duplication of this work by future investigators. Every synthesis is reported in detailed form even though the procedure in a given, homologous series is basically the same.

Throughout this dissertation all temperatures reported, both boiling points and melting points, are corrected values. The thermometers used were calibrated against a set of thermometers standardized by the Bureau of Standards.

In conformity with present practice in preparing reports of this kind, all temperatures are of the centigrade scale, and its symbol is omitted.

The percentage yields of the nitriles and esters, syntheses of which are reported in this dissertation, are based upon the molar quantity of 1-arylpiperazine used. Similarly, the percentage yields of the amino acids and amides are based upon the molar quantity of the nitrile used.

The manner of listing references is the customary one for technical reports. Journal abbreviations are the official ones of Chemical Abstracts.

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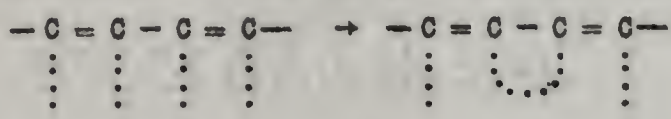
CHAPTER I

REVIEW OF LITERATURE AND INTRODUCTION

An addition compound can be defined as a substance that is formed by a direct combination of two or more simpler substances. This definition of addition will, therefore, eliminate from this category all compounds that do not contain all the atoms that were present in the original reactants.

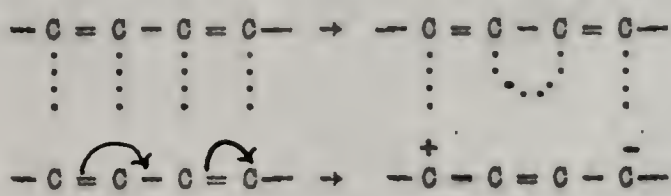
During the early history of organic chemistry abnormalities were observed in the course of certain of the addition reactions which involved substances containing alternate single and multiple linkages. Such an unsaturated system is called a conjugated system. It differs from a simple unsaturated system in that addition takes place at the ends of the conjugated system rather than across the multiple linkages. Thiele, in 1899, proposed the theory of partial valence to account for addition occuring at the ends of a conjugated system.[1] He assumed that not all the available affinity is used by a double bond between two atoms. This unused affinity was called a partial valence; and whenever the multiple linkages occur in alternate positions, the partial valences on intermediate atoms neutralize each other so that the seat of unsaturation is localized at the terminal atoms in the conjugated system. This conception of partial valency

is represented by dotted lines in the following illustration:

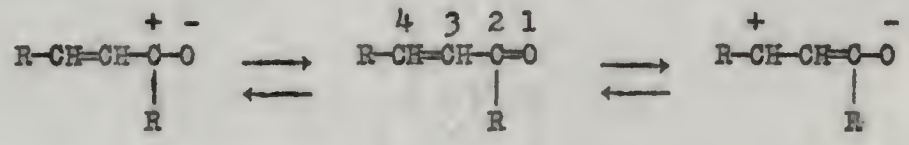


While Thiele's theory was eagerly adopted, its principal defect was in the vagueness of the concept of the affinity that every atom is assumed to have. Not to be overlooked is that the theory of partial valency requires exclusive 1,4-addition, and many cases are known where 1,2-addition takes place with conjugated systems.

Plausible electronic interpretations have been applied successfully in dealing with many types of reactions involving conjugation. Lowry postulated a mechanism of electron displacement known as the tautomeric mechanism.[2] This mechanism may operate only in conjunction with multiple bonds and involves a change in the octet affiliations of one or more electron pairs. No decomposition of the molecule occurs during this displacement. Normally, the displacement is represented by curved arrows which symbolize the tautomeric displacement of electron pairs. This displacement is called the electromeric effect. The earlier partial valence theory of Thiele is explained in terms of the newer electron theory, as is indicated in the similarity of the following representations:

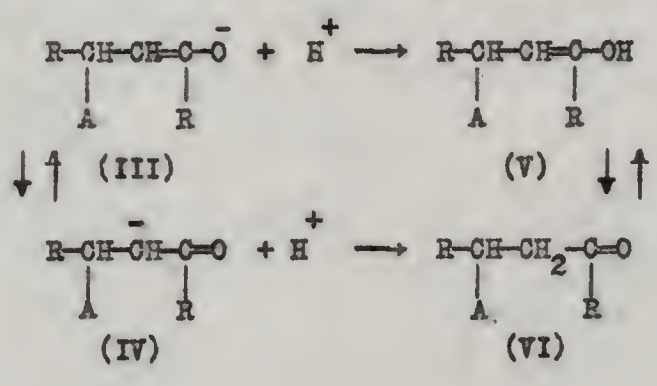


Unsaturated carbonyl compounds possess the properties of olefins as well as those of the saturated carbonyl compounds. If the ethylenic bond is in the α,β-position with respect to the carbonyl group, a conjugated system exists, and 1,4-addition can take place. For example, an α,β-unsaturated ketone has a polarized structure (II) in which the positive center is at the 4-position as well as that in which it resides on the 2-position, or carbonyl atom (I):



(I) (II)

As a consequence, carbonyl reagents may attack at position 4 rather than at the usual site (position 2). The addition of an unsymmetrical reagent, HA, in this manner occurs in at least two stages, the first being the attachment of the negative (A^-) or the positive (H^+) moiety. Considering the case in which the first step is the attachment of the negative moiety (A^-) at position 4, the resultant adduct may correspond to either of two resonance structures, III and IV. As diagramed below, the final result is 1,4— or 3,4-addition:



Nearly all enolic compounds such as those produced by 1,4-addition (V) rearrange spontaneously to the corresponding carbonyl compounds (VI) which would be produced by 3,4-addition. Hence, it ordinarily is not possible to tell whether the addition reaction is of the 1,4- or the 3,4- type. The essential feature of the reaction is the attachment of the negative ion at position 4.

The present research deals more specifically with addition to α,β-unsaturated nitriles and esters; however, the same mechanism as portrayed for addition to α,β-unsaturated ketones applies equally well in kind, if not in degree of reaction, to α,β-unsaturated nitriles and esters.

α,β-Unsaturated nitriles and esters undergo both 1,4- and 1,2-addition. In general, as the activity of the nitrile or carbalkoxy group decreases, the amount of 1,4-addition increases. The mode of addition also will depend upon the number, kind, and positions of the substituents in the nitrile or ester and upon the group or groups present in the addendum. The reactions of these unsaturated systems with malonic esters are typical of 1,4-addition:

$$C_6H_5CH{=}CHCO_2R + CH_2(CO_2R')_2 \rightleftharpoons C_6H_5\underset{\displaystyle CH(CO_2R')_2}{\underset{|}{C}}HCH_2CO_2R$$

$$C_6H_5CH{=}CHC{\equiv}N + CH_2(CO_2R)_2 \rightleftharpoons C_6H_5\underset{\displaystyle CH(CO_2R)_2}{\underset{|}{C}}HCH_2CN$$

A wide variety of organic and inorganic compounds possessing labile hydrogen atoms add readily to acrylonitrile with the formation of molecules containing a cyanoethyl grouping ($-CH_2CH_2CN$).[3] Most authors have considered this addition to occur by 1,4-addition with a subsequent tautomeric shift of the adduct to the saturated nitrile. As already pointed out, it is not ordinarily possible to determine whether 1,4-addition or 3,4-addition occurs. The essential feature is the attachment of the negative moiety of the addendum in the 4-position of the acceptor. Generalized, the reaction -- which is commonly called <u>cyanoethylation</u> -- is represented as follows:

$$HA + CH_2{=}CHCN \longrightarrow ACH_2{-}CH{=}C{=}NH \longrightarrow ACH_2CH_2CN$$

Typical compounds containing reactive hydrogen atoms which have been added to acrylonitrile are compounds having one or more -NH- groups such as ammonia, primary and secondary amines, hydrazine, hydroxylamine, imides, lactams, and amides. A wide variety of other compounds containing labile hydrogen atoms also have been added to acrylonitrile. Bruson has presented a very thorough review of the cyanoethylation reaction.[3]

This reaction, except with certain amines, usually requires the presence of an alkaline catalyst. Typical catalysts which are useful for this purpose are the oxides, hydroxides, alkoxides, hydrides, cyanides, and amides of the alkali metals sodium and potassium as well as the metals themselves. Because of their solubility in organic media, the strongly basic quaternary ammonium hydroxides are particularly

effective as catalysts for this addition. Only small amounts of the catalysts are required. Many of the reactions are strongly exothermic and require external cooling to prevent excessive polymerization of the acrylonitrile. Inert solvents such as benzene, dioxane, pyridine, acetonitrile, and tertiary butyl alcohol have been employed. The latter, while reactive with acrylonitrile at temperatures above 60°, is relatively inert at or near room temperature.

Ammonia and most amines add to acrylonitrile without the aid of a catalyst.[4] Ammonia, having three labile hydrogen atoms, yields a mixture of mono-, di-, and tri- cyanoethylation products:[5,6]

$$NH_3 + CH_2{=}CHCN \longrightarrow \begin{cases} H_2NCH_2CH_2CN \\ HN(CH_2CH_2CN)_2 \\ N(CH_2CH_2CN)_3 \end{cases}$$

In a given reaction the yield of mono-, di-, or tri- cyanoethylamine depends upon the temperature of the reaction and the molar ratio of reactants employed. The tricyanoethylamine, in all cases, is obtained in the lowest yield.

Bruson states that, in general, amines add to acrylonitrile more readily than any other class of compounds, but their ease of addition varies considerably. With those amines which react slowly, an acidic or basic catalyst is desirable. While primary amines may react with one or two moles of acrylonitrile, secondary amines can react with only one mole of acrylonitrile. Because of the latter

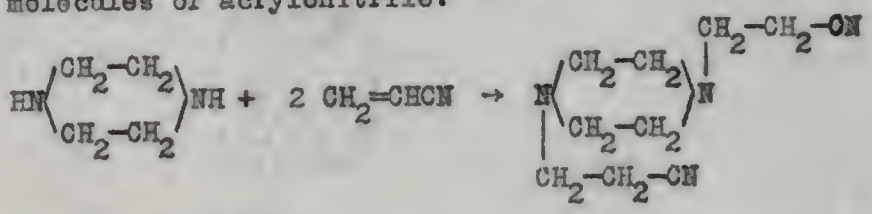
definiteness of addition, the temperature at which the reaction can take place may be varied over a wide range.

Methylamine,[7] ethylamine,[5] propylamine,[8] isopropylamine,[9] n-butylamine, sec-butylamine, and tert-butylamine[8] yield the monocyanoethylated derivatives. Piperidine adds readily to acrylonitrile with the evolution of heat.[5,10] Morpholine is only slightly less reactive than piperidine.[5] Diethylamine, however, adds more slowly than morpholine, although no difficulty is encountered in obtaining a near-quantitative yield of product merely by heating the reactants together.[5]

Whitmore and collaborators indicated that the rate of addition of the amine is primarily dependent upon the size and complexity of the amine. Other researchers have indicated that; since the ionization constants of diethylamine, piperidine, and morpholine are, respectively, 1.2×10^{-3}, 1.6×10^{-3}, and 2.4×10^{-6} and all react quite rapidly; the basicity of the amine is probably not an important factor.[11]

The cyanoethylation reaction has been extended to many complex primary and secondary amines. These are too numerous to include in this review. At 95° such mixed secondary amines as methyl-n-propylamine, ethylisopropylamine, cyclopentylethylamine, sec-butyl-n-propylamine, n-butyl-sec-butylamine,[12] and benzylmethylamine[13] add readily to acrylonitrile. The cyclic bases — pyrrolidine, 2-methylpiperidine, 3-methylpiperidine, 4-methylpiperidine, and 2,6-dimethylpiperidine — are other examples of amines which add readily.[14]

Heterocyclic bases containing two imino groups -- such as piperazine, hydrogenated pyrimidines, and hydrogenated perimidines -- react with two molecules of acrylonitrile:[15,16]



Behr and collaborators did not isolate the dicyanoethylation product obtained from piperazine but reduced it directly to the diamine.[15]

Certain amines, especially those in the aromatic and heterocyclic series, react only very slowly with acrylonitrile in the absence of a catalyst. Methylaniline and 1,2,3,4-tetrahydroquinoline do not react appreciably when heated in a sealed tube at 200°. However, in the presence of glacial acetic acid they react at 120-140° to give good yields of the cyanoethylated derivatives.[5]

Substituted acrylonitriles, such as α-methylacrylonitrile and crotononitrile, react less readily than acrylonitrile with the various classes of compounds that undergo cyanoethylation. Bruson stated that it had not been possible to add aldehydes and ketones to α-methylacrylonitrile, although he succeeded in adding to it the strongly basic amine, piperidine.[3] Crotononitrile is much more reactive than α-methylacrylonitrile. Bruson encountered no difficulties in adding amines and nitroparaffins to crotononitrile.[3]

The addition of compounds possessing active hydrogen to acrylate esters to give β-substituted propionates is very similar to the cyano-

ethylation reaction. This addition, which has at times been called carboxyethylation, may be generalized in the following way:

$$HA + CH_2{=}CHCOOR \longrightarrow A{-}CH_2CH_2COOR$$

As in the cyanoethylation, the carboxyethylation reaction is presumed to proceed by 1,4-addition and a subsequent tautomeric shift, yielding a product identical with that which would be obtained by 3,4-addition. Methacrylate esters, acrylate esters having an alkyl substituent on the α-carbon atom, are less reactive and do not undergo all of the addition reactions which can be carried out with acrylate esters.

A wide variety of inorganic and organic molecules possessing labile hydrogen atoms react with acrylate esters. Halogen acids, alcohols, phenols, hydrogen sulfide, mercaptans, thiophenols, ammonia, amines, amino alcohols, nitroparaffins, and compounds with reactive methylene groups have been added to acrylate esters.[17]

The addition of ammonia to acrylate esters was investigated as a means of producing β-alanine, $H_2NCH_2CH_2COOH$, for use in the preparation of pantothenic acid. Ammonia has three active hydrogens and, therefore, forms the secondary and tertiary amino esters as well as the primary amino ester. McElvain and Stork have shown that formation of the primary, secondary, and tertiary amino esters is a reversible reaction.[18]

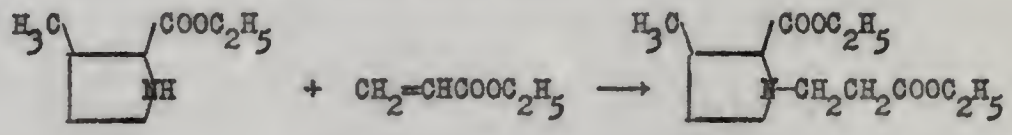
Primary aliphatic amines readily add two moles of acrylate esters to give the tertiary amino esters; no catalyst is required for this addition:

$$RNH_2 + 2\ CH_2{=}CHCOOR' \longrightarrow RN(CH_2CH_2COOR')_2$$

Monoethylamine and ethyl acrylate are reported to give a yield of the adduct of 94 per cent;[19] monomethylamine and ethyl acrylate or methyl acrylate are reported to give a yield of 83-86 per cent.[20,21] Although methacrylate esters are less reactive toward the addition of amines than the acrylate esters, methyl methacrylate and monomethylamine gave a 77 per cent yield of the tertiary amino ester.[21]

In his work with amines Hromatka discovered that yields decrease as branching of chain in a secondary amine increases.[22] This effect of structure and the lesser reactivity of methacrylate esters, compared with acrylate esters, result in greatly reduced yields. He observed that piperidine and ethyl acrylate reacted to give a 96 per cent yield of the tertiary amino ester. Branching of the chain of the secondary amine reduced the yield of the adduct. The yield of the adduct obtained from ethyl-sec-butylamine and ethyl acrylate was 69 per cent when the reaction was carried out at 85-120°. Di-isopropylamine and ethyl acrylate did not react at the boiling point. The reduction of yields with secondary amines of this type and acrylate esters can be compared to a similar reduction in yield with these same amines and acrylonitrile in the cyanoethylation reaction. Weisel and coworkers reacted piperidine with ethyl methacrylate and obtained an 83 per cent yield of the tertiary amino ester by heating the ester with an excess of piperidine at 100°.[23] Despite this success, other workers have found the methacrylate esters to be practically unreactive with aliphatic secondary amines.[21,24] The high order of reactivity of

the heterocyclic amines is shown by the 97 per cent yield in the carboxyethylation of the following pyrrolidine derivative:[25]



Compared to the parent substance, piperazine, the 1-arylpiperazines have been studied in only a limited way. The synthesis of 1-phenylpiperazine was reported simultaneously by different investigators: Pollard and MacDowell prepared this substance by heating aniline hydrochloride at 240° for six to eight hours;[26] Prelog and Driza heated under reflux β,β'-dichlorodiethylamine with a methanolic solution of aniline for 16 hours.[27] Prelog and Blazek extended this reaction of β,β'-dihalodiethylamine salts to other arylamines, other than aniline, to obtain 1-(2-methylphenyl)piperazine, 1-(4-methylphenyl)piperazine, and other 1-arylpiperazines.[28] More recently Wicker and Pollard have synthesized 1-(2-methylphenyl)piperazine, 1-(3-methylphenyl)piperazine, 1-(4-methylphenyl)piperazine, 1-(3-chlorophenyl)piperazine, and other 1-arylpiperazines by heating the appropriate arylamine hydrochloride and diethanolamine under the same conditions that Pollard and MacDowell utilized in making 1-phenylpiperazine.[29]

In preparing synthetic analogs of oxytocic drugs, Phillips prepared the dihydrochloride of methyl 4-benzyl-1-piperazinylpropionate by the addition of 1-benzylpiperazine to methyl acrylate.[30] Adelson and Pollard synthesized alkyl 4-phenyl-1-piperazinylacetates by the action of 1-phenylpiperazine and chloroacetic esters; 4-phenyl-1-

piperazinylethanamide by the action of ammonium hydroxide on ethyl 4-phenyl-1-piperazinylacetate and from 1-phenylpiperazine, chloroethanamide, and sodium carbonate; and 4-phenyl-1-piperazinylethanenitrile from 1-phenylpiperazine, methanal, and hydrogen cyanide and also from 1-phenylpiperazine, chloroethanenitrile, and sodium carbonate.[31]

CHAPTER II

OBJECTIVES, METHODS, AND RESULTS

The object of this investigation has been the study of the addition of 1-arylpiperazines to α,β-unsaturated nitriles and esters. The investigation is limited to the following addenda: 1-phenylpiperazine, 1-(2-methylphenyl)piperazine, 1-(3-methylphenyl)piperazine, 1-(4-methylphenyl)piperazine, and 1-(3-chlorophenyl)piperazine. The acceptors used were acrylonitrile, crotononitrile, methacrylonitrile, ethyl acrylate, butyl acrylate, methyl methacrylate, and ethyl methacrylate. The additions of these compounds are not recorded in the literature; they represent a continuation of the work performed in this laboratory in an effort to synthesize organic molecules which possess physiological activity.

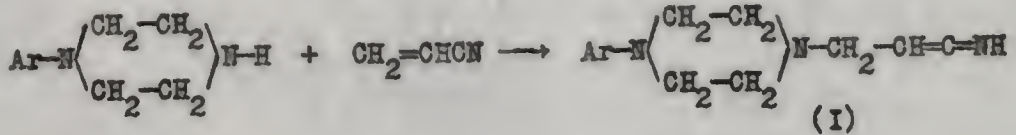
The acceptors outlined above, except crotononitrile, are available on the commercial market. The 1-arylpiperazines, which could not be purchased, and the crotononitrile were prepared in the laboratory as intermediates for this investigation.

The addition of 1-arylpiperazines to acrylonitrile was found to be effected easily by the addition of a slight excess of the nitrile to the 1-arylpiperazine, with stirring, at a temperature higher than room temperature. No catalyst was needed to effect the addition when acrylonitrile was the acceptor molecule. In general, the procedure was:

A fractional mole of the 1-arylpiperazine was heated to 50-55°; while this temperature range and stirring were maintained continuously, a slight excess (0.02 mole, usually) of the nitrile was slowly added to the amine. Occasional external cooling was necessary to maintain this temperature range. Stirring and the temperature recorded above were maintained from 1.5 to 4 hours after the addition of the nitrile was completed. The reaction mixture was allowed to stand for several hours to determine the state of the reaction product. If the mixture was a solid, the solid mass was washed well with water to remove any unreacted nitrile or 1-arylpiperazine. The compound was then air-dried to obtain the crude yield. If the reaction mixture was a viscous oil, the entire contents were purified by distillation under vacuum.

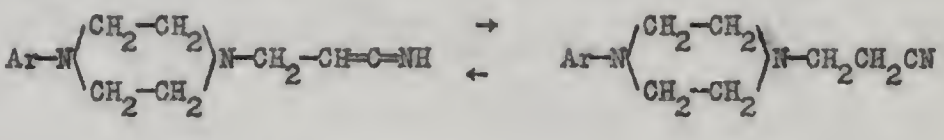
The yields of the purified cyanoethylation reaction product ranged from 48.7 per cent to 86 per cent. The solid products were recrystallized from 95 per cent ethanol; generally it was necessary to recrystallize from two to four times before a product which gave no change in melting point was obtained.

Addition of 1-arylpiperazines to acrylonitrile probably occurs in the usual manner of additions to α,β-unsaturated nitriles. 1-Arylpiporazine adds in the 1- and the 4- positions to produce the imine form (I) of the addition compound, where Ar is an aryl group:



(I)

The imine form is unstable and is rapidly converted to the stable nitrile form (II), with which it exists in reversible equilibrium:



(I) (II)

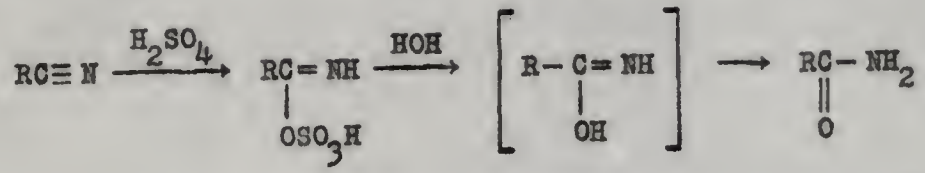
The equilibrium favors the formation of the nitrile, and the major portion of the compound probably exists in this form. As pointed out in the previous chapter, the compound formed is, in effect, a compound obtained by 3,4-addition.

The cases in which additions have been accomplished are enumerated in Chapter III. Crotononitrile and α-methylacrylonitrile did not yield addition products with 1-phenylpiperazine under the experimental conditions which were successful with acrylonitrile; however, it is known that these compounds are very much less reactive than acrylonitrile.

The cyanoethylation products of 1-arylpiperazines are all stable under ordinary conditions. They are readily converted to the amide and amino acid derivatives. In one case, 1-phenyl-(2-cyanoethyl)piperazine, the primary amine was formed by reduction with sodium and ethanol and identified as the phenylthiourea of the amine.

The amide derivatives were prepared by hydration of the nitrile in concentrated sulfuric acid; the iminosulfate formed by the addition

of the acid to the nitrile was then hydrolyzed. The reactions are diagramed below:



The amides were purified by recrystallization from water or from very dilute ethanol. They were obtained in yields ranging between 37 and 66.6 per cent.

The amino acid derivatives were prepared by alkaline hydrolysis in dilute ethanol solution. The usual procedure was to reflux one-tenth mole of the cyanoethylation reaction product with a 50 per cent excess of potassium hydroxide in 60 per cent ethanol. After removal of ethanol and some water by distillation the amino acid was precipitated by careful neutralization with dilute hydrochloric acid. Two cases required the addition of excess hydrochloric acid; these aminoacids were isolated as the hydrochloride salts. These derivatives were purified by recrystallization from water and were obtained in yields between 40.4 and 63.4 per cent. Considerable loss was experienced in purification.

The reduction of 1-phenyl-(2-cyanoethyl)piperazine by sodium and ethanol was accomplished in a manner that is generally known and needs no discussion. However, the 1-phenyl-4-(3-aminopropyl)piperazine was not obtained in a pure condition; a portion of it was isolated and identified as the phenylthiourea derivative.

The additions of 1-arylpiperazines to the acrylate esters were effected by refluxing an excess of the acrylate ester with the piperazine derivative in anhydrous benzene. The mode of addition is analogous to the 1,4-addition which was outlined for ketones and nitriles: A mixture of one-tenth mole of 1-arylpiperazine and two-tenths mole of the acrylate ester in 25 ml. anhydrous benzene was heated under reflux for 18-19 hours. After the solution had cooled it was extracted three times with 3 N hydrochloric acid. The acid solution was made basic with potassium carbonate solution, and the free ester was extracted with ether. An excess of methanolic hydrogen chloride was added to the ether solution, after drying over anhydrous potassium carbonate, to precipitate the hydrochloride of the ester. Purification was accomplished by recrystallization from anhydrous methanol or from a methanol-ether mixture. The crude yields ranged from 71.6 per cent to 98 per cent, while the yields of the purified compounds were between 25 and 72 per cent. The cases in which additions were effected are enumerated in Chapter III.

Under the conditions that yielded addition products with acrylate esters, methyl methacrylate and ethyl methacrylate did not add to 1-phenylpiperazine or 1-(2-methylphenyl)piperazine in yields great enough to permit separation of the hydrochlorides of the esters from the unreacted amines.

From electronic concepts it would appear that the methacrylate esters and methacrylonitrile would not react as readily as the acrylate

esters or acrylonitrile. The methyl group, with reference to hydrogen, releases electrons (– I effect) so that the direction of electron displacement due to the methyl group prevents or decreases the electromeric shift of electrons in the α,β-unsaturated system. This, therefore, reduces the possibility of 1,4-addition.

Analyses of all the addition compounds synthesized were confined to semi-micro Kjeldahl determinations of nitrogen. In those cases in which results of nitrogen determinations required confirmation of molecular formula, chlorine analyses were made by macro, gravimetric precipitation of silver chloride.

CHAPTER III

EXPERIMENTAL PROCEDURES AND TABLES

Intermediates

Acrylonitrile was purchased from American Cyanamid Company. That portion of the nitrile which boiled at 77.3° was used.

Ethyl acrylate was purchased from Carbide and Carbon Chemicals Division of Union Carbide and Carbon Corporation. Methyl methacrylate, ethyl methacrylate, and n-butyl acrylate were purchased from Rohm and Haas Company. Purification of these monomers was not necessary. Methacrylonitrile, which needed no further purification, was obtained from the Shell Development Company.

1-Phenylpiperazine was prepared by the method of Pollard and MacDowell.[26] 1-(2-Methylphenyl)piperazine, 1-(3-methylphenyl)-piperazine, 1-(4-methylphenyl)piperazine, and 1-(3-chlorophenyl)piperazine were prepared by the method of Wicker and Pollard.[29]

Crotononitrile was prepared by the isomerization of allyl cyanide, utilizing the procedure of Bruson.[32] That portion of the distillate boiling at 105-117.5°, which Bruson states is a mixture of the cis- and trans- forms, was used.

Addition Compounds

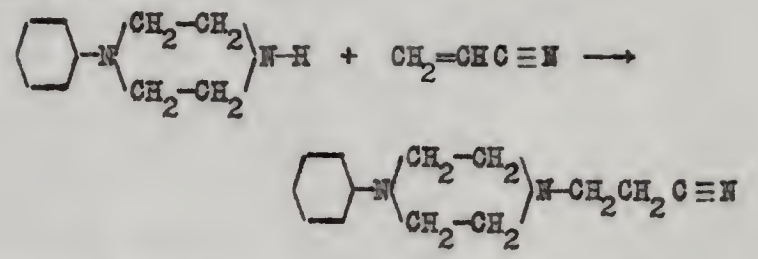
In the pages which follow the method of preparation of each compound is described individually. Following each description is a page on which pertinent data are tabulated.

1. Preparation of 1-Phenyl-4-(2-cyanoethyl)piperazine

One mole (162 g.) of 1-phenylpiperazine was placed in a 1-liter, 3-necked flask equipped with thermometer, mechanical stirrer, and dropping funnel. The 1-phenylpiperazine was heated to 55°, and 1.2 moles (63.5 g.) of acrylonitrile was flowly added. With occasional external cooling the temperature was maintained at 55°. Stirring was continued for one and one-half hours after the addition of acrylonitrile was completed. When cool the reaction mixture was a solid. The solid mass was transferred to a Buchner funnel and washed well with water. The compound was air-dried and recrystallized three times from 95 per cent ethanol, yielding pure white crystals. The yield of the crude product was quantitative, and the yield after three recrystallizations was 86 per cent of theoretical. The purified product was dried in vacuo over concentrated sulfuric acid before it was analyzed. Analysis gave 19.44% N; calculated, 19.52% N. The melting point of the pure compound is 71.3-72.1°.

1. 1-Phenyl-4-(2-cyanoethyl)piperazine

Chemical equation:



Molecular Formula. . . . . $C_{13}H_{17}N_3$

Molecular Weight 215.29

Melting Point. . . . . 71.3-72.1°

Yield of Crude Product . . . . . Quantitative

Yield of Pure Product. 86%

Analysis -- Nitrogen, %:

Calculated 19.52

Found. 19.44

Recrystallizing Solvent. . . . . 95% ethanol

Solubilities:

Water. . . . . .Insoluble

Ethanol. . . . . Fairly Soluble

Ether. . . . . .Soluble

Acetone. . . . . .Soluble

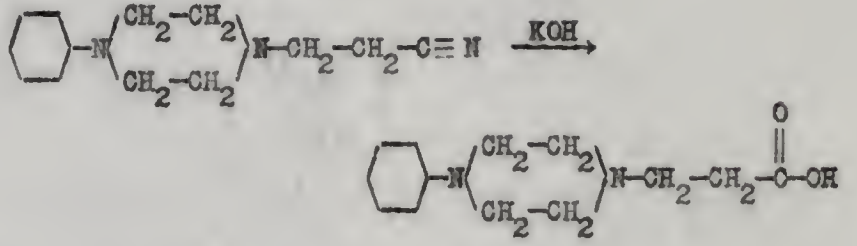
Benzene. . . . . .Soluble

2. Preparation of 1-Phenyl-4-(2-carboxyethyl)piperazine

One-tenth mole (21.5 g.) of 1-phenyl-4-(2-cyanoethyl)-piperazine was heated under reflux with 0.15 mole (8.4 g.) of potassium hydroxide in 250 ml. of 60 per cent ethanol for 4 hours. The condenser was set for distillation, and volatile materials were removed by heating on the steam bath. The residual solution was cooled and extracted once with ether, and the aqueous solution was heated on the steam bath to remove dissolved ether. The cool aqueous solution was carefully neutralized with dilute hydrochloric acid to precipitate the amino acid. The compound was filtered with suction and washed well with water. The product was air-dried and recrystallized two times from water, yielding pure white platelets. The yield of the crude product was 60 per cent of theoretical, and the yield after two recrystallizations was 56.4 per cent of theoretical. The purified product was dried in vacuo over concentrated sulfuric acid before it was analyzed. Analysis gave 12.05% N; calculated, 11.96% N. The melting point of the pure compound was 187.6-188.6°.

2. 1-Phenyl-4-(2-carboxyethyl)piperazine

Chemical Equation:



Molecular Formula. . . . . $C_{13}H_{18}N_2O_2$

Molecular Weight 234.29

Melting Point. . . . . 187.6-188.6°

Yield of Crude Product 60%

Yield of Pure Product. 56.4%

Analysis -- Nitrogen, %:

Calculated. 11.96

Found. 12.05

Recrystallizing Solvent. . . . . Water

Solubilities:

Water. . . . . Insoluble

Ethanol. . . . . Insoluble

Ether . . . . . Insoluble

Acetone . . . . . Insoluble

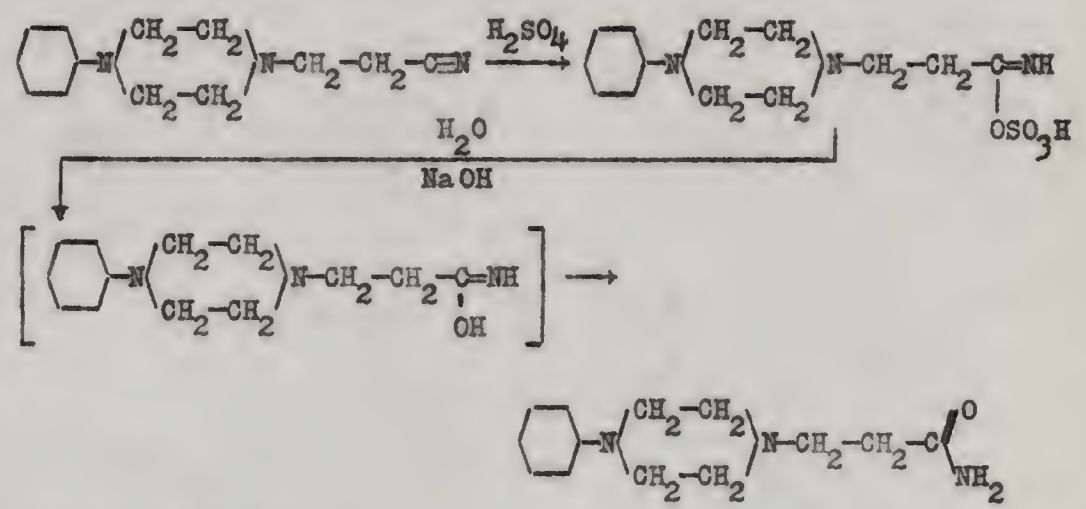
Benzene . . . . . Insoluble

3. Preparation of 1-Phenyl-4-(2-carbonamide-ethyl)piperazine

Forty-three thousandths mole (10 g.) of 1-phenyl-4-(2-cyanoethyl)piperazine was dissolved in 40 ml. of concentrated sulfuric acid. This mixture heated spontaneously. After standing for five minutes at approximately 90° the reaction mixture was cooled and poured into 300 ml. of ice-cold water. The aqueous solution was made basic to litmus with a solution of sodium hydroxide. The compound was filtered with suction and washed well with water. It was air-dried and recrystallized two times from water, yielding silky, white needles. The yield after two recrystallizations was 55.7 per cent. The purified product was dried <u>in vacuo</u> over concentrated sulfuric acid before it was analyzed. Analysis gave 17.98% N; calculated, 18.01% N. The melting point of the pure compound was 170.7-171.6°.

3. 1-Phenyl-4-(2-carbonamide-ethyl)piperazine

Chemical Equation:



Molecular Formula . . . . . $C_{13}H_{19}N_3O$

Molecular Weight. 233.30

Melting Point . . . . . 170.7-171.6°

Yield of Pure Product 55.7%

Analysis — Nitrogen, %:

Calculated 18.01

Found. 17.98

Recrystallizing Solvent . . . . . Water

Solubilities:

Water. . . . . Insoluble

Ethanol. . . . . Slightly soluble

Ether. . . . . Insoluble

Acetone. . . . . Insoluble

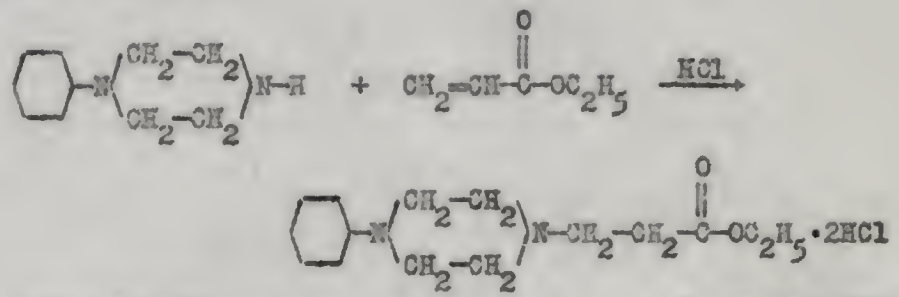
Benzene. . . . . Insoluble

4. Preparation of 1-Phenyl-4-(2-carbethoxyethyl)piperazine dihydrochloride

A mixture of 0.1 mole (16.2 g.) of 1-phenylpiperazine and 0.2 mole (20 g.) of ethyl acrylate in 25 ml. of anhydrous benzene was heated under reflux for 18.5 hours. When cool the reaction mixture was extracted three times with 3 N hydrochloric acid (200 ml.). The acid solution was basified with potassium carbonate solution and then extracted three times with ether. An excess of methanolic hydrogen chloride was added to the dry, filtered ether solution from which the dihydrochloride of the ester precipitated. The compound was filtered with suction, air-dried, and recrystallized three times from anhydrous methanol, yielding pure white crystals. The yield of the crude product was 71.6 per cent of theoretical, and the yield after three recrystallizations was 48.5 per cent of theoretical. The purified product was dried *in vacuo* over concentrated sulfuric acid before it was analyzed. Analysis gave 8.36% N; calculated, 8.36% N. The melting point of the pure compound was 216.2-216.7°.

4. 1-Phenyl-4-(2-carbethoxyethyl)piperazine dihydrochloride

Chemical Equation:



Molecular Formula. . . . . $C_{15}H_{22}N_2O_2 \cdot 2HCl$

Molecular Weight 335.28

Melting Point. . . . . 216.2-216.7°

Yield of Crude Product 71.6%

Yield of Pure Product. 48.5%

Analysis -- Nitrogen, %:

Calculated. 8.36

Found 8.36

Recrystallizing Solvent. . . . . Anhydrous methanol

Solubilities:

Water. . . . . Soluble

Ethanol . . . . . Soluble

Ether . . . . . Insoluble

Acetone . . . . . Insoluble

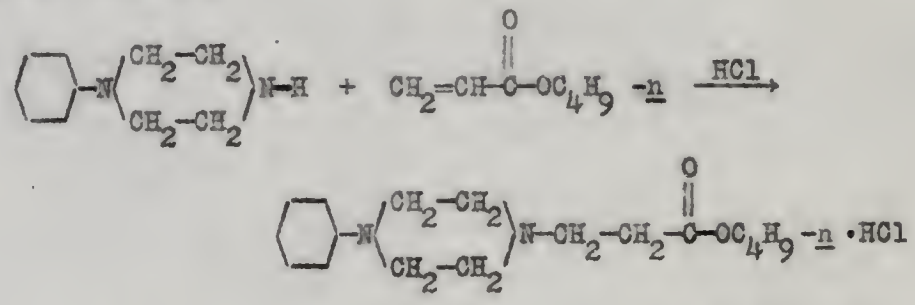
Benzene . . . . . Insoluble

5. Preparation of 1-Phenyl-4-(2-carbo-n-butoxyethyl)piperazine monohydrochloride

A mixture of 0.1 mole (16.2 g.) of 1-phenylpiperazine and 0.2 mole (25.6 g.) of n-butyl acrylate in 25 ml. of anhydrous benzene was heated under reflux for 18 hours. The cool reaction mixture was extracted three times with 3 N hydrochloric acid (200 ml.). On acidification a solid hydrochloride formed in the extraction flask and was dissolved in water with great difficulty. The acid solution was basified with potassium carbonate solution, extracted twice with ether, and the ethereal solution was dried over anhydrous potassium carbonate. An excess of methanolic hydrogen chloride was added to the dry, filtered ether solution from which the monohydrochloride of the ester precipitated. The compound was filtered with suction, air-dried, and recrystallized three times from anhydrous methanol. Treatment with activated carbon during one recrystallization was necessary to yield pure white crystals. The yield of the crude product was 98 per cent of theoretical, and the yield after four recrystallizations was 25 per cent of theoretical. The purified product was dried in vacuo over concentrated sulfuric acid before it was analyzed. Analysis gave 8.39% N; calculated, 8.57% N. The melting point of the pure compound was 211.7-212.2° (decomposition).

5. 1-Phenyl-4-(2-carbo-n-butoxyethyl)piperazine monohydrochloride

Chemical Equation:



Molecular Formula . . . . . $C_{17}H_{26}N_2O_2 \cdot HCl$

Molecular Weight. 326.87

Melting Point . . . . . 211.7-212.2°(dec.)

Yield of Crude Product 98%

Yield of Pure Product 25%

Analysis -- Nitrogen, %:

Calculated 8.57

Found. 8.39

Recrystallizing Solvent . . . . . Anhydrous methanol

Solubilities:

Water. . . . . Soluble

Ethanol. . . . . Soluble

Ether. . . . . Insoluble

Acetone. . . . . Insoluble

Benzene. . . . . Insoluble

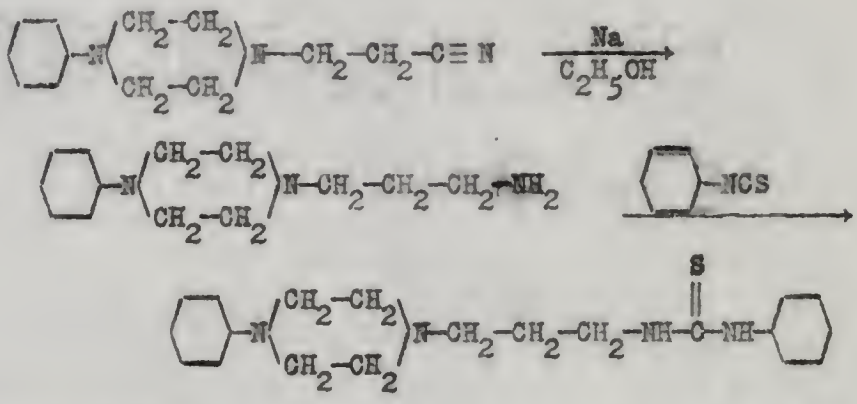
6. Preparation of the Phenylthiourea of 1-Phenyl-4-(3-aminopropyl)-piperazine

Twenty-three thousandths mole (5 g.) of 1-phenyl-4-(2-cyanoethyl)piperazine was dissolved in 120 ml. of absolute ethanol in a 500-ml., round-bottomed flask fitted with a reflux condenser. This solution was reacted with 7 g. of sodium cut into small pieces. When the sodium had disappeared alcohol and water were removed by distillation. Further evaporation of the residual solution produced an oily layer which was a solid when cool. The primary amine was extracted with boiling ether. The ether solution was filtered hot and was allowed to evaporate on the steam bath. An impure, low-melting solid was obtained which was soluble in water, ether, alcohol, and benzene.

Five-tenths gram of this impure amine was mixed with 0.6 ml. of phenyl isothiocyanate. Heat was given off spontaneously. After the initial reaction subsided the reaction mass was melted over a small flame. This was then cooled in an ice-bath until a solid derivative formed. The compound was filtered with suction, washed well with heptane and 50 per cent ethanol, and then recrystallized twice from 95 per cent ethanol, yielding a pure product which melts at 132.6-133.6°. The pure product was dried <u>in vacuo</u> over concentrated sulfuric acid before it was analyzed. Analysis gave 15.61% N; calculated, 15.81% N.

6. Phenylthiourea of 1-Phenyl-4-(3-aminopropyl)piperazine

Chemical Equation:



Molecular Formula . . . . . $C_{20}H_{26}N_4S$

Molecular Weight. 354.50

Melting Point. . . . . 132.6-133.6°

Analysis -- Nitrogen, %:

Calculated 15.81

Found. 15.61

Recrystallizing Solvent . . . . . .95% Ethanol

Solubilities:

Water. . . . . .Insoluble

Ethanol. . . . . .Insoluble

Ether. . . . . .Insoluble

Acetone. . . . . .Soluble

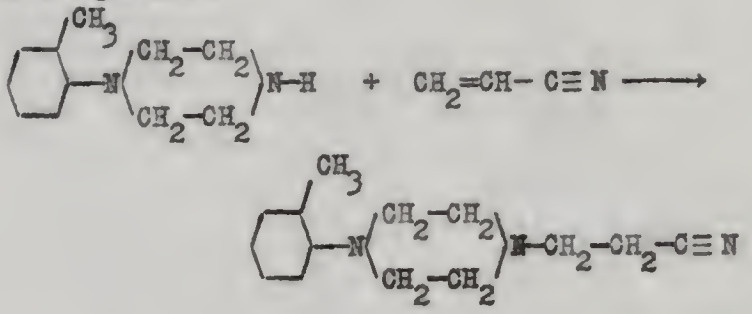
Benzene. . . . . .Soluble

7. Preparation of 1-(2-Methylphenyl)-4-(2-cyanoethyl)piperazine

Four-tenths mole (70.4 g.) of 1-(2-methylphenyl)piperazine was heated to 55° in a 1-liter, 3-necked flask equipped with a thermometer, mechanical stirrer, and dropping funnel. Acrylonitrile (0.42 mole, 22.3 g.) was slowly added during an half-hour while the temperature was maintained between 55-58° by occasional external cooling. After the addition of acrylonitrile was completed stirring was continued for three hours at a temperature of 50-55°. When cool the reaction mixture was a solid. The crude product was transferred to a Buchner funnel and washed well with water. The compound was air-dried. The yield of the crude product was quantitative. A small portion of the crude product was recrystallized three times from 95 per cent ethanol, yielding pure white crystals. The purified product was dried *in vacuo* over concentrated sulfuric acid before it was analyzed. Analysis gave 18.29% N; calculated, 18.32% N. The melting point of the pure compound was 78.4-79.4°.

7. 1-(2-Methylphenyl)-4-(2-cyanoethyl)piperazine

Chemical Equation:



Molecular Formula. . . . . $C_{14}H_{19}N_3$

Molecular Weight 229.31

Melting Point. . . . . 78.4-79.4°

Yield of Crude Product . . . . . Quantitative

Analysis— Nitrogen,%:

Calculated. 18.32

Found. 18.29

Recrystallizing Solvent. . . . . 95% Ethanol

Solubilities:

Water. . . . . Insoluble

Ethanol . . . . . .Slightly soluble

Ether. . . . . .Soluble

Acetone. . . . . .Soluble

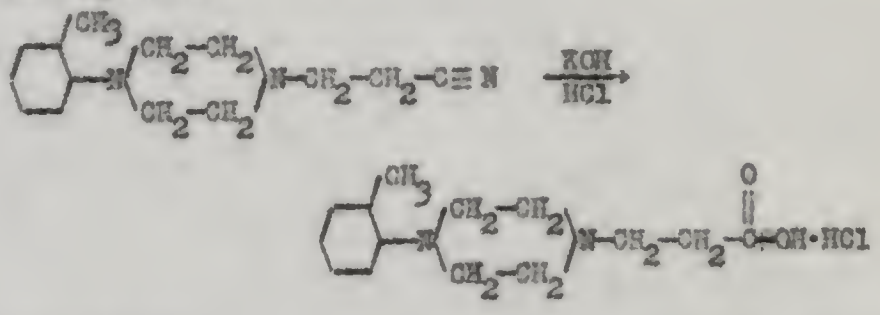
Benzene. . . . . .Soluble

8. Preparation of 1-(2-Methylphenyl)-4-(2-carboxyethyl)piperazine monohydrochloride

One-tenth mole (22.9 g.) of 1-(2-methylphenyl)-4-(2-cyanoethyl)piperazine was heated under reflux with 0.15 mole (8.4 g.) of potassium hydroxide in 250 ml. of 60 per cent ethanol for 4 hours. The condenser was set for distillation, and volatile materials were removed by heating on the steam bath. The residual solution was cooled and extracted once with ether, and then was heated on the steam bath to remove dissolved ether. The cool aqueous solution was acidified with dilute hydrochloric acid to precipitate the amino acid monohydrochloride. The crude compound was filtered with suction and air-dried. Two recrystallizations from water yielded pure white crystals. The yield of the crude product was 86.1 per cent of theoretical, and the yield after two recrystallizations was 63.4 per cent of theoretical. The purified product was dried in vacuo over concentrated sulfuric acid before it was analyzed. Analysis gave 9.91% N; calculated, 9.84% N. Analysis for chlorine gave 12.42% Cl; calculated, 12.45% Cl. The melting point of the pure compound was 221.7-222.7° (decomposition).

8. 1-(2-Methylphenyl)-4-(2-carboxyethyl)piperazine monohydrochloride

Chemical Equation:



Molecular Formula. . . . . $C_{14}H_{20}N_2O_2 \cdot HCl$

Molecular Weight. 284.79

Melting Point. . . . . 221.7-222.7° (dec.)

Yield of Crude Product 86.1%

Yield of Pure Product. 63.4%

Analysis — Nitrogen, %: .

Calculated. 9.84

Found. 9.91

Analysis — Chlorine, %:

Calculated. 12.45

Found 12.42

Recrystallizing Solvent . . . . . Water

Solubilities:

Water. . . . . .Slightly soluble

Ethanol . . . . . Insoluble

Ether . . . . . Insoluble

Acetone . . . . . Insoluble

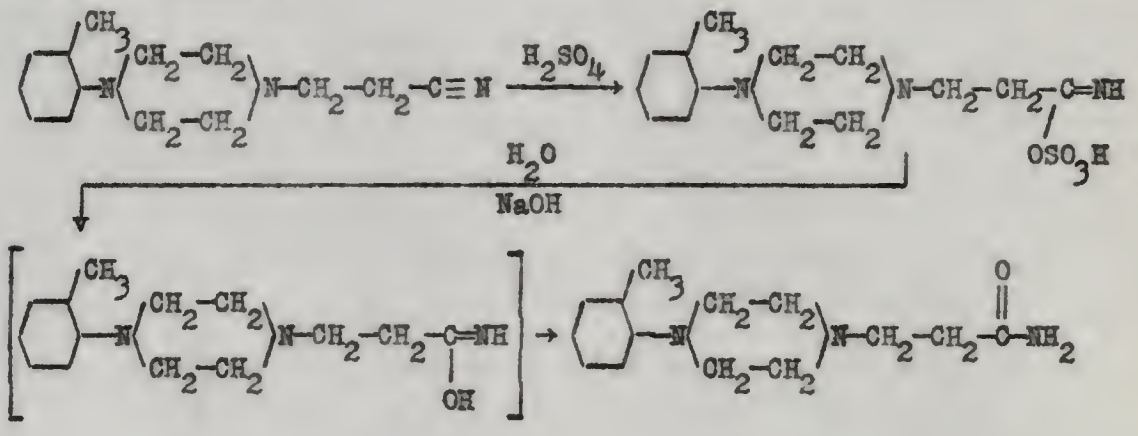
Benzene . . . . . Insoluble

9. Preparation of 1-(2-Methylphenyl)-4-(2-carbonamide-ethyl)piperazine

Forty-four thousandths mole (10 g.) of 1-(2-methylphenyl)-4-(2-cyanoethyl)piperazine was dissolved in 40 ml. of concentrated sulfuric acid. This mixture heated spontaneously. After standing for five minutes at 90-100° the reaction mixture was cooled and poured into 200 ml. of ice-cold water. The aqueous solution was made basic to litmus with a solution of sodium hydroxide. The compound was filtered with suction. The compound was immediately recrystallized two times from 10 per cent ethanol, yielding pure white crystals. The yield after two recrystallizations was 66.6 per cent. The purified product was dried in vacuo over concentrated sulfuric acid before it was analyzed. Analysis gave 17.05% N; calculated, 16.99% N. The melting point of the pure compound was 129.1-129.9°.

9. 1-(2-Methylphenyl)-4-(2-carbonamide-ethyl)piperazine

Chemical Equation:



Molecular Formula. . . . . $C_{14}H_{21}N_3O$

Molecular Weight 247.33

Melting Point. . . . . .129.1-129.9°

Yield of Crude Product . . . . . .Quantitative

Yield of Pure Product. 66.6%

Analysis — Nitrogen, %:

Calculated. 16.99

Found 17.05

Recrystallizing Solvent. . . . . 10% Ethanol

Solubilities:

Water . . . . . Insoluble

Ethanol . . . . . Soluble

Ether. . . . . Insoluble

Acetone. . . . . Insoluble

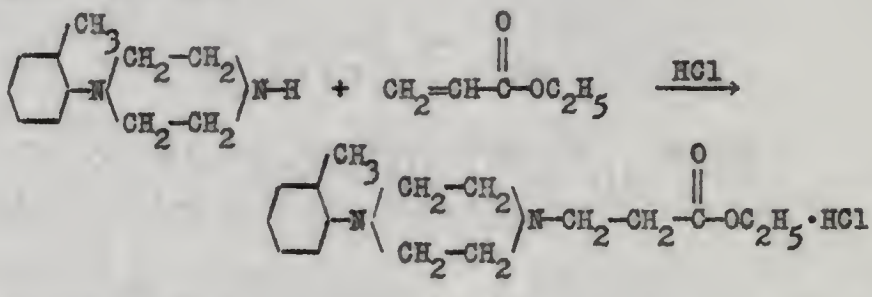
Benzene. . . . . Insoluble

10. Preparation of 1-(2-Methylphenyl)-4-(2-carbethoxyethyl)piperazine monohydrochloride

A mixture of 0.1 mole (17.6 g.) of 1-(2-methylphenyl)-piperazine and 0.2 mole (20 g.) of ethyl acrylate in 25 ml. of anhydrous benzene was heated under reflux for 18 hours. The cool reaction mixture was extracted three times with 3 N hydrochloric acid (200 ml.). The acid solution was basified with potassium carbonate solution and then extracted twice with ether. The ether solution was dried with anhydrous potassium carbonate. An excess of methanolic hydrogen chloride was added to the dry, filtered ether solution from which the hydrochloride of the ester precipitated. The compound was filtered with suction and immediately recrystallized from a methanol-ether solution, yielding pure white crystals. The yield after two recrystallizations was 72 per cent of theoretical. The purified product was dried *in vacuo* over concentrated sulfuric acid before it was analyzed. Analysis gave 8.97% N; calculated, 8.96%. Analysis for chlorine gave 11.52% Cl; calculated, 11.33% Cl. The melting point of the pure compound was 200.7-202.2°.

10. 1-(2-Methylphenyl)-4-(2-carbethoxyethyl)piperazine monohydrochloride

Chemical Equation:



Molecular Formula . . . . . $C_{16}H_{24}N_2O_2 \cdot HCl$

Molecular Weight. 312.83

Melting Point. . . . . 200.7-202.2°

Yield of Pure Product 72%

Analysis -- Nitrogen, %:

Calculated. 8.96

Found. 8.97

Analysis -- Chlorine, %:

Calculated 11.33

Found. 11.52

Recrystallizing Solvent. . . . . Methanol-Ether

Solubilities:

Water. . . . . Slightly soluble

Ethanol. . . . . Slightly soluble

Ether. . . . . .Insoluble

Acetone. . . . . .Insoluble

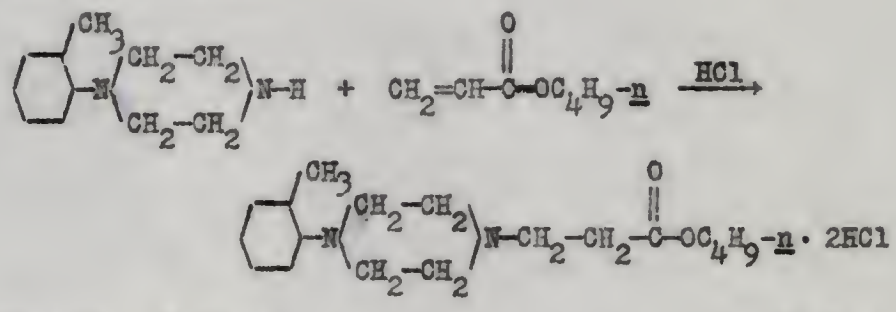
Benzene. . . . . .Insoluble

11. Preparation of 1-(2-Methylphenyl)-4-(2-carbo-n-butoxyethyl)piperazine dihydrochloride

A mixture of 0.1 mole (17.6 g.) of 1-(2-methylphenyl)-piperazine and 0.2 mole (25.6 g.) of n-butyl acrylate in 25 ml. of anhydrous benzene was heated under reflux for 19 hours. The cool reaction mixture was acidified with 200 ml. of 3 N hydrochloric acid. The hydrochloride of the ester precipitated upon acidification. The compound was filtered with suction and air-dried. Basification of the acid filtrate, extraction with ether, and subsequent addition of methanolic hydrogen chloride yielded no appreciable amounts of the hydrochloride of the ester. The crude compound was recrystallized three times from anhydrous methanol, yielding pure white crystals. The yield of the crude product was quantitative, and the yield after three recrystallizations was 53 per cent of theoretical. The purified product was dried in vacuo over concentrated sulfuric acid before it was analyzed. Analysis gave 7.63% N; calculated, 7.43% N. The melting point of the pure compound was 212.7-213.7° (decomposition).

11. 1-(2-Methylphenyl)-4-(2-carbo-n-butoxyethyl)piperazine dihydrochloride

Chemical Equation:



Molecular Formula. . . . . $C_{18}H_{28}N_2O_2 \cdot 2HCl$

Molecular Weight. 377.37

Melting Point. . . . . 212.7-213.7° (dec.)

Yield of Crude Product . . . . . Quantitative

Yield of Pure Product. 53%

Analysis — Nitrogen, %:

Calculated. 7.43

Found. 7.63

Recrystallizing Solvent. . . . . .Anhydrous methanol

Solubilities:

Water . . . . . Insoluble

Ethanol . . . . . .Slightly soluble

Ether . . . . . Insoluble

Acetone . . . . . Insoluble

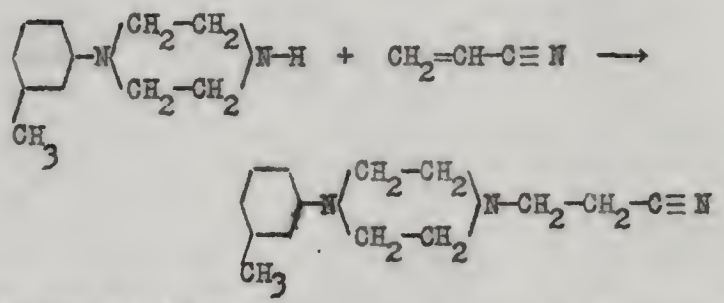
Benzene . . . . . Insoluble

12. Preparation of 1-(3-Methylphenyl)-4-(2-cyanoethyl)piperazine

Four-tenths mole (70.4 g.) of 1-(3-methylphenyl)piperazine was heated to 55° in a 1-liter, 3-necked flask equipped with thermometer, mechanical stirrer, and dropping funnel. Acrylonitrile (0.42 mole, 22.3 g.) was slowly added during an half-hour while the temperature was maintained between 55-58° by occasional external cooling. After addition of acrylonitrile was completed stirring was continued for three hours at 50-55°. The crude reaction mixture was transferred to a Claisen flask and distilled twice at reduced pressure. The desired product was obtained at 197-199° at 1.3 mm. and was a colorless, viscous oil. The yield of pure product was 77.5 per cent of theoretical. Analysis gave 18.04% N; calculated, 18.32% N.

12. 1-(3-Methylphenyl)-4-(2-cyanoethyl)piperazine

Chemical Equation:



Molecular Formula . . . . . $C_{14}H_{19}N_3$

Molecular Weight. 229.31

Boiling Point . . . . . 197-199°/1.3 mm.

Yield After Two Distillations 77.5%

Analysis -- Nitrogen, %:

Calculated 18.32

Found. 18.04

$n^{25}D$ 1.5580

d^{25}_{25}. 1.052

Solubilities:

Water . . . . . Insoluble

Ethanol . . . . . Soluble

Ether . . . . . Soluble

Acetone . . . . . Soluble

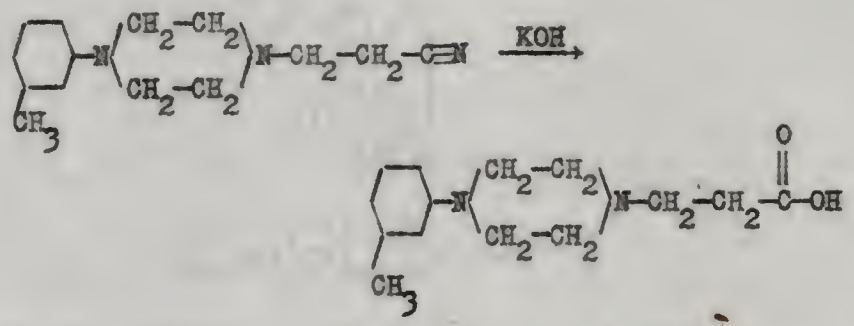
Benzene . . . . . Soluble

13. Preparation of 1-(3-Methylphenyl)-4-(2-carboxyethyl)piperazine

One-tenth mole (22.9 g.) of 1-(3-methylphenyl)-4-(2-cyanoethyl)piperazine was heated under reflux with 0.15 mole (8.4 g.) of potassium hydroxide in 250 ml. of 60 per cent ethanol for 4 hours. The condenser was set for distillation, and volatile materials were removed by heating on the steam bath. The residual solution was cooled and extracted once with ether, and the aqueous solution was heated on the steam bath to remove dissolved ether. The cool aqueous solution was carefully neutralized with dilute hydrochloric acid. Further cooling of the solution and scraping the sides of the beaker caused the crude amino acid to be precipitated as silky, white needles. The compound was filtered with suction and air-dried. Two recrystallizations from water produced a pure product. The yield of the crude product was 69.5 per cent of theoretical, and the yield after two recrystallizations was 40.4 per cent of theoretical. The purified product was dried in vacuo over concentrated sulfuric acid before it was analyzed. Analysis gave 11.02% N; calculated, 11.28% N. The melting point of the pure compound is 138.8-139.8° (softens at 120°).

13. 1-(3-Methylphenyl)-4-(2-carboxyethyl)piperazine

Chemical Equation:



Molecular Formula. . . . . $C_{14}H_{20}N_2O_2$

Molecular Weight 248.32

Melting Point . . . . . 138.8-139.8°

(Softens at . . . . . 120°

Yield of Crude Product 69.5%

Yield of Pure Product. 40.4%

Analysis -- Nitrogen, %:

Calculated. 11.28

Found 11.02

Recrystallizing Solvent. . . . . .Water

Solubilities:

Water . . . . . .Insoluble

Ethanol . . . . . .Insoluble

Ether . . . . . .Insoluble

Acetone . . . . . .Insoluble

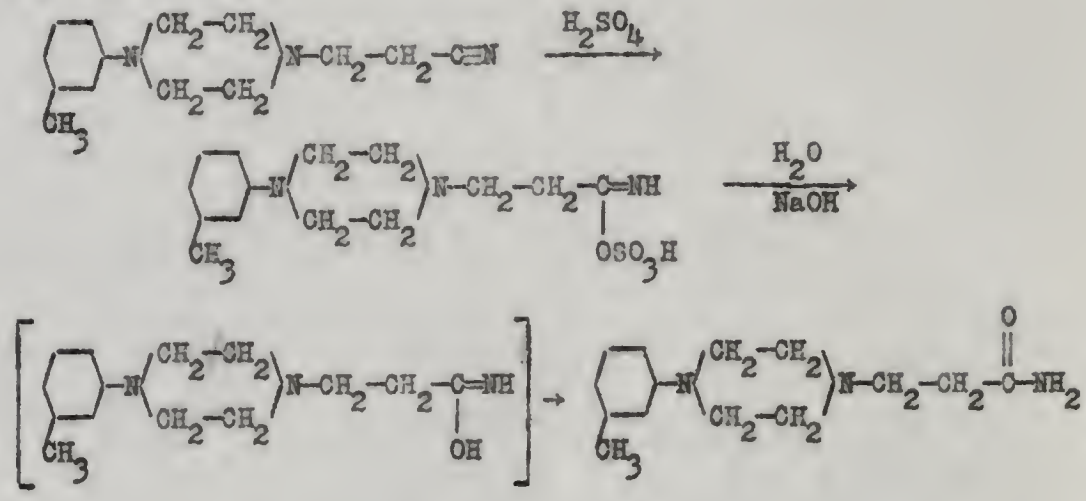
Benzene . . . . . .Insoluble

14. Preparation of 1-(3-Methylphenyl)-4-(2-carbonamide-ethyl)piperazine

Forty-four thousandths mole (10 g.) of 1-(3-methylphenyl)-4-(2-cyanoethyl)piperazine was dissolved in 40 ml. of concentrated sulfuric acid. This mixture heated spontaneously. After standing for five mimutes at 90-100° the reaction mixture was poured into 200 ml. of ice-cold water. The aqueous solution was made basic to litmus with a solution of sodium hydroxide. The compound was filtered with suction. The crude product was air-dried and recrystallized two times from water, yielding pure white crystals. The yield of the crude product was 69.5 per cent, and the yield after two recrystallizations was 37 per cent. The purified product was dried <u>in vacuo</u> over concentrated sulfuric acid before it was analyzed. Analysis gave 16.95% N; calculated, 16.99% N. The melting point of the pure compound was 144.9-145.9°.

14. 1-(3-Methylphenyl)-4-(2-carbonamide-ethyl)piperazine

Chemical Equation:



Molecular Formula	$C_{14}H_{21}N_3O$
Molecular Weight	247.33
Melting Point	144.9-145.9°
Yield of Crude Product	69.5%
Yield of Pure Product	37%

Analysis -- Nitrogen, %:

Calculated	16.99
Found	16.95

Recrystallizing Solvent . . . . . Water

Solubilities:

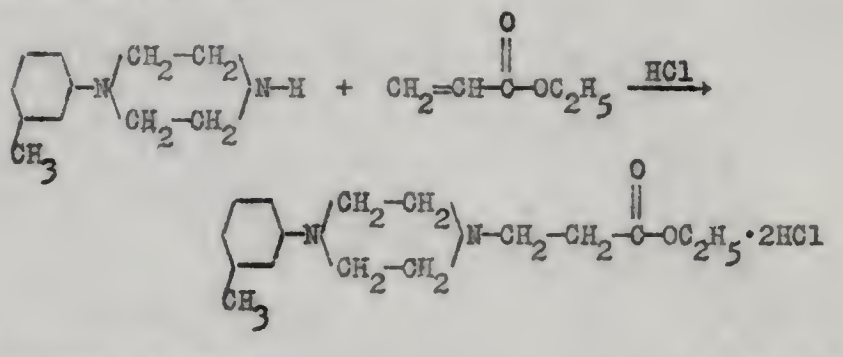
Water	Insoluble
Ethanol	Soluble
Ether	Insoluble
Acetone	Slightly soluble
Benzene	Insoluble

15. Preparation of 1-(3-Methylphenyl)-4-(2-carbethoxyethyl)piperazine dihydrochloride

A mixture of 0.1 mole (17.6 g.) of 1-(3-methylphenyl)-piperazine and 0.2 mole (20.0 g.) of ethyl acrylate in 25 ml. of anhydrous benzene was heated under reflux for 18 hours. The cool reaction mixture was extracted three times with 3 N hydrochloric acid (200 ml.). The acid solution was basified with potassium carbonate solution and then extracted three times with ether. The ether solution was dried with anhydrous potassium carbonate. An excess of methanolic hydrogen chloride was added to the dry, filtered ether solution from which the hydrochloride of the ester precipitated. The compound was filtered with suction, air-dried, and recrystallized two times from anhydrous methanol, yielding pure white crystals. The yield of the crude product was 73.1 per cent of theoretical, and the yield after two recrystallizations was 57.6 per cent. The purified product was dried *in vacuo* over concentrated sulfuric acid before it was analyzed. Analysis gave 8.22% N; calculated, 8.02% N. The melting point of the pure compound was 196.6-197.2°.

15. 1-(3-Methylphenyl)-4-(2-carbethoxyethyl)piperazine dihydrochloride

Chemical Equation:



Molecular Formula . . . . . $C_{16}H_{24}N_2O_2 \cdot 2HCl$

Molecular Weight. 349.30

Melting Point . . . . . 196.6-197.2°

Yield of Crude Product. 73.1%

Yield of Pure Product 57.6%

Analysis — Nitrogen, %:

Calculated 8.02

Found. 8.22

Recrystallizing Solvent . . . . . Anhydrous Methanol

Solubilities:

Water. . . . . .Soluble

Ethanol. . . . . .Soluble

Ether. . . . . .Insoluble

Acetone. . . . . .Insoluble

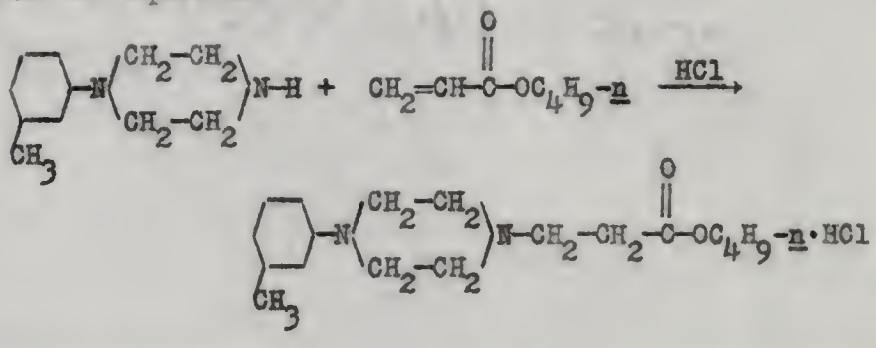
Benzene. . . . . .Insoluble

16. Preparation of 1-(3-Methylphenyl)-4-(2-carbo-n-butoxyethyl)-piperazine monohydrochloride

A mixture of 0.1 mole (17.6 g.) of 1-(3-methylphenyl)-piperazine and 0.2 mole (25.6 g.) of n-butyl acrylate in 25 ml. of anhydrous benzene was heated under reflux for 18 hours. The cool reaction mixture was extracted three times with 3 N hydrochloric acid (200 ml.). The acid solution was basified with potassium carbonate solution and then extracted three times with ether. The ether solution was dried over anhydrous potassium carbonate. An excess of methanolic hydrogen chloride was added to the dry, filtered ether solution from which the monohydrochloride of the ester precipitated. The compound was filtered with suction, air-dried, and recrystallized two times from anhydrous methanol, yielding pure white crystals. The yield of the crude product was 91.8 per cent of theoretical, and the yield after two recrystallizations was 38.2 per cent of theoretical. The purified product was dried in vacuo over concentrated sulfuric acid before it was analyzed. Analysis gave 8.01% N; calculated, 8.22% N. The melting point of the pure compound was 191.5-192.5°.

16. 1-(3-Methylphenyl)-4-(2-carbo-n-butoxyethyl)piperazine monohydrochloride

Chemical Equation:



Molecular Formula . . . . . $C_{18}H_{28}N_2O_2 \cdot HCl$

Molecular Weight. 340.90

Melting Point . . . . . 191.5-192.5°

Yield of Crude Product. 91.8%

Yield of Pure Product 38.2%

Analysis -- Nitrogen,%:

Calculated 8.22

Found. 8.01

Recrystallizing Solvent . . . . . Anhydrous methanol

Solubilities:

Water. . . . . Soluble

Ethanol. . . . . Soluble

Ether. . . . . Insoluble

Acetone. . . . . Insoluble

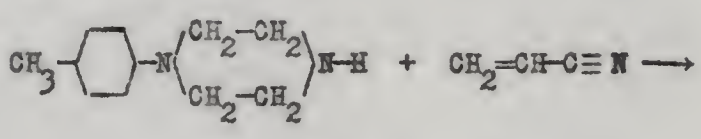
Benzene. . . . . Insoluble

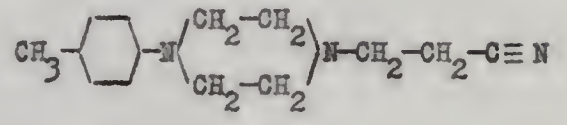
17. Preparation of 1-(4-Methylphenyl)-4-(2-cyanoethyl)piperazine

One-half mole (88 g.) of 1-(4-methylphenyl)piperazine was heated to 55° in a 1-liter, 3-necked flask equipped with thermometer, mechanical stirrer, and dropping funnel. Acrylonitrile (0.52 mole, 27.6 g.) was slowly added during an half-hour while the temperature was maintained at 55° by occasional external cooling. After the addition of acrylonitrile was completed stirring was continued for two hours at 50-55°. The cool reaction mixture was a solid. The crude product was transferred to a Buchner funnel and washed well with water. The crude compound was air-dried and recrystallized once from 95 per cent ethanol, yielding pure white crystals. The yield of the crude product was quantitative, and the yield after one recrystallization was 86 per cent of theoretical. A small amount of this product was recrystallized three times from 95 per cent ethanol to obtain an analytical sample. The purified product was dried <u>in vacuo</u> over concentrated sulfuric acid before it was analyzed. Analysis gave 18.14% N; calculated, 18.32% N. The melting point of the pure compound was 70.4-71.4°.

17. 1-(4-Methylphenyl)-4-(2-cyanoethyl)piperazine

Chemical Equation:





Molecular Formula. . . . . $C_{14}H_{19}N_3$

Molecular Weight 229.31

Melting Point. . . . . 70.4-71.4°

Yield of Crude Product . . . . . Quantitative

Yield of Pure Product. 86%

Analysis -- Nitrogen, %:

Calculated. 18.32

Found 18.14

Recrystallizing Solvent . . . . . .95% Ethanol

Solubilities:

Water. . . . . Insoluble

Ethanol. . . . . Soluble

Ether. . . . . Soluble

Acetone. . . . . Soluble

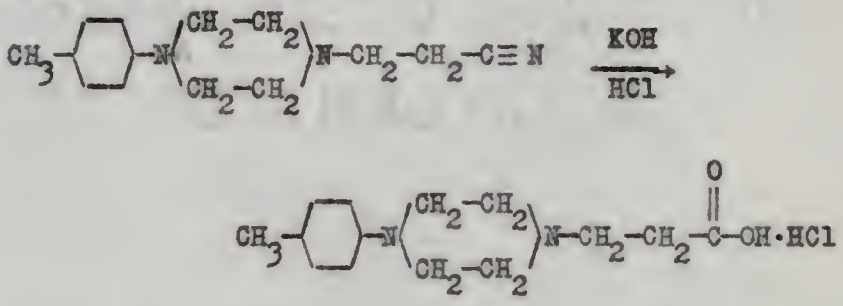
Benzene. . . . . .Soluble

18. Preparation of 1-(4-Methylphenyl)-4-(2-carboxyethyl)piperazine monohydrochloride

One-tenth mole (22.9 g.) of 1-(4-methylphenyl)-4-(2-cyanoethyl)piperazine was heated under reflux with 0.15 mole (8.4 g.) of potassium hydroxide in 250 ml. of 60 per cent ethanol for 4 hours. The condenser was set for distillation, and volatile materials were removed by heating on the steam bath. The residual solution was cooled and extracted once with ether, and the aqueous solution was heated on the steam bath to remove dissolved ether. The cool aqueous solution was acidified with dilute hydrochloric acid to precipitate the amino acid hydrochloride salt. The compound was filtered with suction and air-dried. Two recrystallizations from water yielded pure white crystals. The yield of the product after two recrystallizations was 42.2 per cent of theoretical. The purified product was dried <u>in vacuo</u> over concentrated sulfuric acid before it was analyzed. Analysis gave 9.70% N; calculated, 9.84% N. Analysis for chlorine gave 12.49% Cl; calculated, 12.45% Cl. The melting point of the pure compound was 221.2-222.2°.

18. 1-(4-Methylphenyl)-4-(2-carboxyethyl)piperazine monohydrochloride

Chemical Equation:



Molecular Formula. . . . . $C_{14}H_{19}N_2O_2 \cdot HCl$

Molecular Weight. 284.79

Melting Point. . . . . 221.2-222.2°

Yield of Pure Product. 42.2%

Analysis -- Nitrogen, %:

Calculated. 9.84

Found. 9.70

Analysis -- Chlorine, %:

Calculated. 12.45

Found. 12.49

Recrystallizing Solvent. . . . . Water

Solubilities:

Water. . . . . .Slightly soluble

Ethanol. . . . . Insoluble

Ether. . . . . Insoluble

Acetone. . . . . Insoluble

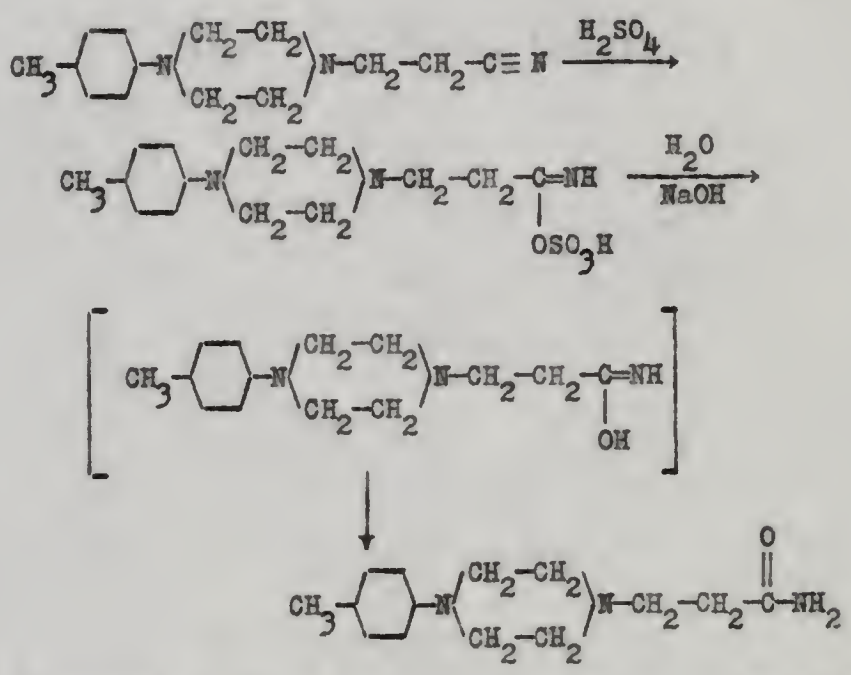
Benzene. . . . . Insoluble

19. Preparation of 1-(4-Methylphenyl)-4-(2-carbonamide-ethyl)piperazine

Forty-four thousandths mole(10 g.) of 1-(4-methylphenyl)-4-(2-cyanoethyl)piperazine was dissolved in 40 ml. of concentrated sulfuric acid. This mixture heated spontaneously. After standing five minutes at 90° the reaction mixture was cooled and poured into 300 ml. of ice-cold water. The aqueous solution was made basic to litmus with a solution of sodium hydroxide. The compound was filtered with suction, air-dried, and recrystallized two times from water, yielding pure white crystals. The yield of the crude product was 79.8 per cent of theoretical, and the yield after two recrystallizations was 46.4 per cent of theoretical. The purified product was dried in vacuo over concentrated sulfuric acid before it was analyzed. Analysis gave 16.87% N; calculated, 16.99% N. The melting point of the pure compound was 191.5-192.5°.

19. 1-(4-Methylphenyl)-4-(2-carbonamide-ethyl)piperazine

Chemical Equation:



Molecular Formula. . . . . $C_{14}H_{21}N_3O$

Molecular Weight 247.33

Melting Point . . . . . .191.5-192.5°

Yield of Crude Product 79.8%

Yield of Pure Product. 46.4%

Analysis -- Nitrogen, %:

Calculated 16.99

Found 16.87

Recrystallizing Solvent . . . . . .Water

Solubilities:

Water. . . . . .Insoluble

Ethanol. . . . . Slightly soluble

Ether. . . . . .Insoluble

Acetone. . . . . .Insoluble

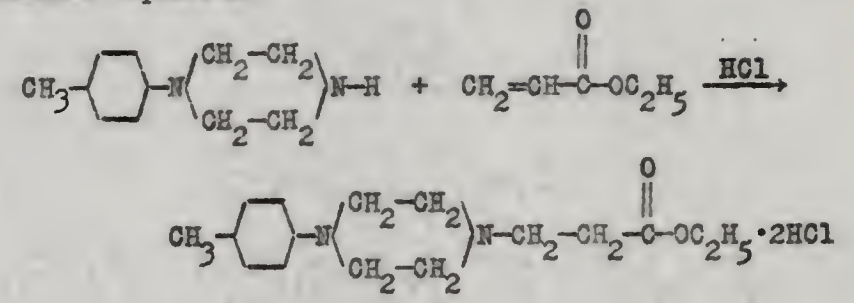
Benzene. . . . . .Insoluble

20. Preparation of 1-(4-Methylphenyl)-4-(2-carbethoxyethyl)piperazine dihydrochloride

A mixture of 0.1 mole (17.6 g.) of 1-(4-methylphenyl)-piperazine and 0.2 mole (20.0 g.) of ethyl acrylate in 25 ml. of anhydrous benzene was heated under reflux for 18 hours. The cool reaction mixture was extracted three times with 3N hydrochloric acid (200 ml.). The acid solution was basified with potassium carbonate solution and then extracted three times with ether. The ether solution was dried with anhydrous potassium carbonate. An excess of methanolic hydrogen chloride was added to the dry, filtered ether solution from which the dihydrochloride of the ester precipitated. The compound was filtered with suction, air-dried, and recrystallized three times from anhydrous methanol, yielding pure white crystals. The yield of the crude product was 48.8 per cent of theoretical, and the yield after three recrystallizations was 25.8 per cent of theoretical. The purified product was dried in vacuo over concentrated sulfuric acid before it was analyzed. Analysis gave 8.05% N; calculated, 8.02% N. The melting point of the pure compound was 203.2-204.2°.

20. 1-(4-Methylphenyl)-4-(2-carbethoxyethyl)piperazine dihydrochloride

Chemical Equation:



Molecular Formula . . . . . $C_{16}H_{24}N_2O_2 \cdot 2HCl$

Molecular Weight. 349.31

Melting Point . . . . . 203.2-204.2°

Yield of Crude Product. 48.8%

Yield of Pure Product 25.8%

Analysis -- Nitrogen, %:

Calculated 8.02

Found. 8.05

Recrystallizing Solvent . . . . . Anhydrous methanol

Solubilities:

Water. . . . . .Soluble

Ethanol. . . . . .Soluble

Ether. . . . . .Insoluble

Acetone. . . . . .Insoluble

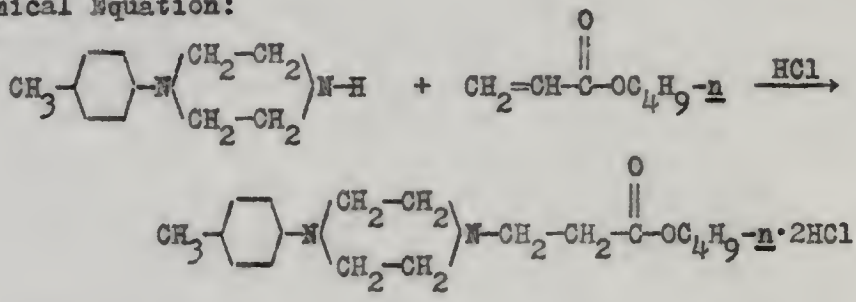
Benzene. . . . . .Insoluble

21. Preparation of 1-(4-Methylphenyl)-4-(2-carbo-n-butoxyethyl)-piperazine dihydrochloride

A mixture of 0.1 mole (17.6 g.) of 1-(4-methylphenyl)-piperazine and 0.2 mole (25.6 g.) of n-butyl acrylate in 25 ml. of anhydrous benzene was heated under reflux for 19 hours. The cool reaction mixture was extracted three times with 3 N hydrochloric acid (200 ml.). The acid solution was basified with ether, and the ethereal solution was dried over anhydrous potassium carbonate. An excess of methanolic hydrogen chloride was added to the dry, filtered ether solution from which the dihydrochloride of the ester precipitated. The compound was filtered with suction, air-dried, and recrystallized three times from anhydrous methanol, yielding pure white crystals. The yield of the crude product was 71.6 per cent of theoretical, and the yield after three recrystallizations was 26.5 per cent of theoretical. The purified product was dried in vacuo over concentrated sulfuric acid before it was analyzed. Analysis gave 7.24% N; calculated, 7.43% N. The melting point of the pure compound was 201.7-202.7°.

21. 1-(4-Methylphenyl)-4-(2-carbo-n-butoxyethyl)piperazine dihydrochloride

Chemical Equation:



Molecular Formula . . . . . $C_{18}H_{28}N_2O_2 \cdot 2HCl$

Molecular Weight 377.37

Melting Point. . . . . 201.7-202.7°

Yield of Crude Product 71.6%

Yield of Pure Product. 26.5%

Analysis -- Nitrogen, %:

Calculated. 7.43

Found 7.24

Recrystallizing Solvent. . . . . .Anhydrous methanol

Solubilities:

Water. . . . . Slightly soluble

Ethanol. . . . . .Soluble

Ether. . . . . .Insoluble

Acetone. . . . . .Insoluble

Benzene. . . . . .Insoluble

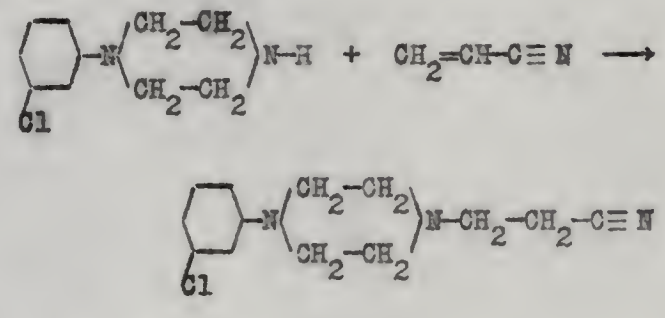
22. Preparation of 1-(3-Chlorophenyl)-4-(2-cyanoethyl)piperazine

Sixty-seven hundredths mole (132.0 g.) of 1-(3-chlorophenyl)piperazine was heated to 55° in a 1-liter, 3-necked flask equipped with thermometer, mechanical stirrer, and dropping funnel. Acrylonitrile (0.69 mole, 36.5 g.) was slowly added during twenty minutes while the temperature was maintained between 50-55°. by occasional external cooling. After the addition of acrylonitrile was completed stirring was continued for four hours at 50-55°.

The reaction mixture was transferred to a 200 ml. round-bottomed flask attached to an efficient fractionation column; and after de-gassing at 5 mm. pressure, distillation was conducted at 1.3 mm. The desired product was obtained at 210.6-212.6° at 1.3 mm. as a slightly yellow-colored, viscous oil. The yield of pure product was 48.7 per cent of theoretical. Analysis gave 16.80% N; calculated, 16.83% N.

22. 1-(3-Chlorophenyl)-4-(2-cyanoethyl)piperazine

Chemical Equation:



Molecular Formula. . . . . $C_{13}H_{16}N_3Cl$

Molecular Weight 249.74

Boiling Point. . . . . 210.6-212.6°/1.3 mm.

Yield after Distillation 48.7%

Analysis -- Nitrogen, %:

Calculated. 16.83

Found. 16.80

$n^{25}D$ 1.5762

d^{25}_{25}. 1.168

Solubilities:

Water. . . . . Insoluble

Ethanol. . . . . Soluble

Ether. . . . . Soluble

Acetone. . . . . Soluble

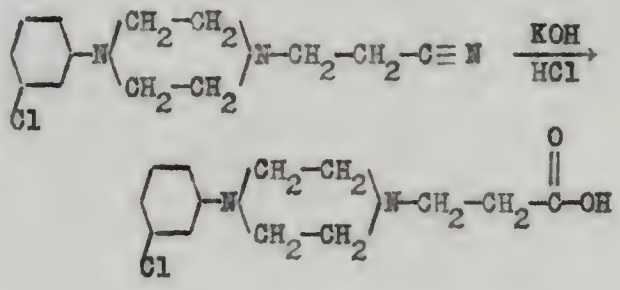
Benzene. . . . . Soluble

23. Preparation of 1-(3-Chlorophenyl)-4-(2-carboxyethyl)piperazine

One-tenth mole (24.97 g.) of 1-(3-chlorophenyl)-4-(2-cyanoethyl)piperazine was heated under reflux with 0.15 mole (8.4 g.) of potassium hydroxide in 250 ml. of 60 per cent ethanol for 5.25 hours. The condenser was set for distillation, and volatile materials were removed by heating on the steam bath. The residual solution was cooled and extracted once with ether, and the aqueous solution was heated on the steam bath to remove dissolved ether. The cool aqueous solution was carefully neutralized with dilute hydrochloric acid. On cooling the amino acid precipitated. The compound was filtered with suction and air-dried. The crude material was decolorized with activated carbon and recrystallized from very dilute ethanol (10 per cent) to yield pure white crystals. The yield of the crude product was quantitative, and the yield after three recrystallizations was 62 per cent of theoretical. The purified product was dried in vacuo over concentrated sulfuric acid before it was analyzed. Analysis gave 10.52% N; calculated, 10.43% N. The melting point of the pure compound was 164.4-165.3°.

23. 1-(3-Chlorophenyl)-4-(2-carboxyethyl)piperazine

Chemical Equation:



Molecular Formula . . . . . $C_{13}H_{17}N_2O_2Cl$

Molecular Weight. 268.75

Melting Point. . . . . 164.4-165.3°

Yield of Crude Product. . . . . Quantitative

Yield of Pure Product 62.0%

Analysis -- Nitrogen, %:

Calculated 10.43

Found. 10.52

Recrystallizing Solvent . . . . . 10% Ethanol

Solubilities:

Water. . . . . Insoluble

Ethanol. . . . . Insoluble

Ether. . . . . Insoluble

Acetone. . . . . Insoluble

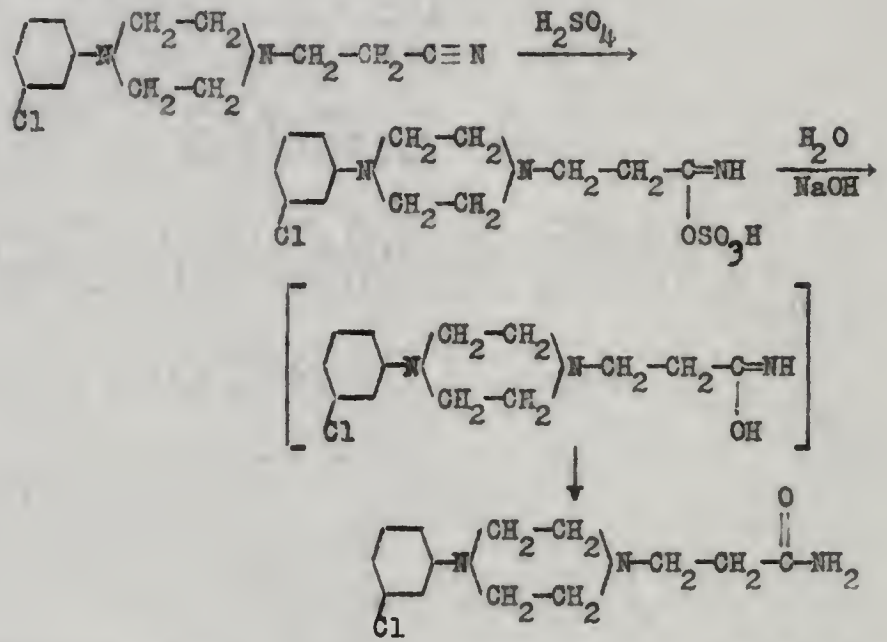
Benzene. . . . . Insoluble

24. Preparation of 1-(3-Chlorophenyl)-4-(2-carbonamide-ethyl)piperazine

Four one-hundredths mole (10 g.) of 1-(3-chlorophenyl)-4-(2-cyanoethyl)piperazine was dissolved in 40 ml. of concentrated sulfuric acid. This mixture heated spontaneously. After standing for five minutes at 90-100° the reaction mixture was cooled and poured into 200 ml. of ice-cold water. The aqueous solution was made basic to litmus with a solution of sodium hydroxide. The compound was filtered with suction and washed well with water. Filtration was extremely slow. The compound was air-dried and recrystallized two times from 15 per cent ethanol, yielding pure white plates. The yield after two recrystallizations was 59.9 per cent of theoretical. The purified product was dried in vacuo over concentrated sulfuric acid before it was analyzed. Analysis gave 15.67% N; calculated, 15.70% N. The melting point of the pure compound was 147.5-148.2°.

24. 1-(3-Chlorophenyl)-4-(2-carbonamide-ethyl)piperazine

Chemical Equation:



Molecular Formula . . . . . $C_{13}H_{18}N_3OCl$

Molecular Weight. 267.76

Melting Point. . . . . .147.5-148.2°

Yield of Pure Product 59.9%

Analysis -- Nitrogen, %:

Calculated 15.70

Found. 15.67

Recrystallizing Solvent . . . . . 15% Ethanol

Solubilities:

Water. . . . . Insoluble

Ethanol. . . . . Insoluble

Ether. . . . . Insoluble

Acetone. . . . . Insoluble

Benzene. . . . . Insoluble

SUMMARY

Twenty-four new addition compounds and derivatives of 1-phenylpiperazine, 1-(2-methylphenyl)piperazine, 1-(3-methylphenyl)-piperazine, 1-(4-methylphenyl)piperazine, or 1-(3-chlorophenyl)-piperazine with acrylonitrile, ethyl acrylate, or n-butyl acrylate have been prepared and studied. Data on these compounds are summarized in Table I.

Four α,β-unsaturated nitriles and esters which did not react with 1-phenylpiperazine under conditions which were successful with acrylonitrile and unsubstituted acrylate esters are:

1. Crotononitrile
2. α-Methylacrylonitrile
3. Methyl methacrylate
4. Ethyl methacrylate

Methyl methacrylate and ethyl methacrylate did not react with 1-(2-methylphenyl)piperazine under conditions which were successful with unsubstituted acrylate esters.

TABLE I

SUMMARY OF PHYSICAL CONSTANTS AND ANALYTICAL DATA FOR SOME 1,4-SUBSTITUTED PIPERAZINES

Compound	Yield, %	M.p., °C.	N, %		Additional Data
			Calc.	Found	
1-Phenyl-4-(2-cyanoethyl)piperazine	86.0	71.3-72.1	19.52	19.44	
1-Phenyl-4-(2-carboxyethyl)piperazine	56.4	187.6-188.6	11.96	12.05	
1-Phenyl-4-(2-carbonamide-ethyl)piperazine	55.7	170.7-171.6	18.01	17.98	
1-Phenyl-4-(2-carbethoxyethyl)piperazine dihydrochloride	48.5	216.2-216.7	8.36	8.36	
1-Phenyl-4- (2-carbo-n-butoxyethyl)piperazine monohydrochloride	25.0	211.7-212.2[a]	8.57	8.39	
Phenylthiourea of 1-Phenyl-4-(3-aminopropyl)-piperazine	–	132.6-133.6	15.81	15.61	
1-(2-Methylphenyl)-4-(2-cyanoethyl)piperazine	....[b]	78.4-79.4	18.32	18.29	
1-(2-Methylphenyl)-4-(2-carboxyethyl)piperazine monohydrochloride	63.4	221.7-222.7[a]	9.84	9.91	Cl,%: Calc., 12.45; Found, 12.42
1-(2-Methylphenyl)-4-(2-carbonamide-ethyl)-piperazine	66.6	129.1-129.9	16.99	17.05	

[a]Decomposition. [b]Crude Yield was quantitative.

TABLE I (Continued)

Compound	Yield, %	M.p., °C.	N, %		Additional Data
			Calc.	Found	
1-(2-Methylphenyl)-4-(2-carbethoxyethyl)-piperazine monohydrochloride	72.0	200.7-202.2	8.96	8.97	Cl, %: Calc., 11.32; Found, 11.52
1-(2-Methylphenyl)-4-(2-carbo-n-butoxyethyl)-piperazine dihydrochloride	53.0	212.7-213.7[a]	7.43	7.63	
1-(3-Methylphenyl)-4-(2-cyanoethyl)piperazine	77.5	.....	18.32	18.04	B.p.: 197-199°/1.3 mm. $n^{25}D$: 1.5580; d^{25}_{25}: 1.052
1-(3-Methylphenyl)-4-(2-carboxyethyl)piperazine	40.4	138.8-139.8[c]	11.28	11.02	
1-(3-Methylphenyl)-4-(2-carbonamide-ethyl)-piperazine	37.0	144.9-145.9	16.99	16.95	
1-(3-Methylphenyl)-4-(2-carbethoxyethyl)-piperazine dihydrochloride	57.6	196.6-197.2	8.02	8.22	
1-(3-Methylphenyl)-4-(2-carbo-n-butoxyethyl)-piperazine monohydrochloride	38.2	191.5-192.5	8.22	8.01	
1-(4-Methylphenyl)-4-(2-cyanoethyl)piperazine	86.0	70.4-71.4	18.32	18.14	
1-(4-Methylphenyl)-4-(2-carboxyethyl)piperazine monohydrochloride	42.2	221.2-222.2	9.84	9.70	Cl, %: Calc., 12.45; Found, 12.49
1-(4-Methylphenyl)-4-(2-carbonamide-ethyl)-piperazine	46.4	191.5-192.5	16.99	16.87	

[c] Softens at 120°.

TABLE I (Continued)

Compound	Yield, %	M.p., °C.	N, %		Additional Data
			Calc.	Found	
1-(4-Methylphenyl)-4-(2-carbethoxyethyl)-piperazine dihydrochloride	25.8	203.2-204.2	8.02	8.05	
1-(4-Methylphenyl)-4-(2-carbo-n-butoxyethyl)-piperazine dihydrochloride	26.5	201.7-202.7	7.43	7.24	
1-(3-Chlorophenyl)-4-(2-cyanoethyl)piperazine	48.7	.....	16.83	16.80	B.p.: 210.6-212.6°/1.3 mm. $n^{25}D$: 1.5762; $d^{25}25$: 1.168
1-(3-Chlorophenyl)-4-(2-carboxyethyl)-piperazine	62.0	164.4-165.3	10.43	10.52	
1-(3-Chlorophenyl)-4-(2-carbonamide-ethyl)-piperazine	59.9	147.5-148.2	15.70	15.67	

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BIOGRAPHICAL ITEMS

Robert Robbins was born in Gainesville, Florida, on June 11, 1916. He pursued his undergraduate studies at the University of Florida and was awarded the degree of Bachelor of Science in June, 1936.

Mr. Robbins entered the Graduate School of the University of Florida in June, 1936. In February, 1938, he entered the Graduate School of Cornell University, returning to the University of Florida in September, 1939. He continued his graduate study until he entered the U. S. Army in July, 1940. He was honorably discharged, as a Captain, from the U. S. Army in November, 1945. In September, 1949, Mr. Robbins resumed his graduate studies in chemistry at the University of Florida.

From January, 1946, to September, 1949, Mr. Robbins was employed by the Division of Tests, Florida State Road Department, at Gainesville, Florida, where he became Chief Chemist before returning to the University of Florida.

Mr. Robbins is a member of Gamma Sigma Epsilon, honorary chemical fraternity, and Tau Epsilon Phi, a social fraternity. He held a graduate assistantship in chemistry from September, 1949, to October, 1950, and a graduate fellowship from October, 1950, until completion of the requirements for the degree of Doctor of Philosophy.

Committee Report

This dissertation was prepared under the direction of the Chairman of the candidate's Supervisory Committee and has been approved by all members of the Committee. It was submitted to the Graduate Council and was approved as partial fulfilment of the requirements for the degree of Doctor of Philosophy.

Date June 11, 1951

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