The writer wishes to express
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# SOME SULFANILAMIDE DERIVATIVES

by

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TABLE OF CONTENTS

# INTRODUCTION

The preparation and the study of some sulfanilamide derivatives was begum because of the great progress in chemotherapy now being made, and the usefulness of the sulfa compounds especially, in combating various forms of infection. Even though it is realized that the number of compounds synthesized by the chemist is far in excess of those that have been actually investigated for their medicinal value, more and more compounds are steadily being made.

It was with a hope that perhaps some of the compounds synthesized in this study might be investigated further for their medicinal value that this work was first begun.

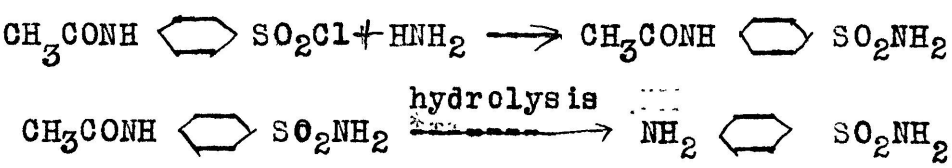
## RESUME OF SOME PREVIOUS INVESTIGATIONS

The preparation of sulanilamide dates back to the work of P. Gelmo[1] and of G. Schroeter[2].

Schroeter was primarily interested in dyes and consequently also in sulfanilic acid since many of the technical dyes contain either a sulfonic acid or a carboxylic acid grouping together with an amino or a hydroxy grouping. His work consisted of the acetylation of sulfanilic acid for the protection of the amino group which was accomplished by the reaction of acetic anhydride on dry sodium salt of sulfanilic acid. He also gave the details of converting the acetylated sodium salt of sulfanilic acid into the acid chloride. This he accomplished by the use of phosphorus pentachloride. Further, he coupled the acid chloride with p-phenetidine and found the reaction to proceed smoothly. The resulting compound was perhaps one of the first sulfanilamide derivative to have been made.

1. P.Gelmo Journal for Praktische Chemie 77 372 1908
2. G.Schroeter Ber. 39 1559 1906

In 1908 P.Gelmo of the technical high school of Vienna, having read Schroeter's studies tried to devise a method to de-acetylate the compound after its coupling reaction through the acid chloride. He coupled p-acetylamino benzene sulfonyl chloride with ammonia, and then hydrolyzed the resulting compound to obtain sulfanilamide. The equation for this reaction is as follows:



In like manner he prepared ortho, meta, and para toluidids, the anilide, and the naphtidids.

Sulfanilamide does not seem to have been of very great importance except as a dye intermediate until the year 1935. Only a few articles are recorded in the literature.

In 1915 W.Fuchs[1] reports on the preparation of 2-6 dibromo aniline in which he used sulfanilamide as an intermediate.

1. W.Fuchs. M.36 124 1915

Then again in 1917 Jacobs and Heidelberger[1] reported a reaction between sulfanilamide and chloroacetylchloride. They were investigating amides, uramine compounds, and ureides containing and aromatic nucleus.

Two years later the same authors[2] used sulfanilamide to prepare a dye, p-sulfonamido-phenylazo-hydrocupreine.

Para acetylaminobenzenesulfonylchloride, which is used in the synthesis of many of the sulfa derivatives was first prepared by J.Stewart[3] in 1922, from the reaction of acentanilide and chlorosulfuric acid. Gilman[4] also describes this method although the process had been known earlier.

Resin formation from the reaction of sulfanilamide and formaldehyde has been reported through a German patent[5] and by Wood and Battye[6]. The resins are hard and brittle.


1. Jacobs& Heidelberger J.A.C.S. 39 2429 1917
2. Jacobs & Heidelberger J.A.C.S. 41 2145 1919
3. J.Stewart J. Chem. Soc. 121 2558 1922
4. H.Gilman Org. Synthesis Collective Vol. 1 p.8.
5. German Patent 714,560 1931.
6. Wood, Battye J. Soc. Chem. Ind. 52 346 1933

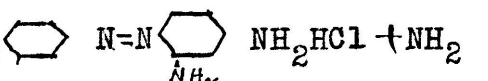
The report of Domagk[1] who was working with azo dyes, describes the protective action of prontosil against hemolytic streptococcus infection even after administering but one dose. This work has been confirmed by various other investigators[2,3,4].

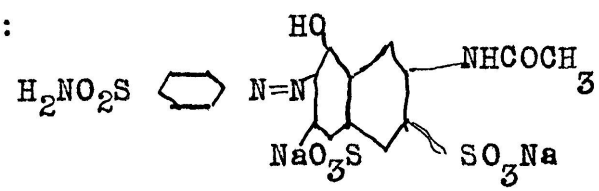
Later in the work of Trefouels, Nitti, and Bovet,[5] it was shown that the activity resided in the sulfanilamide part of the molecule. The hydrochloride of sulfanilamide was tested on mice inoculated with hemolytic streptococci isolated from a fatal case of puerperal sepsis. It proved just as effective in the treatment as prontosil itself.

These two articles led to a frenzied search for new derivatives of the parent substance sulfanilamide. Almost every class of sulfanilamide derivatives has been investigated. A good summary of these derivatives up to 1940 has been given by E.H.Northey[6]. The chemical synthesis of derivatives

1. G.Domagk Deutsche Med. Woch. 61 250 1935
2. Levaditi, Vaisman C.R.Ac. Sc. 200 1694 1935
3. ColeBrook & Kenny The Lancet 230 1279 1936
4. Goissedet, Despois, Gailliot, Mayer. C.R. Soc. of Biol. 121 1082 1936
5. Trefouet, Nitti, Bovet. Compt. Rend. Soc. of Biol. 120 756-758 1935
6. E.H.Northey Che. Reviews. 27 85-197 1940.

has far surpassed the determination of their chemotherapeutic value.

As early as 1935 K.Imhauser[1] reported the use of prontosil in the treatment of septic illness, erysipelas, and infections of the urinary tract. Prontosil itself is  and is only slightly soluble in water (.25%)/ Prontosil soluble, formerly issued under tha name Streptozon S. is the disodium salt of 4' sulfamidophenyl-2-azo-7-acetylamino-1-hydroxynaphthalene 3:6 disulphoric acid and is represented by the formula:



This compound is water soluble up to 4%. It was used by Colebrook and Kenny to confirm the work of Domagk.

Buttle, Gray, Stephenson[2] in 1936 state that para aminolbenzenesulfonamide will protect mice against strepl infection and has the same activity as prontosil, but it is less toxic when given by

1. K.IMhauser Med. Klin. 31 282-285 1935
Buttle, Gray, Stephenson, The Lancet 230 1286 1936

mouth so that it is possible to obtain better protection by giving larger doses. They demonstrated some protection of mice against meningococcal infection but could not demonstrate it against staph. or pneumococci. They also found that an increase in the number of sulfonamide groups attached to the benzene nucleus to three, was accompanied not by an increase but by a decrease of streptococcicidal activity. The anilide of sulfanilic acid is as active as the amide.

The preparation of a benzthiazole derivative of the anilide will be discussed later in a different section of this thesis.

In a later work Trefouel, Nitti, and Bovet[1] in reporting on sulfanilamide made the following assertions:

1. That the ortho and meta isomers of sulfanilamide are inactive.
2. Replacing the $SO_2NH_2$ by $NH_2$, $CH{:}SO_3H$; as $O_3H_2$: $CONH_2$ causes the compound to become inactive.

1 Trefouel. Nitti, and Bovet. Ann. de Institit. Pasteur 58 30-47 1937

3. Alcoholation of the sulfamide group diminishes the activity at least for the higher alcohols.
4. The free para $NH_2$ is much more active than the $CH_3CONH$.
5. If the para $NH_2$ is replaced by OH or $CH_3$ then only the OH has a feeble reaction. The $CH_3$ shows no protection.
6. The substitution of the hydrogen in the para-amine group yields compounds with more or less activity.
7. Substitution in the ring leads generally to inactivity.

In order to illustrate the wide application of the sulfonamide drugs in chemotherapy the following summary[1] is included:

" The therapeutic effect of sulfanilamide ( or allied compounds) is excellent in experimental mouse infections due to beta hemolytic streptococcus, meningococcus and pneumococcus. It is still good, but less satisfactory in mouse infections produced by strains of gonococcus and staphylococcus: proteus, colon, typhoid, and parathyphoid organisms: the Sonne strain of dysentery bacillus; a strain of

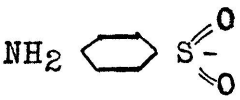
1. Marshall Science 91 345-350 1940

Listerella; Hemophilus influenza, the Welch bacillus and certain members of the Pasteurella group, including the plague bacillus. Prolongation of life, with few or no survivals, is reported for infections produced by strains of Salmonella typhimurium, Friedlander's bacillus: Pasteruella pseudotuberculosis and the Anthrax bacillus. A definite inhibitory effect on the development of experimental tuberculosis in the guinea pig and rabbit, an alteration of the natural cause of experimental Brucella infections in guinea pigs and Bacterium necrophorum infection in rabbits, and the remarkable curative effect in certain human urinary tract infections also attest to the widespread antibacterial powers of the sulfonamide group of drugs. In protozoan infections, the only conclusive evidence of effectiveness is that reported for malarial infection of monkeys. In virus infections, the results so far obtained are negative or inconclusive."

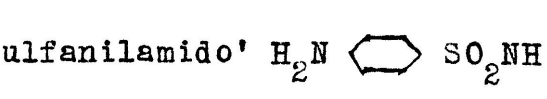
The naming of the derivatives of sulfanilamide follows the system proposed by Crossley, Northey and Hultquist[1] which has been generally accepted.

1. Crossley, Northey, Hultquist. J.A.C.S. 60 2217 1938

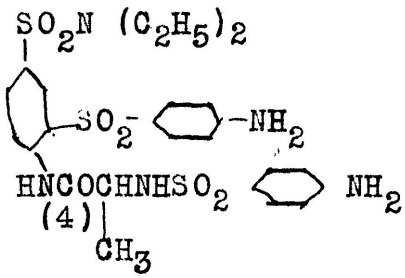
The simple derivatives are named as derivatives of sulfanilamide and to distinguish between the nitrogens the groups substituted in the amido group are classed as $N^1$ substituents, while those of the amino group are $N^4$ substituents. Other radicals which are useful are the 'sulfanilyl'



and the 'sulfanilamido'



To illustrate the usefulness of the radicals and nomenclature the following compound



may be named $N^1$, $N^1$ diethyl-$N^4$- (2-sulfanilamido-propionyl)-3-sulfanilsulfanilamide.

Some of the derivatives of sulfanilamide reported in the literature have been studied and a few of the conclusions are recorded here.

The nuclear substituted sulfanilamides are generally inactive and also more difficult to make. Many $N^1$ substituted sulfanilamides have been made.[1]

1. Fourneau, Trefouel, Nitti, & Bovet. Comp. R. Soc. Biol. 122 258 1936

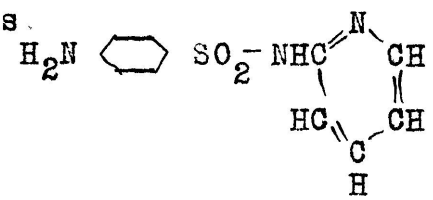
The series of $N^1$-alkyl and $N^1$-dialkyl sulfanilamides show protective activity about the same as sulfanilamide up to the di-ethyl derivative. For the higher alkyl derivatives the activity is again less. $N^1$hydroxyalkyl and $N^1$ carboxyalkyl sulfanilamides are not very active when compared to sulfanilamide and their esterification destroys this activity yet $N^1$-sulfanilglycine $H_2N$⟨⟩$SO_2NHCH_2COOH$ has found a sale in Sweden under the name of Streptasol.

The $N^1$-isocyclic substituted sulfanilamides show as a rule very little protective activity. Gelmo synthesized $N^1$-phenylsulfanilamide when he first made sulfanilamide. The activity of both is about the same yet when chlorine is introduced into the phenyl group whether ortho or para, the compound loses its activity. Again when[2] a hydroxyl group is placed in the para position of the phenyl group the activity remains although if the OH is in the ortho or meta position the activity decreases. It is interesting to note that the $N^1$-p-nitro phenyl sulfanilamide is more active but also more toxic than sulfanilamide.

1.Fourneau, Trefouel, Nitti, & Bovet. Comp R. Soc. Biol. 122 652 1936
2. Northey. Chem. Reviews 27 96 1940 table 3.

Crossley et al.[1] report that the 2-sulfanilamide benzoic acid is slightly more active than when the carboxyl group is in the meta or para position, yet all are of low activity against pneumococcus.

The class of $N^1$-heterocyclic derivatives of sulfanilamide has been widely explored. This is due in part to the great success in the use of sulfapyridine against pneumonia. The formula for sulfapyridine is

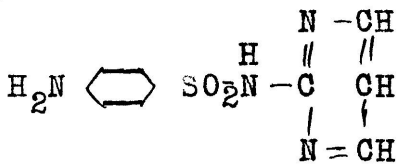


This compound was first reported by Whitby[2] The sulfanilamideo group may be attached to the pyridine ring in position 2 oe 3 without any noticeable difference, in activity on either streptococci or pneumococci[3]. It is remarkable to note the differences in the activity of their substitution products, however. Substitution of halogen in the 5-position in 2-sulfanilamido-pyridine destroys the activity while nitro or amine groups in the 5 position gives a slightly enhanced

1. Crossley, Northey, Hultquist J.A.C.S. 60 2217 1938
2. Whitby The Lancet 1 1210 1938
3. Roblin & Winnek J.A.C.S. 62 p. 1999 1940

activity against strep. and a slightly decreased activity against pneumococci. By reversing the positions of the groups and substituting in the 2-position in 5-sulfanilamido pyridene, the halogen derivative is active and the nitro and amino derivatives are inactive.

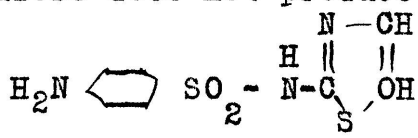
2-sulfanilamidopyrimidine (sulfadiazine) is reported by Roblin[1] et. al. as being more active than sulfanilamide and has the advantage over sulfanilamide in that it is more readily absorbed. In a 10% water solution it is also more nearly neutral, pH 9.6 than sulfapyridine pH 11. The sulfanilamidepyrimidine appears to have the same activity as sulfathiazole itself. The formula for sulfadiazine is



Sulfathiazole (2-sulfanilamidothiazole) and sulfamethylthiazole (2-sulfanilamido-4-methylthiazole) are very active against strep. and pneumococci and also effective against staphylococci. Sulfamethylthiazole was drawn from clinical study because

1. Roblin, Williams, Wennak,, English. JA.C.S. 62 2002 1940

about 2% of the patients developed peripheral neuritis of more or less serious character. Sulfathiazole does not produce this effect.



As reported by Key[1], sulfanilamide and sulfathiazole are used locally in surgery for protection against postoperative infection.

It should also be added that these compounds along with sulfadiazine have found extensive use on our battle fields of this war.

The series of straight-chain acyclic-acyl derivatives of $N^1$-sulfanilamide has been practically completed up to 17 carbon atoms. This series was of the type $H_2N$  $SO_2NHCOR$ where R was alkyl from 1 to 17 carbons in length. The investigators[2] hoped to get compounds which might penetrate the tubercle of, and be effective against, tuberculosis. The $N^1$-dodecanoylsulfanilamide was investigated more fully than the other members of the series. It appears to be equal or slightly superior to sulfanilamide, on an equal weight dosage, in experimental mouse infection with various beta hemolytic strep. Cavies infected with a human strain of

1. J.Albert Key J.Am. Med. Assn 117 409-412 1941
2. Crossley, Northey, Fultquist J.A.C.S. 61 2950 1939
3. Reinstone, Wolff, Williams Proc. Soc. Expt. 1 Biol. Med. 1940

mycobacterium tuberculosis showed only localized lesions when treated with the drug.

In this series the activity[1] seems to attain two peaks, one in $N^1$-butyrylsulfanilamide and the other in $N^1$-dodecanoylsulfanilamide.

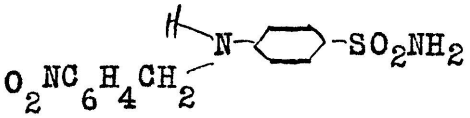
It is claimed that 39% of $N^1$-acetylsulfanilamide is hydrolyzed in the body to sulfanilamide. $N^1$-butyrylsulfanilamide is much more active than $N^1$-isobutyrylsulfanilamide which is curious if one explains activity on the assumption of the hydrolysis to sulfanilamide.

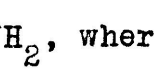
Crossley et. al.[2] report a series of $N^1$ alkanesulfonylsulfanilamides which appear to be completely inactive. This work was stimulated by the pharmacological results obtained from di-sulfanilamide[3]. It followed the general structure of $H_2N$  $SO_2NHSO_2R$ where R is alkane, from 2 to 12 carbons in length.

Derivatives of sulfanilamide where the substituted group is in $N^4$ position appear to be active only if the substituted group is hydrolyzed.

1. Feinstone, Wolff, Williams. Proc. Soc. Expt. 1 Biol. Med. 1940
2. Crossley et. al J.A.C.S. 60 2222 1938
3. Crossley, Northey, Hultquist J.A.C.S. 62 1415-1416 1940

reduced or otherwise removed in vivo. Evidence of such processes have been obtained by finding diazotizable amine in the blood of animals after feeding sulfanilamide derivatives containing 4-nitro, hydroxylamino, azo or $N^4$ acyl groups.

The $N^4$-isocyclicsulfanilamides with the exception of $N^4$ (4 nitrobenzylsulfanilamide)  are of relatively low activity and very likely owe their activity to cleavage to sulfanilamide in vivo[1]. The high activity reported for the $4^1$-nitrobenzyl derivative is possibly due to the action produced on cleaving since both p-nitrotoluene and p-nitrobenzoic acid have been reported to show activity.

Miller, Rock, and Moore[2] prepared a series of compounds of the type $N^4$ acyl derivatives, $CH_3CONH$  $SO_2NH_2$, where the number of carbons in the acyl group is varied. The activity increases from slight in the lower members to greatest activity, equal to sulfanilamide, in Caproyl-sulfanilamide, $C_5H_{11}CONH.C_6H_4SO_2.NH_2$, then decreases gradually again up the scale.

1. Molitor & Robinson J. Pharmacol. 65 405-423 1939
2. Miller, Rock, & Moore. J.A.C.S. ~~61~~ 1198-1200 1939

It was previously stated that in the $N^1$ acyl series the corresponding branched chain substituent was much less active than the normal chain substituent. This is also true of the $N^4$ acyl sulfanilamides.

The anils or Schiff bases of the type $R{=}N\langle\rangle SO_2NH_2$ and the azo derivatives of sulfanilamide of the type $RN{=}N\langle\rangle SO_2NH_2$ in general show a considerable amount of activity which is to be expected if the cleavage principle holds true. Their Chemotherapeutic activity then would be due to the formation in vivo of sulfanilamide. Trefouel, Trefouel, Nitti, and Bovet[1] have reported that the azo compounds do not show antibacterial activity in vitro, but show activity in vivo for dyes where the sulfanilamide part of the molecule was not changed in structure. Sulfanilamide has been isolated from the urine of patients treated with Prontosil[2].

Koloff and Hunter[3] made some arylidine derivatives of $N^1$-substituted sulfanilamide by

1. Trefouel, Trefouel, Nitti, & Bovet. Compt. Reno. Soc. Biol. 120 756 1935
2. Fuller, A.T. The Lancet 1 194 1937
3. Koloff & Hunter J.A.C.S. 63 158-160 1940

condensing $N^1$-substituted sulfanilamide with the appropriate aldehydes.

This results in a product which shows a slight decrease in anti strep. and anti pneumococci activity. The compound, however, has a lower toxicity.

Daniels and Iwamoto[1] report on the preparation of $N^1$, $N^4$ Pyrazinoyl derivatives of Sulfanilamide. The $N^4$ pyrazinoylsulfanilamide has been prepared from the reaction of pyrazinoylchloride and sulfanilamide in dry pyridine. Since $N^4$ nicotinylsulfanilamide has been successfully used in treating various bacterial infections, and has low toxicity the authors find it desirable to introduce a second N into the acyl ring. Its activity has not yet been determined.

Kolloff and Hunter[2] have made an interesting series of $N^4$ acyl-sulfanilyl and sulfanilyl derivatives of 2-,3- and 4- aminopyridine, 2-, 3-, and 4- (pyridyl) methylamine, and [1-(2-3- & 4 pyridyl) ethyl] amine with the aim of studying the relationship between structure and antibacterial

1. Daniels & Iwamoto J.A.C.S. 63 257 1941
2. Kolloff & Hunter J.A.C.S. 63 490 1941

action. The biological data is now being collected.

Sprague and Kissinger[1] have synthesized a series of sulfonamido derivatives of thiazoles. It is particularly interesting to note one of them, 2-p-nitrobenzene-sulfonamido-4-methyl-thiazole, which has a greater anti strep. activity than sulfathiazole but its anti pneumococcal activity is negligable.

E.H.Northey[2] has given a brief summary of his findings in regard to the activity of sulfanilamide derivatives. He states that:

1. Nuclear-substituted sulfanilamides are usually inactive.
2. $N^1$ substitution has given the most promising new derivatives.

a. The $N^1$ acyclic derivatives have not been so active as the parent sulfanilamide.

b. $N^1$-heterocyclicsulfanilamides have shown great activity against pneumococci and equal or better ac activity against strep. than sulfanilamide.

1. Sprague & Kissinger J.A.C.S. 63 1941
2. Northey, E.H. Chem. Rev. 27 173 1940

Substituents on the heterocyclic ring modify the activity and postion isomerism of such substituents may have a profound influence on the activity, which is difficult to explain in terms of current theories on the mode of action of sulfanilamide and its derivatives.

c. $N^1$-arylsulfanilamides are in general not so active as sulfanilamide. Isomerism of substituents of the $N^1$-aryl nucleus has an important effect on activity.

d. Some $N^1$-acyl sulfanilamides show activities somewhat greater than sulfanilamide on an equi-molecular dosage. Branched-chain $N^1$ acylsulfanilamides are much less active than straight-chain derivatives.

e. $N^1$-sulfonylsulfanilamides are generally inactive.

3. An hypothesis which needs verification by pharmacological study is: Blocking the $H^4$-nitrogen in sulfanilamide by a g group which is not removed in vivo destroys the activity. Groups which destroy the activity are alkyl, aryl, or

sulfonyl Groups which may be removed or converted in vivo to the free amine(or an active substance derived from the free amine) ar are anils, certain reduced anils, formaldehydes-bisulfite, and formaldehydes-sulfoxalate derivatives.

4. $N^1$-nuclear, $N^4$-nuclear, $N^1$,$N^4$, and $N^1$, $N^4$ nuclear-substituted sulfanilamides follow in general the activities to be expected as a result of combining substituents on the basis of paragraphs 1,2,& 3 above.

Northey goes on to point out that (metanilamide and orthanilamide and their derivatives are inactive.

Replacement of the amino group in sulfanilamide by -H, -OH, -R, -COOH, $-SO_2NH$, alkyl or halogen practically destroys the activity. Replacement of the sulfonamido group by $-NH_2$, -CN, $-SO_3H$, $-AsO_3H_2$, $-CONH_2$, $-NHCOCH_3$, and $NO_2$ destroys the activity, but replacement by $-SO_2H$ retains most of the activity.

## METHOD EMPLOYED IN SYNTHESIS OF THE DERIVATIVES OF SULFANILAMIDE.

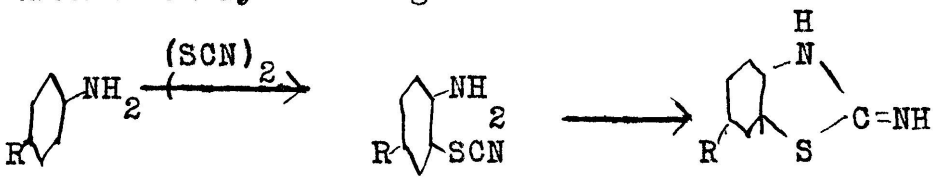
In many of the reactions where derivatives of sulfanilamide have been made through the nitrogen atom of the sulfonamide group, the coupling has been accomplished through acetylsulfanilylchloride and the amino group of the appropriate compound. Both of the reactants are dissolved or suspended in a suitable solvent such as ethyl alcohol or dry pyridine and then permitted to react. The product is obtained from the reaction mixture by pouring it into cold water where the product precipitates.

This is the general prodedure followed in making the following series of compounds and follows closely the method described by Schroeter and by Gelmo in their original work.

In those derivatives where the para-amino group referred to as $N^4$ forms part of a thiazole ring the method used follows that of Kaufmann[1] and of Brewster and Dains[2], for the direct

1. Kaufmann Arch. der. Phar. 266 p.197-218 1928
2. Brewster & Dains. J.A.C.S. 58 1364 1936

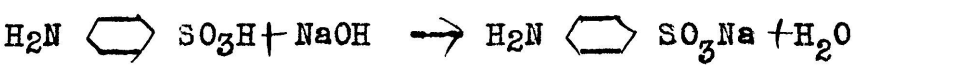
thiocyanogenation of the amine[1]. In this method the amine and ammonium thiocyanate are dissolved in glacial acetic acid and Bromine is slowly added. If the para position of the arylamine is occupied then the liberated thiocyanogen is substituted in the position ortho to the amino group. Such ortho thiocyanogenated products then automatically rearrange to iminobenzthiazoles.




1. Kaufmann & Schulz Arch. der. Phar. 273 31-52 1935

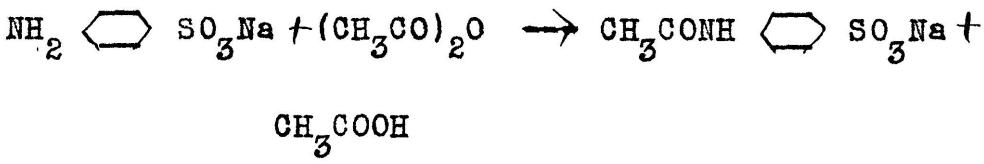
# EXPERIMENTAL

A number of preliminary compounds had to be prepared which were to be used as starting products in the following investigations. The sodium salt of sulfanilic acid was prepared by suspending 519 grams (3m) of sulfanilic acid in 2 liters of water and adding 120 grams (3m) of sodium hydroxide. The resulting solution was concentrated in a large evaporating dish over a free flame until crystals began to appear after which it was evaporated to dryness on a steam bath. The yield was about the theoretical.



In order to protect the amino group in the sodium sulfanilate it was acetylated in the following manner. The sodium salt was dried in the oven. 150 grams of redistilled acetic anhydride were added to 90 grams of the dry sodium salt while constantly stirring the same. This reaction heated itself but it may be aided by warming the mixture. The reaction was allowed to complete itself and after the product was cool it was filtered by suction from the excess acid and then

washed 3 or 4 times with small quantities of ether. The product was then dried and weighed. The yield here too was nearly theoretical.

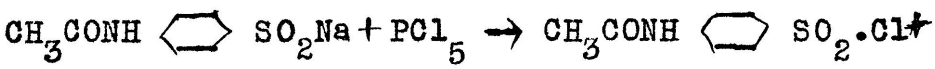


## PREPARATION OF ACETYL SULFANILYL CHLORIDE

Since acetyl sulfanilyl chloride is the product used through which most of the coupling reactions of sulfanilamide derivatives are accomplished, its preparation from the sodium salt will be shown.

Ten grams of the sodium salt of acetyl sulfanilic acid, $CH_3CONH\langle\rangle SO_2ONa$, and 15 grams of phosphorus pentchloride, $PCl_5$, are ground together in a mortar. This procedure should take place under a well ventilated hood. The mixture liquefies while grinding. The yield can be increased appreciably if after the reaction subsides, the mixture is carefully warmed for a short time. After the reaction mixture has cooled it is washed well with ice water which removes the phosphorus oxychloride and the hydrochloric acid. The crude white cheesy crystals of acetyl sulfanilylchloride are removed by suction filtration and, after being washed with cold water, are dried on paper. For

most of the coupling reactions this crude acetyl sulfanilylchloride need not be purified further.[1] The yield obtained is approximately 75%.



$POCl_3$ + HCL. The melting point after recrystalization from benzene is 149°.

1. Schroeter Ber. 39 1559 1906

## PREPARATION OF ALLYL-THIO-UREA

As allyl-thio-urea is used for the preparation of a substituted thiazole which, in turn is coupled to sulfanilylchloride a unique method to make the allyl-thio-urea was developed. The method consists of the reaction between allyl mustard oil and liquid ammonia.

a 400 cc beaker is wrapped in heavy paper and suspended in a 600 cc beaker. The space between the beakers acts as an insulator. 225 cc of liquid ammonia are drawn into the insulated beaker and placed under a ventilated hood. One mole, 99 grams of allyl-iso-thio-cyanate is carefully addtd in small portions and with constant stirring. The reaction causes the liquid ammonia to boil rather vigorously and so care must be exercised not to cause the mixture to boil over the edge of the beaker. After all the allyl mustard oil has been added stirring should be continued until the excessive

1. Schroeter Ber. 39 1559 1906

ammonia boils off and the allyl-thio-urea crystallizes. It is then allowed to stand under the hood for 45 minutes to allow the reaction to complete itself and to permit more of the excessive ammonia to excape.

The reaction product is now placed in a liter Florence flask and 300 cc of distilled water added. The product is distilled with steam until 1500 cc of distillate pass over. During this process any uncombined allyl mustard oil as well as free ammonia are carried into the distillate with the steam. It is advisable at the beginning of the distillation to use a bent adapter at the end of the condenser, with its end beneath a small quantity of water in a beaker in order to absorb the ammonia vapors.

After distillation, the distilling flask contains a clear liquid composed mainly of allyl-thio-urea in water. The liquid is poured into a large beaker and chilled in ice water until crystallization begins and set into a refrigerator where it is allowed to stand over night. Now the crystals of allyl-thio-urea are filtered off by suction and washed with a small amount of

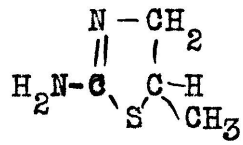
cold water, adding the washings to the filtrate. The crystals are then dried. A second crop of crystals can be obtained by concentrating the filtrate to about 1/3 of its volume and then chilling it in ice water. The yield obtained is approximately 93%.

$NH_3 + CH_2 = CH.CH_2NCS \longrightarrow S = C(NH_2)(NHC_3H_5)$ or its isomer $HS-C(=NH)(NHC_3H_5)$

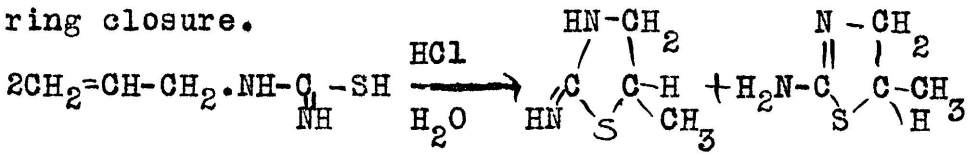
In order to determine the most efficient method of making the allyl-thio-urea two compounds were added as catalysts, or in order to increase the ammonium concentration. Onemole of allyl mustard oil was divided into 3 equal portions of 33 grams each. To the first beaker containing one of the 3 portions no catalyst was added, to the second two grams of Sodamide, $NaNH_2$, were added, and to the third two grams of Ammonium chloride. The process explained above was used on all three portions. The yield obtained from the portion without the catalyst was 35 grams, and from the portions with $NaNH_2$ and $NH_4Cl$, 33.5 grams and 34 grams respectively. These results indicate that the addition of two compounds has no positive catalytic effect.

All three samples were recrystallized from 50% methyl alcohol, 50% ethyl alcohol, and acetone. Their melting points were constant at an uncorrected temperature of $70^{\circ}$-$71^{\circ}$ C.

## PREPARATION OF 2 AMINO 4 HYDRO 5 METHYL THIAZOLE



The allyl-thio-urea prepared in the above manner is converted into the thiazole as follows: One molecular weight of allyl-thio-urea is heated on a water bath, under a reflux condenser with 200 cc, 1:1 HCl for a period of three hours. The reaction causes the allyl-thio-urea to form a ring closure.

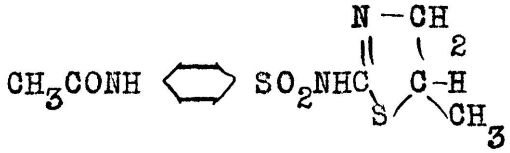


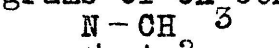
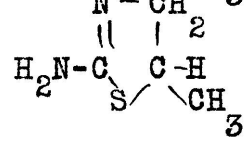
The product is then concentrated on a steam bath until crystals appear. Stirring is necessary during evapporatinn. A solution of 33% sodium hydroxide is then added until basic and the thiazole rises to the surface as an oil. Efforts to extract the thiazol with benzene according to Gabriel[1] were not successful. The oil was then separated by means of a separatory funnel, washed with four 10 cc portions of water, dried with anhydrous magnesium sulfate, and distilled in a high vacuum. At 37 mm pressure of Hg the oil boils at 160°C. and a large portion of it decomposes. The yield of 2

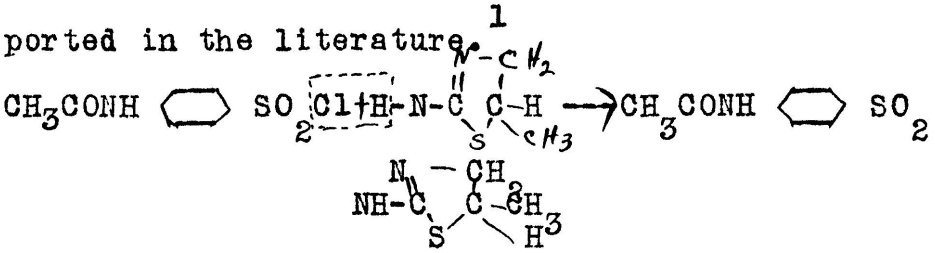
amino 4 hydro 5 methyl thiazole is approximately 18% of the theoretical. Because of the high percentage of decomposition the coupling reaction of this substance with acetyl sulfanilylchloride was made with the crude product.

1. Gabriel Ber 22 2985

## PREPARATION OF $N^1$ 4 HYDRO 5 METHYL THIAZOLE $N^4$ ACETYL SULFANILAMIDE



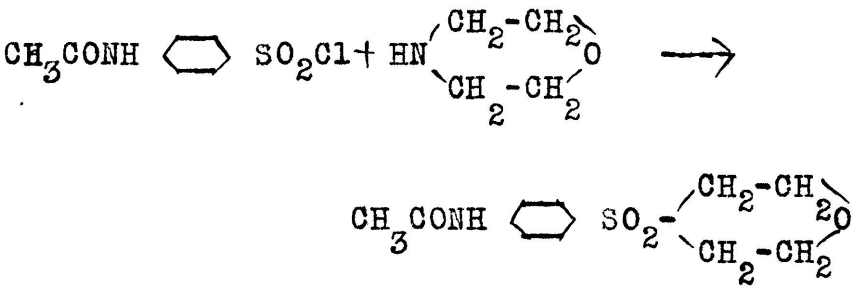
Six grams of  and three grams of  were separately dissolved in alcohol. The solutions were then mixed, heated to 60° and allowed to stand for 20 minutes. The mixture was then concentrated on a steam bath to a small volume, cooled and poured into 200 cc of cold water. A milky colloidal suspension was formed which was partially precipitated by careful neutralization with dilute acetic acid. If the neutralization point is overstepped it can be adjusted with dilute ammonium hydroxide. A small amount of white crystals were obtained. The yield is very poor, only 2½ grams of product being obtained. Subsequent trials gave even smaller yields. Analysis: N, found 13.4%: N Calc. 13.2%. This product has been reported in the literature.[1]



1. British Patent 517,212 May & Baker Co. 1940

# PREPARATION OF $N^4$ ACETYL SULFANILYL MORPHOLINE

Although this product has been reported by Adams[1] it was also made by the writer before the report appeared in the literature. It is again reported here because the product is used in a further preparation. Then grams of acetyl sulfanilylchloride solution were poured into the morpholine solution with vigorous stirring. The mixture was allowed to stand for 20 min. and then was concentrated on the steam bath. The product was next precipitated by pouring the alcoholic solution into 200 cc of water from which the precipitated product then was separated by filtration and recrystallized from dilute alcohol. It is composed of pretty white crystals.

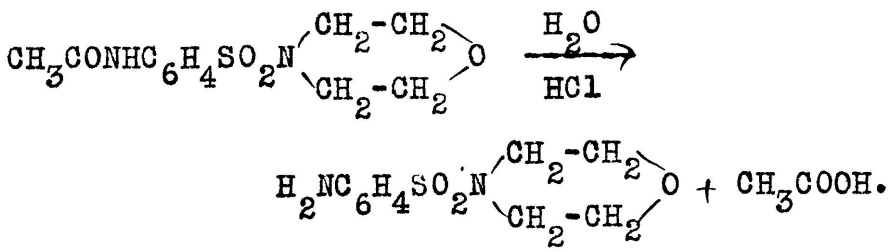


1. Adams J.A.C.S. 61 2346 1939

## HYDROLYSIS OF $N^4$ ACETYL SULFANILYL MORPHOLINE TO SULFANILYL MORPHOLINE

To illustrate the process of removing the acetyl group by acid hydrolysis the following experiment was performed.

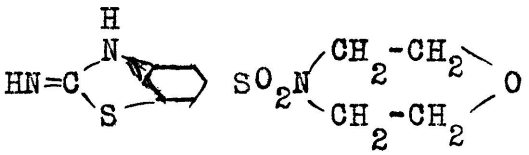
For each six grams of acetyl sulfanilyl morpholine 40 cc of 1:1 hydrochloric acid were added and the mixture was heated on a steam bath, under a reflux condenser for a period of twenty minutes. The contents were then thoroly chilled in ice water and neutralized with ammonium hydroxide.



After recrystallizing from dilute alcohol the white crystals of sulfanilylmorpholine melted sharply at 212° C.

PREPARATION OF 2 IMINO 6 SULFON

MORPHOLINE BENZTHIAZOLE

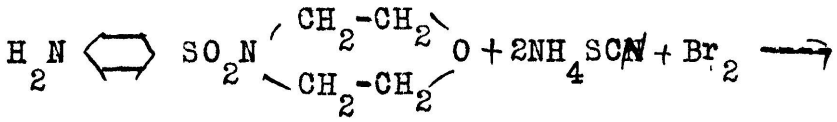


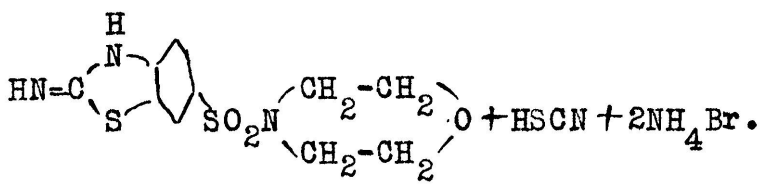
Because of the great medical application of the derivatives of sulfanilamide it was thought advisable to try to make 2 imino 6 sulfon morpholine benzthiazole from sulfanilylymorpholine.

Seven grams (.03M) of sulfanilylmorpholine were dissolved in twenty cubic centimeters of glacial acetic acid. To this were added 4.56 grams (.06M) of ammonium thio cyanate, and after the solution had taken place, the whole mixture was set into an ice salt mixture and cooled to $10^{o}$-$20^{o}$ C. A mechanical stirring device was introduced and while constantly stirring this mixture, a solution of 4.8 grams (.03M) of bromine in 7 cc of glacial acetic acid were added dropwise. Stirring was continued for 30 minutes after all the bromine had been added and the temperature was kept below $20^{o}$ during this process. The contents were then filtered and the residue washed with cold water and redissolved in warm water. A small amount of polymerized

product which is insoluble in warm water was separated by filtration and the filtrate clarified with charcoal. The clarified filtrate was then thoroughly cooled and neutralized with $NH_4OH$. During this process the crystals of 2 imino 6 sulfon morpholine benzthiazole were precipitated and could be separated by filtration. More of the product was obtained by neutralizing the acetic acid filtrate with ammonium hydroxide, filtering and recrystallizing from dilute alcohol or boiling water.

The white crystals of benzthiazole sulfon morpholine recrystallized from boiling water melt at 244°-245°. Nitrogen anal. Found 13.85% calc. 14.0%.





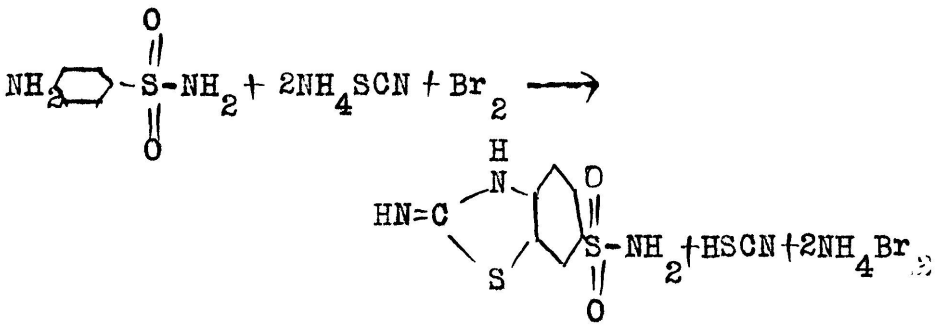
## PREPARATION OF 2 IMINO BENZTHIAZOLE SULFON AMIDE

A compound quite similar to sulfanilamide was made in which the amino group attached to the benzene ring in sulfanilamide was thiocyanogenated accordint to the method stated above. 17.2 Grams (.1M) sulfanilamide and 15.2 grams (.2M) ammonium thiocyanate were dissolved in 50 cc glacial acetic acid and cooled to 10-20° C. While stirring mechanically 16 grams (.2M) bromine dissolved in 20 cc glacial acetic acid were added dropwise through a dropping funnel keeping the temperature constantly below 20° . The stirring was continued for 30 minutes after all the bromine had been added. The product was filtered with suction while cold. The residue was then dissolved in warm water and filtered from any polymerized substance. After cooling the filtrate well the product, which is 2 iminobenzthiazole 6 sulfonamide was precipitated from the solution with ammonium hydroxide. The 2 iminobenzthiazole 6 sulfonamide was then separated by filtration and dried. The yield of crude product obtained was 94% of the theoretical. In order to purify

the substance it was dissolved in hot water and slightly acidified with HCl then filtered and re-precipitated with $NH_4OH$. It can be recrystallized from hot water alone or from a dilute alcohol solution. The product is composed of white, needle like crystals which melt at 280°C.

Analysis for nitrogen by Kjeldahl method:
Calc. 18.3% found 18.1%

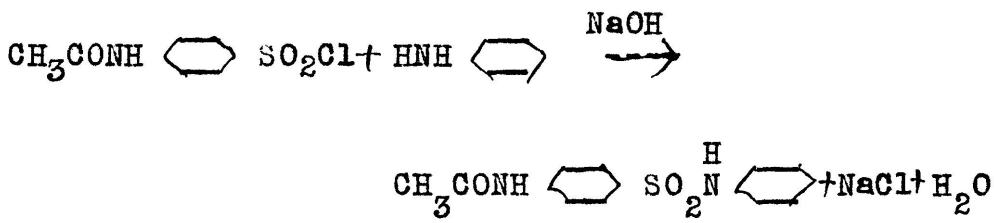
An attempt was made to determine the medicinal value of 2 imino benzthiazole 6 sulfonamide on strep infection, however, it proved to be highly toxic. This seems to bear out investigations made by others that the amino group attached to the benzene ring should be left intact or be substituted in such manner that the free amino group is formed in vivo.



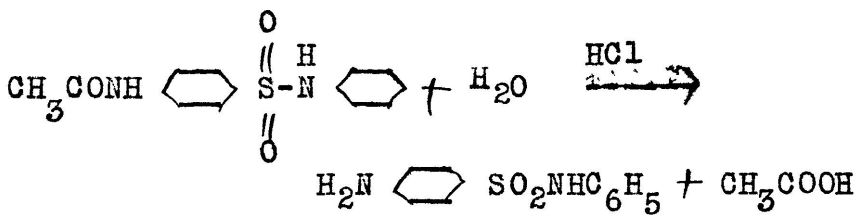
## PREPARATION OF 2 IMINO BENZTHIAZOLE SULFONANILIDE

To make this compound the starting product was acetyl sulfanilylchloride made as previously described. The chloride was coupled with aniline and then the actyl group was hydrolyzed to the amino group which in turn was thio cyanogenated according to the following procedure. Fifty grams of acetyl sulfanilylchloride and 20 grams of aniline were each dissolved in small amounts of alcohol respectively and then mixed with constant stirring. During this process enough 40% sodium hydroxide was added to keep the mixture just slightly basic. The stirring was continued for an hour after the mixing of the two solutions and then the mixture was set aside to stand over night.

The product was poured into 250 cc of water after which the solution was just neutralized with dilute acetic acid. The precipitated product was next separated by filtration and dried. The yield, approximately 55 grams was composed of white crystals of acetyl sulfanilylanilide.



The next step in the process was the removal of the acetyl radical which was accomplished by acid hydrolysis. 40 grams of acetyl sulfanilylanilide were weighed into a 500 cc round bottom flask. To this were added 150 cc of 1:1 HCl and the mixture boiled under a reflux condenser for 20 minutes. The solid acetylsulfanilylanilide dissolved during this process as it became deacetylated. After hydrolysis was complete and equal volume of water was added and the solution decolorized by boiling with a small amount of charcoal. The charcoal was removed by filtration from the hot solution and the filtrate was then thoroughly cooled in ice water from which the amine was precipitated by neutralizing with $NH_4OH$ while stirring constantly. The product was then removed by filtration, recrystallized from dilute alcohol, dried and used for the preparation of the thio cyanogenated compound described below. The crystals of sulfanilylanilide are white. The reaction of hydrolysis can be represented as follows:



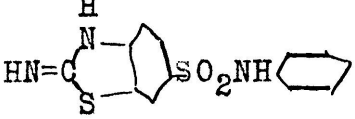
The conversion of theabove compound into the benzthiazole derivative was accomplished in the manner mentioned previously as follows: 15 grams (.06M) of sulfanilanilide and 9.12 grams (.12M) ammonium thiocyanate was weighed into a 250 cc beaker and dissolved in 90 cc of glacial acetic acid. This solution was then cooled in an ice bath and brine solution to $10^{0}$ C. and mechanically stirred. While cold and with constant stirring, 9.6 (.06) grams of bromine in 15 cc of glacial acetic acid were added dropwise through a dropping funnel and the stirring continued for .5 hour after all bromine had been added. The product, which was a mushy semisolid at this temperature due to the excess of acetic acid, was dissolved in 600 cc of hot water. A small amount of a yellow colored polymer of the thiocyanate which formed was insoluble in the acid hot water solution and could be thus removed by filtration . The filtrate was heated

to boiling with charcoal to clarify the solution, and after removing the charcoal by filtration, the solution was cooled, chilled in ice water and carefully neutralized with ammonium hydroxide. This precipitated the 2 imino benzthiazole sulfonanilide as white crystals which were then separated by filtration, and recrystallized from dilute alcohol. After separating the white crystals by filtration, and drying them carefully the melting point was determined and found to be 188-189° C.

Analysis for $N_2$ Calc. 13.7%, found 13.6%

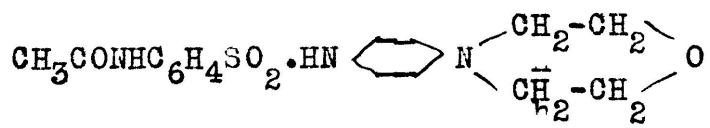
The yield wasapproximately 48% but varied according to the length of the time interval before the hot thiocyanogenated solution was neutralized. More of the polymer is formed if the time interval is long. The reaction involved is

$$H_2NC_6H_4SO_2NHC_6H_5 + 2NH_4SCN + Br_2 \longrightarrow$$



$$+ HSCN + 2NH_4Br$$

## PREPARATION OF P-ACETYL SULFANILYL ANIDO PHENYLENE MORPHOLINE

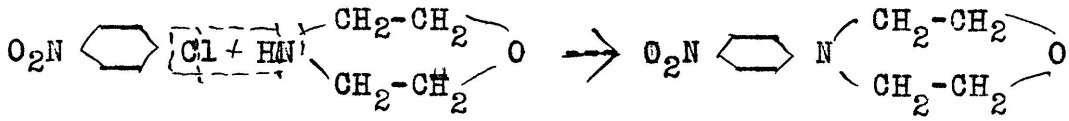


The first step in the preparation of this compound is to prepare some para nitro phenylene morpholine which can then be reduced to the amino compound and coupled with acetylsulfanilylchloride.

One mole (157G) of para nitrochlorobenzene and 2 moles (174G) morpholine were dissolved in the least amount of ethyl alcohol respectively and then mixed with vigorous stirring. The reaction mixture was allowed to stand for 30 minutes and then heated on a steam bath under a reflux condenser fo 3 hrs. The solution was then poured into cold water in order to precipitate the product. This product was separated by filtration and steam distilled for purification. The original p-nitrochloro-benzene was obtained showing that it had not coupled with the morpholine.

The p-nitrochlorobenzene and morpholine mixture in alcohol was then heated under a reflux condenser in an oil bath at 170° C. for 3 hours and then on a steam bath all night. A precipitate

was formed from the hot solution. This solution was steam distilled, until the alcohol and excess morpholine were removed, then the p nitro phenylene morpholine was removed by filtration, washed in water and dried. The yield was approximately 90%. The reaction is:



# REDUCTION OF P-NITROPHENYLENE MORPHOLINE TO P-AMINO PHENYLENE MORPHOLINE

The reduction[1] of p-nitrophenylene morpholine was accomplished by the action of hydrogen under pressure in the presence of a catalyst.

Fifty grams of p-nitrophenylene morpholine were suspended in 750 cc ethyl alcohol and poured into the 2½ liter flask of the reduction apparatus. To this suspension 13 gram of platinum oxide was added as a catalyst and the flask was tightly closed. The air was then flushed out with hydrogen and the flask was connected with the supply tank of hydrogen under 25 lbs. of pressure. The flask and contents were then shaken by a motor driven device in order to saturate the mixture with the hydrogen. The reaction proceeded smoothly, and most of the reduction took place in the first 10-15 minutes. Then the rate of hydrogen absorption decreased. After approximately an hour no more hydrogen was absorbed and the reaction was complete.

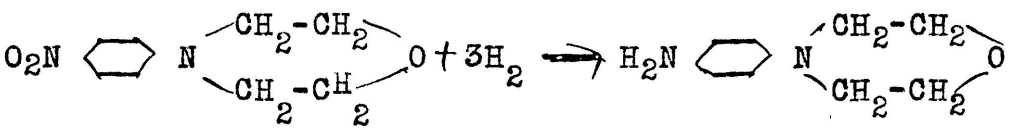
1. Conant, Chem. of Org. Compounds. 74-75
revised 1939 ed.

Leffler & volwiler J.A.C.S. 60 896 1938

The suspended p-nitrophenylen morpholine had been reduced to the more soluble p-amino phenylene morpholine which was now in solution.

The solution was now filtered rapidly in order to prevent oxidation of the phenylene derivative and in order to recover the platinum oxide catalyst.

The filtrate, consisting of p-aminophenylene morpholine dissolved in alcohol, was the concentrated by distilling off 400 cc alcohol. On cooling, red crystals of the product were formed.

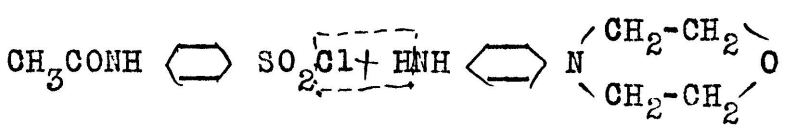


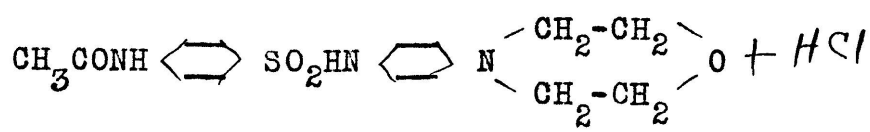
In the next step, this p-amino phenylene morpholine was coupled to acetyl sulfanilyl-chloride. A suspension of 56 grams of acetyl sulfanilyl chloride in alcohol was slowly added to the concentrated alcoholic solution of p-aminophenylenemorpholine while stirring vigorously and from time to time 40% NaOH was added in just sufficient quantities to keep the mixture slightly basic. The acidity of the solution is indicated by the highly colored solution itself as an indicator. On the acid side the solution is a deep blue, while when basic the solution

is red. After all the acetyl sulfanilylchloride had been added, the solution was allowed to stand 30 minutes for the reaction to complete itself. Most of the alcohol was then removed by distillation and the solution was concentrated to a small volume. If this solution is chilled in ice, blue crystals of the coupled product, para acetyl sulfanilylamido phenylmorpholine are produced. More of the product was obtained by pouring the concentrated alcoholic solution into 500 cc of cold water. The water solution was then carefully neutralized with dilute acetic acid to insure complete precipitation and the crystals removed by filtration.

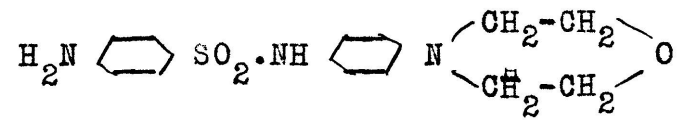
To purify the product it was dissolved in 50% alcohol boiled with charcoal, filtered while hot and then chilled in ice water. Shiny white crystals were produced which could be removed by filtration and were then dried. The yield of recrystallized product was approximately 37%. The melting point was determined as 218 $^{o}$ C. Kjeldahl anal. for $N_2$, calc 11.2%, found 11.0%.

Reaction:

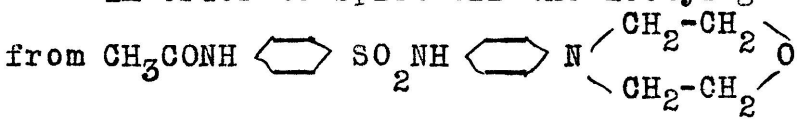




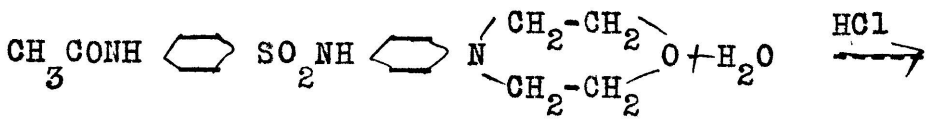
## PREPARATION OF PARA SULFANILYLAMIDO PHENYLMORPHOLINE

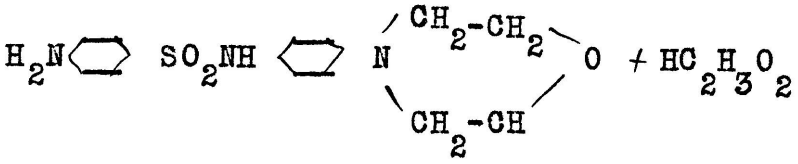


In order to split off the acetyl group from



it was boiled for twenty minutes under a reflux condenser in dilute HCl. The proportions used were 6 grams of compound for 40 cc of 1:1 HCl. It was then diluted with and equal part of water and a few grams of decolorizing charcoal added and again heated to boiling. The charcoal was then removed by filtration and the filtrate chilled in ice water. While the solution was kept cold, ammonium hydroxide was slowly added with vigorous stirring. The para sulfanilylamido phenylmorpholine was precipitated as gray crystals, which became silvery white after recrystallizing from 50% alcohol. The yield was approximately 80%. Melting point of thrice recrystallized product is 196-197° C. Nitrogen determination. calc. 12.6%, found 12.7%.


CH3CONH
SO2NH
N
CH2-CH2
CH2-CH2
O+H2O
HCl


H2N
SO2NH
N
CH2-CH2
CH2-CH
O
+HC2H3O2

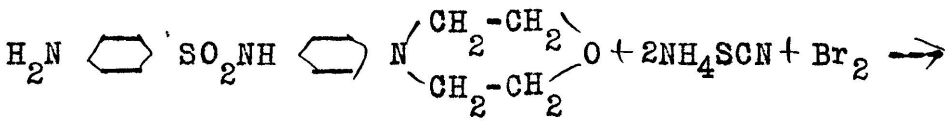
## THIOCYANOGENATION OF P-SULFANILYLAMIDO PHENYL MORPHOLINE

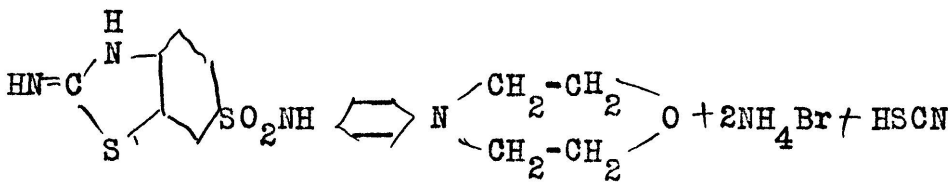
Several attempts were made to thiocyanogenate p-sulfanilyl amido phenyl morpholine and the best results were obtained from the following procedure and quantities used:

3.7 grams of the amine were dissolved in 30 cc of glacial acetic acid. The suspension was warmed to insure complete solution, then cooled. 1.6 grams of ammonium thiocyanate were added and dissolved. The beaker containing the entire solution was then placed in a pan of shaved ice and cooled to $10^{\circ}$ C. 1.7 grams of bromine were weighed out in 3 cc of glacial acetic acid and added dropwise to the cold solution. During this process the solution was stirred vigorously with a mechanical stirrer and the stirring continued for 30 minutes after the addition of all the bromine. The contents were then dissolved in 200 cc of warm water and the resulting solution filtered. One gram of animal charcoal was then added to the filtrate which was then heated, with stirring, almost to boiling.

The carbon was then removed by filtration, the filtrate cooled in ice water and neutralized with ammonium hydroxide. The precipitate that is first thrown down consists of a light colored substance which has a low nitrogen content (6.&%) with a melting point above 334° C. and a darker precipitate which is separated from the solution near the neutral point. The latter precipitate is redissolved in dilute HCl, treated with charcoal and reprecipitated with ammonium hydroxide, washed with water and dried.

The precipitated (re) crystals of 2 imino 6 sulfon amido phenyl morpholine benzthiazole darken at 220° C. and melt at 227°-228° C. The yield is 36% Analysis by the Kjeldahl method. Calc. 14.3% found 14.5% The reaction is represented by the equation:





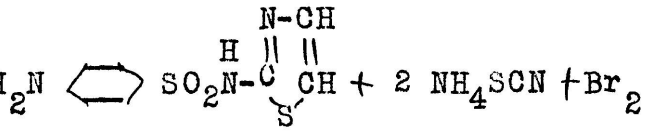
## THIOCYANOGENATION OF SULFATHIAZOLE

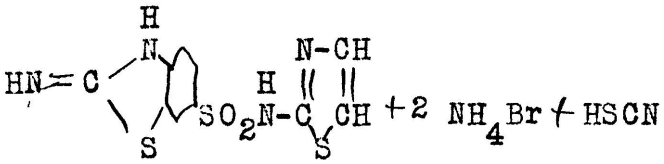
Since the direct thiocyanogenation of many substitued arylamines work so well it was decided to try it on sulfathiazole itself.

A large quantity of glacial acetic acid had to be used becuase of the slight solubility of the sulfathiazole in the acid.

Four grams of sulfathiazole were dissolved in 75 cc of warm glacial acetic acid. Some of the thiazole crystallized as the solution was cooled. The beaker and contents were set into a pan of ice water and stirred mechanically. 2.2 grams $NH_4SCN$ were added and dissolved in the solution. After the temperature had dropped to $10^{o}$ C 2.3 grams of bromine dissolved in 5 cc glacial acetic acid were added dropwise. Stirring was continued for thirty minutes after all the bromine had been added. The reaction mixture was then dissolved in 300 cc of warm water. A small amount of yellow colored polymer remained in suspension and was removed by filtration. The filtrate was cooled, cracked ice added and the 2 imino benzthiazole 6 sulfon amido thiazole

precipitated with NaOH while stirring vigorously. The precipitate dissolved in a basic as well as in an acid solution. It was then purified by redissolving in dilute acetic acid, warming with charcoal, filtering, and neutralizing with dilute NaOH. After separating the precipitate it was next dissolved in dilute NaOH treated with charcoal, filtered, and neutralized with dilute acetic acid. The precipitate was then washed with water, and recrystallized from dilute alcohol. The melting point was determined at 252°-253° C. Analysis by Kjeldahl method for $N_2$, calc. 17.94%, found 17.92%. The reaction is:





Yield approximately 85%.

## PREPARATION OF 2 ACETYL SULFANILYLAMIDO 6 METHYL BENZTHIAZOLE

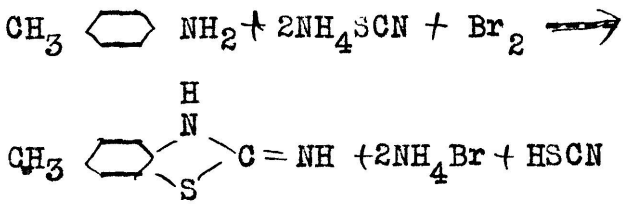
The starting product for the preparation of 2 acetylsulfanilylamido 6 methyl benzthiazole is para toluidine. The p-toluidine is converted into 2 amino 6 methyl benzthiazole which in turn is coupled to acetyl sulfanilyl chloride. Hydrolysis and thiocyanogenation of this coupled product were unsuccessfully a attempted.

The 2 amino 6 methyl benzthiazole was made from para toluidine according to the method of direct thiocyanogenation described previously by Kaufmann, Brewster, and Dains, in which the amine and $NH_4SCN$ were allowed to react in glacial acetic acid with bromine being added slowly. The product was precipitated from the solution by adding $NH_4OH$. After recrystallization from hot water the melting point was found to be 136° C. which is the recorded melting point for this compound

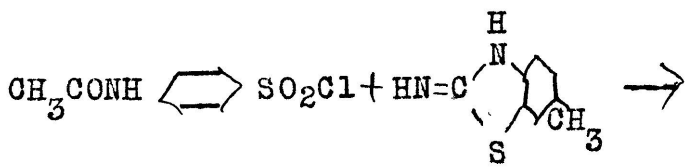
The coupling reaction proceeded as follows: Twenty grams of acetyl sulfanilyl chloride and

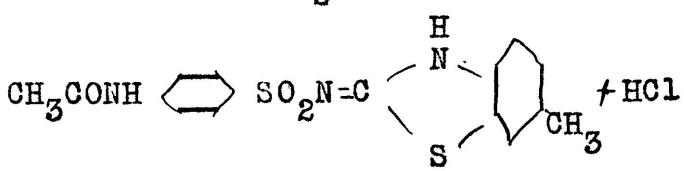
fourteen grams of the benzthiazole were dissolved respectively in the least amount of 95% ethyl alcohol. Both solutions were heated to 60° C. The chloride solution was then slowly poured into the benzthiazole solution which was stirred vigorously and tested from time to time for acidity with litmus. A few drops of strong NaOH were added as needed to keep the solution just basic. The solution was kept at 60° C.for and hour with occasional stirring after which it was set aside for a period of six hours. Some crystals separated during this time. The crystals were removed by filtration and the filtrate was poured into 400 cc of cold water from which an additional amount of crystals were obtained. The crystals of 2 acetyl sulfanilylamido 6 methyl benzthiazole were purified by dissolving in dilute acetic acid, cleaming with charcoal, filtering and reprecipitating the crystals with dilute ammonium hydroxide. The separated precipitate was then recrystallized from dilute alcohol Melting point after one recrystallization from alcohol 212° c. Analysis for Nitrogen Calc. 11.6%, found 11.4%

Yield 17 grams crude, 13 grams after recrystallization. Reactions:









Various attempts were made to hydrolyze this compound and if possible to thiocyanogenate the hydrolyzed product, but so far without success. Acid hydrolysis was tried in which the compound was heated on a steam bath, under a reflux condenser, in 1:1 HCl for 30 minutes, as well as basic hydrolysis. In most cases after hydrolysis the original 2 amino 6 methyl benzthiazole was recovered.

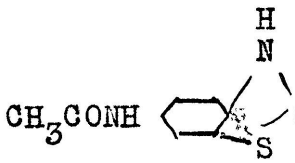
# PREPARATION OF 2 IMINO 6 SULFANIL AMIDO BENZTHIAZOLE

To make 2 imino 6 sulfanilamido benzthiazole it is possible to begin with para amino acetanilide, thiocyanogenate it, then remove the acetyl group by acid hydrolysis. The free amine is then coupled with acetyl sulfanil chloride. The acetyl group then is removed from this coupled product by hydrolysis.

Para amino acetanilide was converted into 2 imino 6 amino benzthiazole by the method of Kaufmann and Shulz[1].

.1 mole (15grams) of p-amino acetanilide and .2 mole (15.2 grams) $NH_4SCN$ were dissolved in 150 cc of glacial acetic acid and treated slowly with 16 grams of bromine in 25 cc of glacial acetic acid at $10^{o}$ C. The product was then dissolved in warm water from which it was precipitated with NaOH. The yield obtained was 25 grams of the crude product, melting at $230^{o}$ C. After recrystallization from hot $H_2O$ the crystals of

1. Kaufmann & Schulz Arch. der Phar. 273 31-52 1935



melt at 239° C.

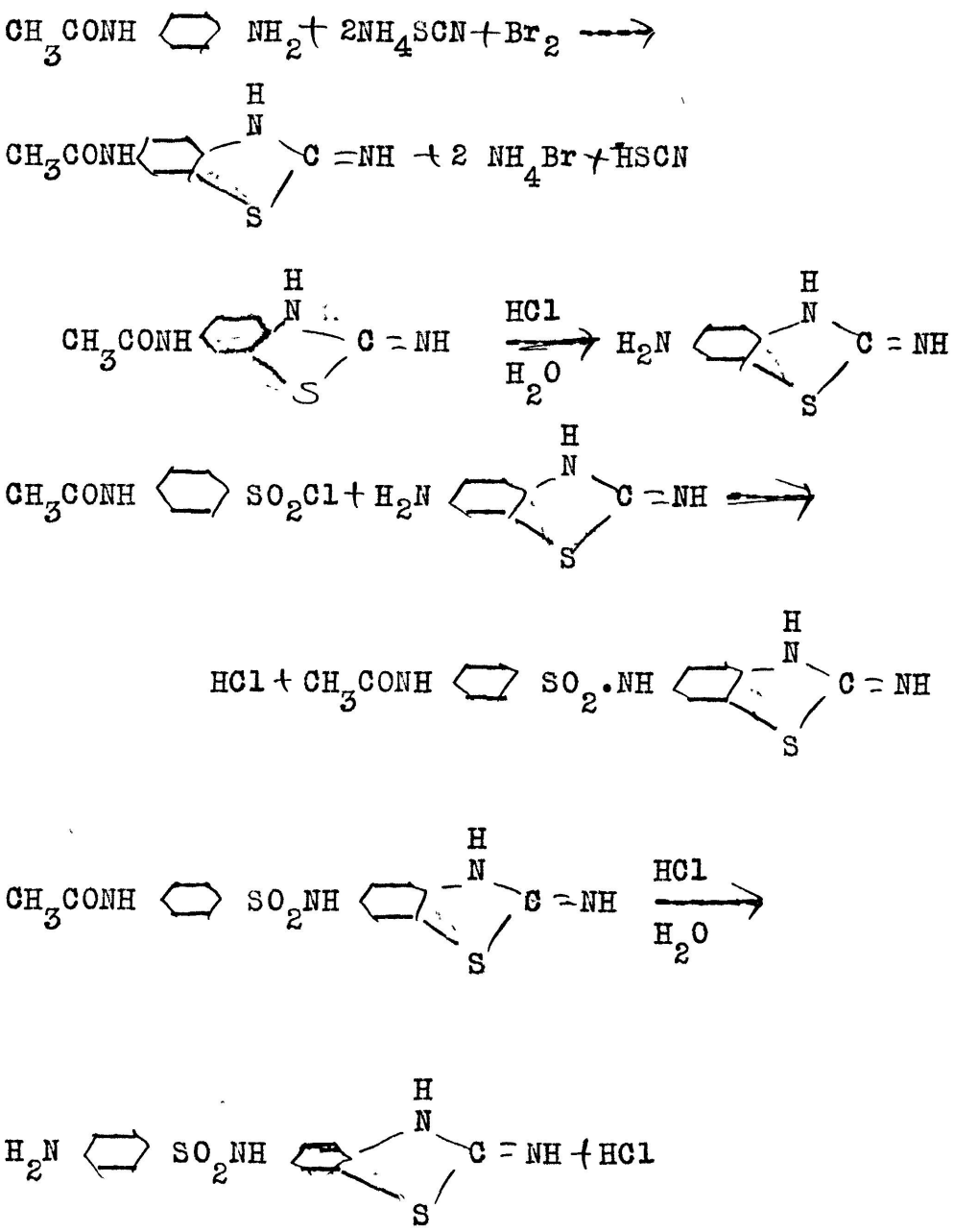
The hydrolysis of the acetyl group was accomplished in the usual way. Ten grams of 2 imino 6 acetaminobenzthiazole were dissolved in 25 cc of 1:1 HCl and heated on a steam bath under a reflux condenser for 30 minutes. The solution was then cooled and neutralized with NaOH. The resulting precipitate of 2 imino 6 amino benzthiazole was separated by filtration. dissolved in boiling water, cleaned with charcoal, and allowed to crystallize from the filtered solution. The crystals when first removed were white but due to the oxidation from the air soon became gray, then brown. The shiny flaky crystals melt at 207° C. Yield 85%.

For the coupling reaction, 15.6 grams of freshly prepared acetyl sulfanilchloride were dissolved in 40 cc ethyl alcohol, and similarly 10 grams of 2 imino 6 amino benzthiazole were dissolved in 60 cc of alcohol. The chloride was poured into the amine with constant stirring. the solution was kept just basic by adding

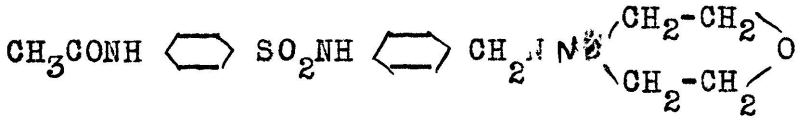
concentrated NaOH when necessary. Much heat was liberated from the reaction solution. The solution was then heated on a steam bath under a reflux condenser for 2½ hours. At the end of this period the reaction contents were drowned in 400 cc of cold water. The resulting precipitate had a gummy texture which became crystalline when the water was warmed. The crystals of 2 imino 6 acetyl sulfanilamido benzthiazole were separated from the liquid by filtration and purified by dissolving them in dilute NaOH? cleaning with charcoal and reprecipitating them with dilute acetic acid. The crystals have a white color when first removed from the liquid but soon become light tan in the air. Yield 79%. Melting point 270-272° C.

Hydrolysis of 2 imino 6 acetyl sulfanilamido benzthiazole was accomplished by the acid method. Six grams of the acetyl derivative were dissolved in 40 cc of 1:1 HCl and heated under a reflux condenser for 30 minutes. After this period of time an equal volume of water was added and a gram of charcoal introduced. The solution was next heated to boiling and filtered from the charcoal, cooled and neutralized with $NH_4OH$. Crystals of

the free amine were precipitated. These crystals were removed from the liquid by filtration and washed with water. Melting point 219-221° C. Yield 72%. Nitrogen anal. calc. 17.50% found 17.23%. The series of reactions involved are:



# PREPARATION OF $N^1$ PARABENZYL MORPHOLINE $N^4$ ACETYL SULFANILAMIDE



The preparation of $N^1$ parabenzyl morpholine $N^4$ acetyl sulfanilamide was achieved through the reaction of paro nitro benzyl chloride with morpholine, the subsequent reduction of the nitro group to the amine, which was then coupled with acetyl sulfanil chloride. Care was taken to protect the hands when working with p-nitro benzylchloride.

To make p-nitro benzyl chloride the procedure of Alway[1] was followed. 120 grams of benzyl chloride were cooled in a brine solution to $-5^{\circ}$ C. A mechanical stirring device was introduced and while stirring constantly, a cold solution of 90 grams fuming nitric acid and 180 grams of concentrated sulphuric acid were added dropwise. Stirring was continued for 70 minutes after all the acid had been added. The yield decreases if the temperature is permitted to go above $0^{\circ}$C.

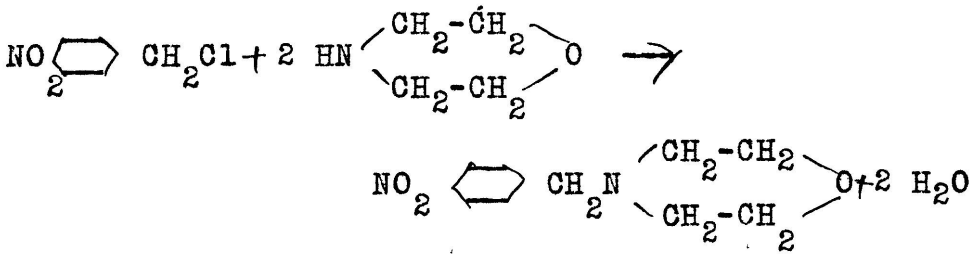
1. Alway J.A.C.S. 24 1062 1902

After the reaction period the contents were poured into a large quantity of ice water. A pasty mass resulted which was transferred to a Buchner funnel and filtered under powerful suction. The residue was recrystallized from alcohol and yielded 72 grams of para nitro benzyl chloride.

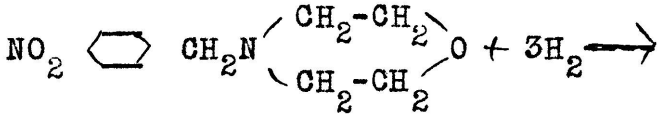
One mole[1] of p-nitrobenzene and 2.1 mole morpholine were dissolved in 200 cc dry benzene and refluxed on a steam bath over night. The benzene layer was then filtered from the precipitated morpholine hydro chloride. 75 cc of fresh dry benzene were refluxed with the morpholine hydro chloride for two more hours after which the benzene extract was removed by filtration and added to the first benzene filtrate. The benzene solution was then washed twice with water and dried over anhydrous sodium sulphate. This dried benzene solution then was poured into a filter flask from which the benzene was evaporated under reduced pressure. The crude p-nitro benzylmorpholine remained in the filter flask

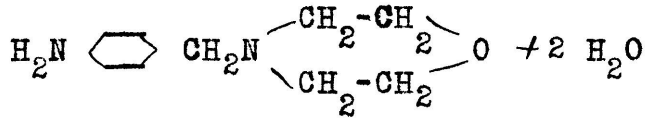
1. Leffler & Volwiler J.A.C.S. 60 896 1938

and was recrystallized from alcohol. Melting point 79-80° C. Yield 168 grams.



The p-nitro benzyl morpholine was reduced with hydrogen in the following manner: 100 grams of the nitro compound were suspended in 700 cc of ethyl alcohol. Most of the product dissolved but the alcohol became saturated. The contents were transferred to the hydrogen reduction apparatus and .3 gram of platinum oxide was added as catalyzer. The reduction was accomplished under 25 pounds hydrogen pressure and was completed in about 1 hour, and the suspended nitro compound went into solution as it was being reduced. After filtration to remove the catalyst, the alcohol was removed by vacuum evaporation and the crystals of para amino benzyl morpholine remained in the filter flask. The crystals were dried and the melting point determined at 101° C. Yield was almost theoretical.

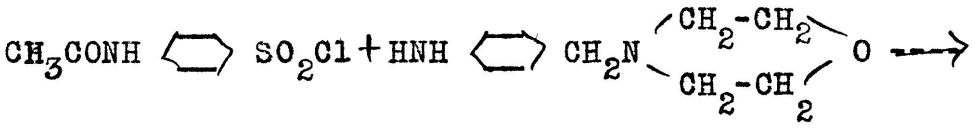


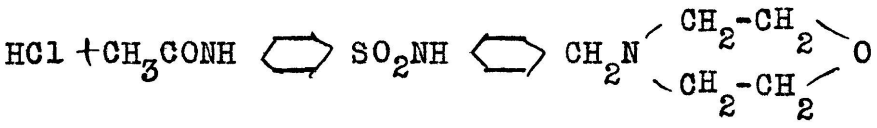


Twenty grams of parp aminobenzyl morpholine dissolved in 75 cc of ethyl alcohol, and 24 grams of acetyl sulfanil chloride dissolved in 50 cc of alcohol were heated to 60° C. and the chloride was slowly added to the amine with constant stirring. NaOH was added dropwise as needed to keep the reacting solution just basic. The temperature was kept at 60°C. for an hour and the solution was stirred occasionally. It was then set aside for 3 hours after which it was poured into 500 cc of water. A light creamy yellow precipitate separated which was removed by filtration and recrystallized from 20% alcohol. Yield 18 grams. Melting point 207° C. Nitrogen analysis calc. 10.79%. found 10.74%.

Attempts to remove the acetyl group by either acid or basic hydrolysis resulted in the

an amber colored gummy substance which solidified in ice water but melted at room temperature.





# SUMMARY

A number of derivatives of sulfanilamide have been prepared through the coupling reaction of acetylsulfanil chloride with the amino group of the appropriate compound.

In a series of these compounds the para amino group of the sulfanil derivative has been utilized to make a benzthiazole derivative by the direct thiocyanogenation method.

It is hoped that a number of the benzthiazole derivatives may be tested for their antibacterial activity. One of these compounds has been tested and was found to be highly toxic. Others are now ready to be tested.

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