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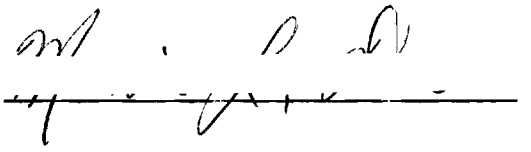

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THE CHEMISTRY OF URAMIL

A THESIS

Presented to

The Faculty of the Graduate Division

by

Marvin LeRoy Doerr

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

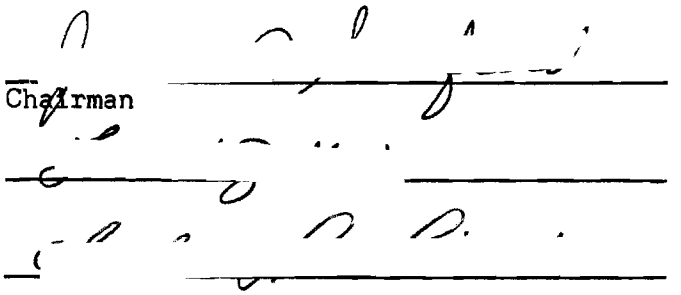
in the School of Chemistry

Georgia Institute of Technology

June, 1967

THE CHEMISTRY OF URAMIL

Approved:



Chairman

Date approved by Chairman: May 24, 1967

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SUMMARY

The object of this research was to prepare certain barbituric acids containing a sulfanilamido, an N-acetylsulfanilamido, or a N-succinoylsulfanilamido group at their 5-positions. It was thought that such compounds may have therapeutic value, due to reports of synergism of "sulfa" drugs with barbiturates. All of the compounds eventually synthesized also contained an alkyl or aryl substituent at the 5-position. This gave rise to 5,5-disubstituted barbituric acids. The 5,5-dialkyl barbituric acids are a class of compounds known to possess pronounced hypnotic activity.

In an attempt to prepare the simplest of these compounds, 5-sulfanilamidobarbituric acid, N-acetylsulfanilyl chloride was allowed to react directly with uramil, 5-aminobarbituric acid. Media for this reaction included aqueous sodium hydroxide, aqueous sodium carbonate, alcoholic sodium carbonate, ethanol, 1-butanol, pyridine, dimethylsulfoxide, N,N'-dimethylformamide, and chloroform, but in all cases, the desired condensation failed. In most instances, uramil was recovered unchanged; the use of dimethylsulfoxide at 150° resulted in destruction of both reactants. One difficulty in this approach arose from the inability to find an inert mutual solvent for uramil and N-acetylsulfanilyl chloride.

A second approach envisioned a base catalyzed cyclization of diethyl N-acetylsulfanilamidomalonate with urea, followed by hydrolysis, to produce the desired barbituric acid derivative. The former compound was successfully prepared by the condensation of N-acetylsulfanilyl

chloride with diethyl aminomalonate hydrochloride in pyridine. The hydrochloride salt was readily synthesized from diethyl malonate by nitrosation followed by catalytic reduction and conversion of the amine to its salt with gaseous hydrogen chloride. However, under the conditions necessary to effect the cyclization with urea the sulfur-nitrogen bond of the sulfonamide was ruptured. This produced derivatives of sulfanilic acid and not 5-substituted barbituric acids.

Since it was known that barbituric acids could also be synthesized from malonic acids and ureas under acidic conditions, the task of converting diethyl N-acetylsulfanilamidomalonate to N-acetylsulfanilamidomalonic acid was undertaken. Saponification of the diester afforded trisodium N-acetylsulfanilamidomalonate (the sulfonamide nitrogen losing its hydrogen to the base). It was discovered that each sodium atom could be exchanged, one at a time, by choosing the proper acidic conditions; however, the desired N-acetylsulfanilamidomalonic acid could never be isolated. Unfortunately, total acidification of this salt, even under very mild conditions, instead resulted in decarboxylation to give N-acetylsulfanilamidoacetic acid.

Finally, a successful procedure was developed by first structurally modifying uramil itself. It was found that 5-alkyluramils, and especially 1,3,5-trialkyluramils, reacted with N-acetylsulfanilyl chloride to give the corresponding alkylated 5-(N-acetylsulfanilamido)barbituric acids. The free amines were obtained by selective hydrolysis of the acetyl group in refluxing dilute aqueous hydrochloric acid. The trialkyluramils prepared were: 1,3,5-trimethyluramil, 5-ethyl-1,3-dimethyluramil, and 1,3-

dimethyl-5-phenyluramil. Each of these was synthesized by first reacting the proper diethyl alkylmalonate, in sodium ethoxide, with N,N'-dimethylurea to give the corresponding trialkylbarbituric acid. Each was next brominated, at the 5-position, and then converted, under pressure, to its uramil with gaseous ammonia.

The success of the reactions of trialkyluramils with N-acetylsulfanilyl chloride, in view of the continued failures with uramil itself has led to the conclusion that the classic structure of uramil as 5-amino-2,4,6-trioxohexahydropyrimidine does not adequately describe uramil's chemical behavior. The complete lack of basicity and nucleophilicity of uramil are certainly inconsistent with the properties of primary amines. Although it appears that a much better representation would be a structure involving one or more enolizations, its actual structure was not fully elucidated during this investigation. Other possible structures of uramil have also been suggested.

N-succinoylsulfanilamidobarbituric acids were likewise of interest due to their ability to form water soluble sodium salts, a property which is important for possible medicinal use. One such compound, 1,3,5-trimethyl-5-(N-succinoylsulfanilamido)barbituric acid, was successfully prepared by reacting 1,3,5-trimethyl-5-sulfanilamidobarbituric acid with a large excess of succinic anhydride in refluxing chloroform. Although not synthesized during this investigation, it has been predicted that related succinoyl compounds, containing a 5-ethyl or a 5-phenyl substituent, could also be prepared employing similar techniques.

Infrared and nuclear magnetic resonance spectra of a number of the compounds synthesized during this study were recorded. A Perkin-Elmer Infracord Model 137 spectrophotometer and a Varian Associates Model A-60 spectrometer, respectively, were used. All infrared spectra of compounds contained in the Appendix were determined as potassium bromide pellets. The insolubility of the uramils in the commonly used inert nuclear magnetic resonance solvents prevented obtaining their nuclear magnetic resonance spectra.

It has been recommended that several of the 5-sulfanilamido-barbituric acids synthesized during this investigation be submitted for physiological evaluation.

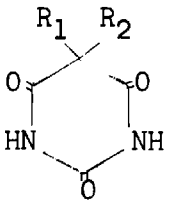
CHAPTER I

INTRODUCTION

Synergism is defined as the combined action of two or more agents that is greater than the sum of the action of the agents used alone. One of the important types of synergism is encountered in the field of medicine. Simultaneous administration of two or more therapeutic agents to a patient, to accomplish that which these agents separately could not, or could with less efficiency, is not an uncommon practice. One such example of synergism involving the effects of barbiturates and sulfanilamides (so called "sulfa" drugs) has been reported in medical journals (1, 10, 11, 27).

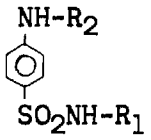
Concerning these two classes of compounds separately, certain substituted barbituric acids, commonly known as barbiturates, possess unusual physiological activity. They have a depressant action on the central nervous system and are, therefore, valuable as sedatives and soporifics (21). The "sulfa" drugs, coming under the category of chemotheropeutic agents, have been successfully used since about 1938 for the treatment of human diseases of bacterial and protozoal origin (34). A few of the most common barbiturates and "sulfa" drugs are shown in Figures 1 and 2.

The reports of synergism of barbiturates with "sulfa" drugs have thus prompted the work presented in this thesis culminating in the synthesis of new potential therapeutic agents. Basically, these compounds are substituted 5-sulfanilamidobarbituric acids incorporating



	R_1	R_2
Barbital	C_2H_5	C_2H_5
Phenobarbital	C_2H_5	C_6H_5
Amytal	C_2H_5	$(CH_3)_2CHCH_2CH_2$
Nembutal	C_2H_5	$CH_3CH_2CH_2$-CH-CH_3
Seconal	CH_2=$CHCH_2$	$CH_3CH_2CH_2$-CH-CH_3

Figure 1. Common Barbiturates



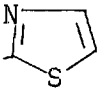
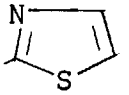
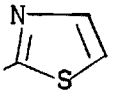
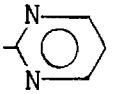
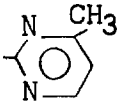
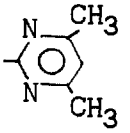
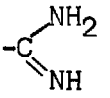
	R_1	R_2
Sulfathiazole		H
Sulfasuxidine		$COCH_2CH_2COOH$
Sulfathalidine		ortho-COC_6H_4COOH
Sulfadiazine		H
Sulfamerizine		H
Sulfamethazine		H
Sulfaguanidine		H

Figure 2. Common "Sulfa" Drugs

both the sulfa and the barbiturate into one molecule. The reason for preparing 5-sulfonamide substituted barbituric acids rather than other isomers, becomes apparent upon inspection of the structure of the acid. Thus, 5-aminobarbituric acid, commonly known as uramil, and various substituted uramils have demanded most of the attention during the course of this investigation.

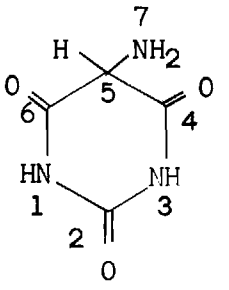
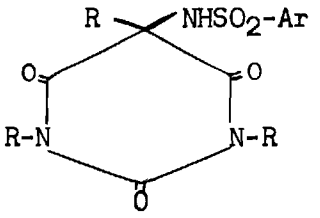


Figure 3. Uramil

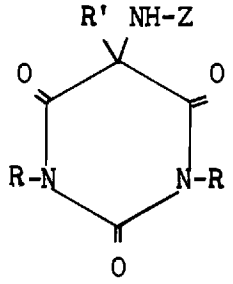
In all cases, the 5-amino group is ultimately transformed into a sulfonamide of the type shown below.



Where R = H, Alkyl, Aryl

Figure 4. Sulfonamides of Uramil and Substituted Uramils

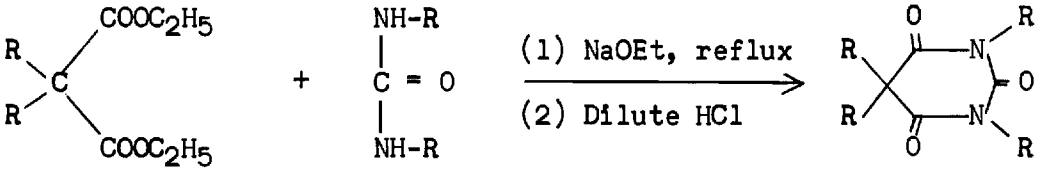
A rather large number of 7-alkyl and acyl uramils have been reported, a representative few being tabulated. Also reported have been a number of 7,7-dialkyl and 7-alkyl-7-acyl uramils. But prior to and during the time this program was being undertaken, no preparations for 5-sulfanilamidobarbituric acids were reported.



R	R'	Z	Reference
CH_3	H	$COCH_3$	8
H or CH_3	H	$COOCH_3$	4, 7
H	H	CH_2COOH	39
H	C_2H_5	C_6H_5	24
H	C_2H_5	$COCH_2Cl$	41

Figure 5. Typical Substituted Uramils

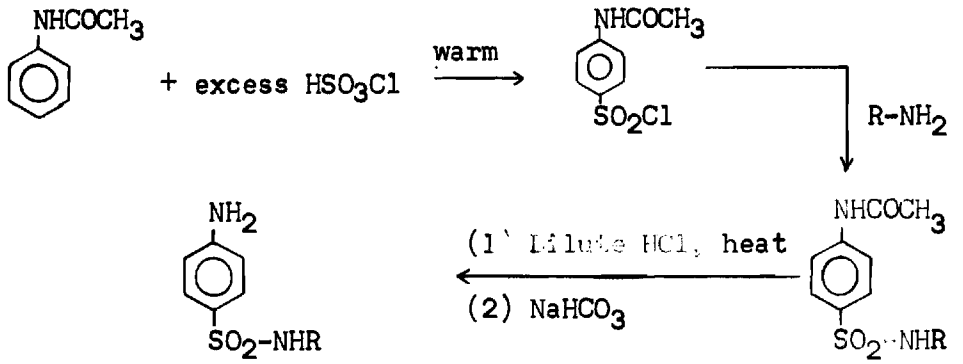
In approaching this problem, knowledge and application of the standard methods for the syntheses of barbituric acids and sulfanilamides were imperative. Generally, this was a rather routine part of the investigation since the literature is quite prolific in both. Figures 6 and 7 give examples of typical syntheses of each of these types.



Where R = H, Alkyl, Aryl

Figure 6. Synthesis of Typical Barbituric Acids

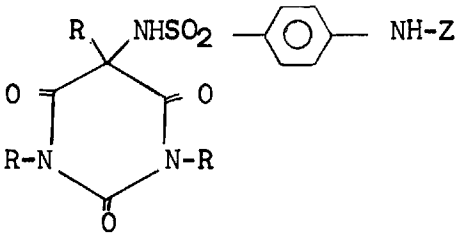
As previously implied, no references were found in the literature concerning the synthesis of 5-sulfanilamidobarbituric acids.



Where R = H, Alkyl, Aryl, Heterocycle, etc.

Figure 7. Synthesis of Typical Sulfanilamides

Some examples are shown in Figure 8. In actuality, the syntheses



Where R = H, CH_3, C_2H_5, C_6H_5

Z = H, $COCH_2CH_2COOH$

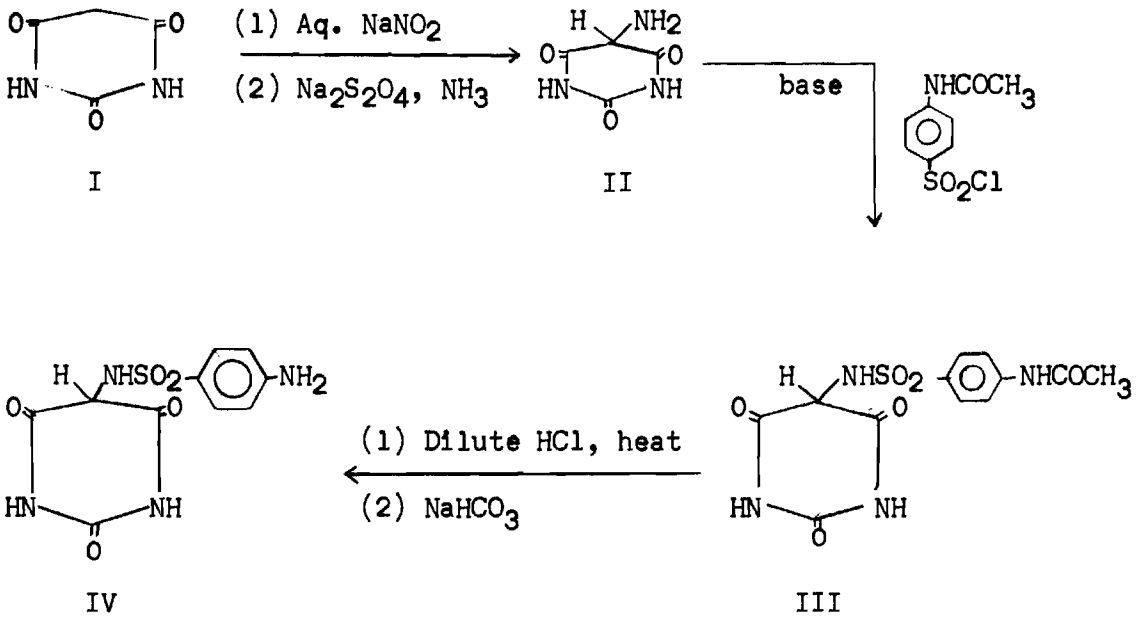
Figure 8. 5-Sulfanilamidobarbituric Acids

of these barbituric acid derivatives were found to be far more problematic than was originally expected.

CHAPTER II

DISCUSSION OF EXPERIMENTAL INVESTIGATIONS

Several methods of preparing the desired compounds were attempted. The initial work involved attempts to synthesize the simplest of these, 5-sulfanilamidobarbituric acid. An outline of this method starting with barbituric acid is shown in Figure 9.



I II III IV

Figure 9. First Proposed Path to 5-Sulfanilamidobarbituric Acid

Uramil, II, was quite easily prepared, but all attempts to condense it with N-acetylsulfanilyl chloride failed, unchanged uramil being recovered in most cases. One of the major difficulties at this point was the lack of an inert, mutual solvent for uramil and the sulfanilyl chloride. However, based upon conclusions arrived at by later experimentation, it must suffice for the moment to say that lack of a

common solvent alone was not responsible for the failure of this approach.

Because of the lack of success of this first approach, a second path was proposed as shown in Figure 10. Diethyl aminomalonate

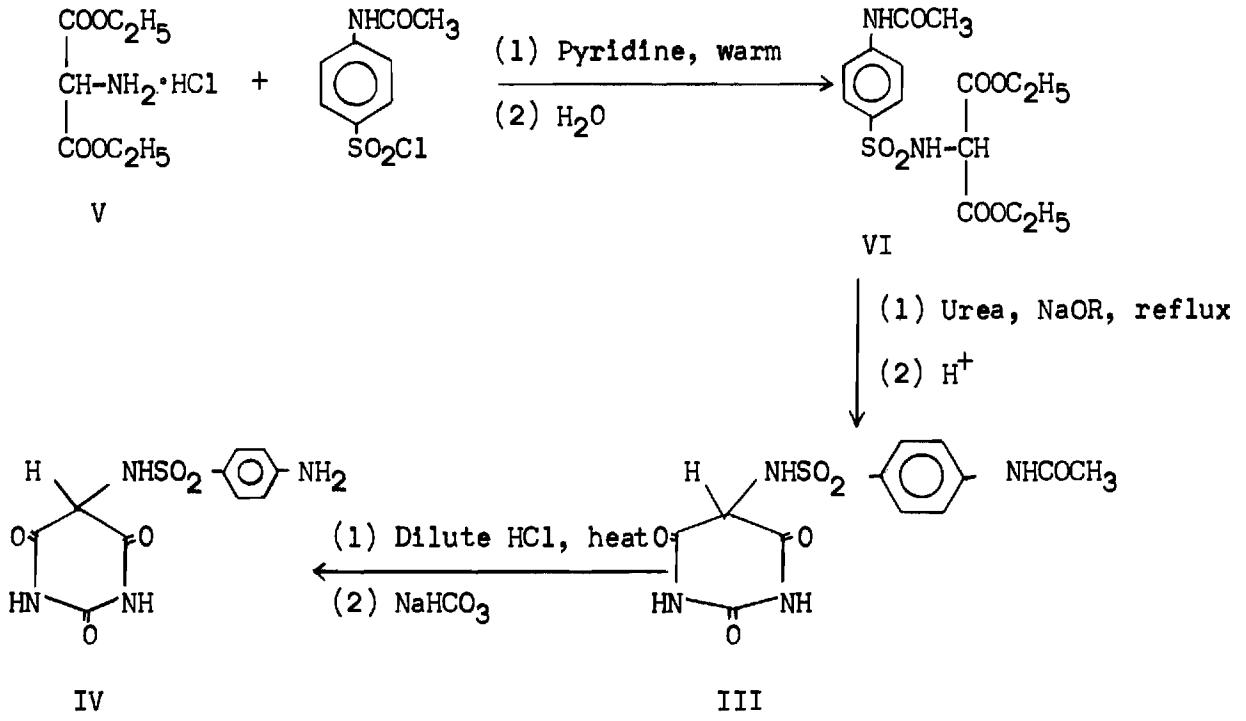


Figure 10. Second Proposed Path to 5-Sulfanilamidobarbituric Acid

hydrochloride, obtained from diethyl malonate by the method shown in Figure 11 below, reacted with N-acetylsulfanilyl chloride with no difficulty, to give diethyl N-acetylsulfanilamindomalonate, VI. Subsequent reaction of VI with urea and sodium ethoxide or potassium tert-butoxide continually failed to give the much sought after cyclized product, III. It was soon ascertained that the presence of such strong base, required by this barbituric acid synthesis, was extremely detrimental to the sulfonamide reactant. In all attempts, cleavage occurred to give, in most cases, unidentified fragments. Occasionally, after work-up, sul-

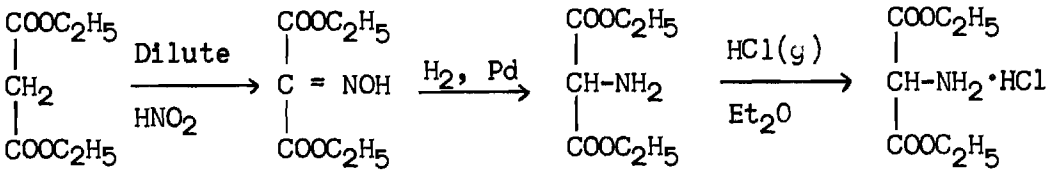
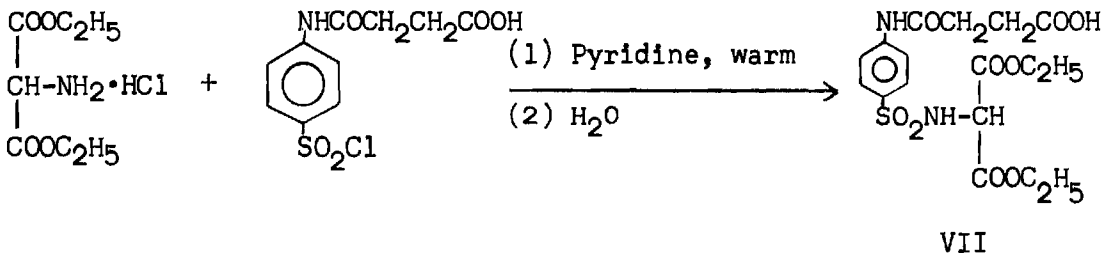


Figure 11. Synthesis of Diethyl Aminomalonate Hydrochloride

fanilic acid was identified as one of the fragmentation products, resulting not only from the sulfonamide cleavage, but also from the acylamide cleavage. Therefore, this second approach was abandoned in favor of one which did not require strongly basic conditions.

Concurrently, a similar synthesis to that indicated in Figure 10 was in progress, the goal being to produce diethyl N-succinoyl-sulfanilamidomalonate, VII, as shown in Figure 12. Condensation of this product with urea was then planned. The N-succinoylsulfanilyl chloride was produced by chlorosulfonation of succinic acid monoanilide obtained by the reaction of succinic anhydride with aniline.



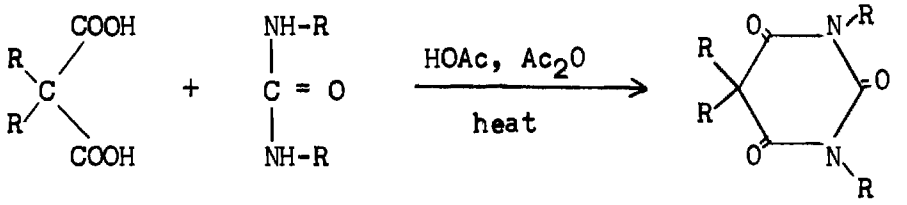
VII

Figure 12. Synthesis of Diethyl N-Succinoylsulfanilamidomalonate

The synthesis of VII, as was the case with VI, proceeded also with no difficulties. However, after discovering the fate of VI in the presence of strong base, the reaction of VII with urea and sodium ethoxide was not even performed, since it would obviously fragment in the same fashion. Also, before abandoning the synthesis of 5-(N-succinoyl-

sulfanilamido)barbituric acid completely, the reaction of N-succinoylsulfanilyl chloride with uramil, II, was attempted also with no success, for reasons to be discussed later.

A third proposal was based upon the fact that there exists a method of synthesizing barbituric acids in the absence of base, as outlined in Figure 13. This required that diethyl N-acetylsulfanilamido-



Where R = H, Alkyl, Aryl

Figure 13. Alternate Synthesis of Typical Barbituric Acids

malonate, VI, must first be converted to its corresponding diacid before the acid catalyzed reaction with urea could be tried. Thus, a third approach to 5-sulfanilamidobarbituric acid was undertaken as outlined in Figure 14, starting with VI. Initially, there was great speculation as to whether VIII was a di- or trisodium salt, as its purification and characterization were found quite challenging. But eventually, complete elucidation of its structure proved it to be the trisodium salt as written. The first attempts at obtaining 5-sulfanilamidobarbituric acid via this proposal involved reacting the trisodium salt, in the presence of glacial acetic acid and acetic anhydride, with urea directly rather than first isolating the malonic acid derivative, IX. Unfortunately, the products of this reaction were identified as N,N'-diacetylsulfanilamidoacetic acid, XI,(obtained in almost quantitative yield), N,N'-diacetylurea, XII, sodium acetate, and a gas assumed to be carbon dioxide. A reaction scheme accounting for these products is shown

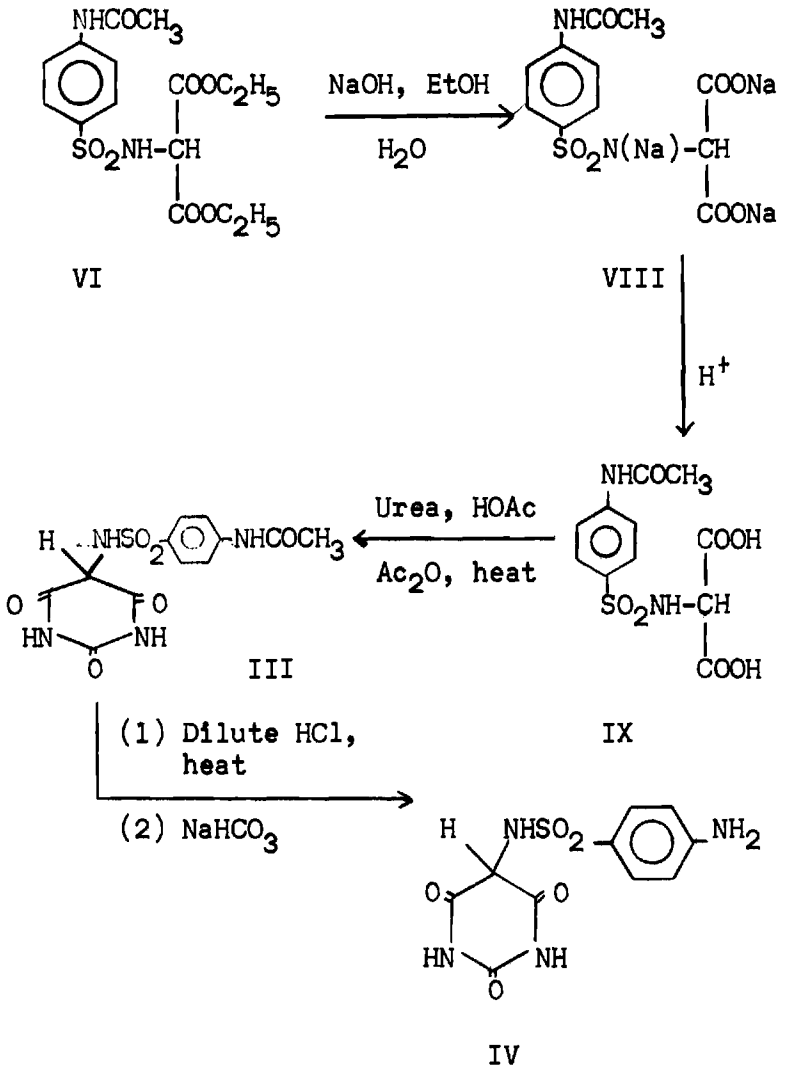


Figure 14. Third Proposed Path to 5-Sulfanilamidobarbituric Acid

in Figure 15. It then became apparent that, under these conditions, decarboxylation takes place much more rapidly than the reaction of the diacid with urea. It was now obvious that less drastic conditions were called for if the diacid, IX, was to be isolated. In attempting this, attention was focused mainly upon two cation exchange resins, Amberlite IRC-50 and Dowex 50W-X8, a weak and a strong acid exchange resin, respectively. This work, along with other data concerning this

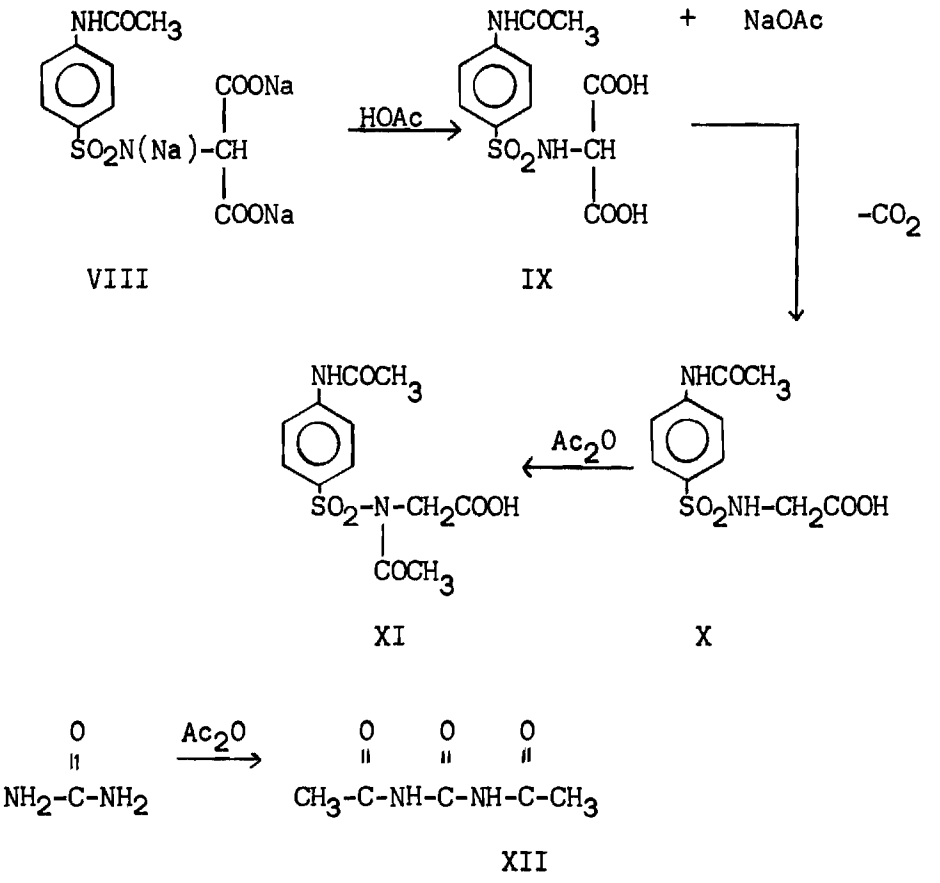


Figure 15. Reaction of Trisodium N-Acetylsulfanilamidomalonate with Urea

this immediate problem, is summarized in Figure 16. Uniquely enough, it was found that each sodium atom could be exchanged one at a time, by choosing the proper method of acidification. But in all cases, regardless of the conditions used, the sought after N-acetylsulfanilamidomalonic acid, IX, could never be isolated. Apparently, this compound is quite unstable and spontaneously decarboxylates and X, N-acetylsulfanilamidoacetic acid, was always the product obtained upon complete acidification. To help support the structure assigned to X, it was subjected to the same conditions as those outlined in Figure 15 and the product was also found to be N,N'-diacetylsulfanilamidoacetic

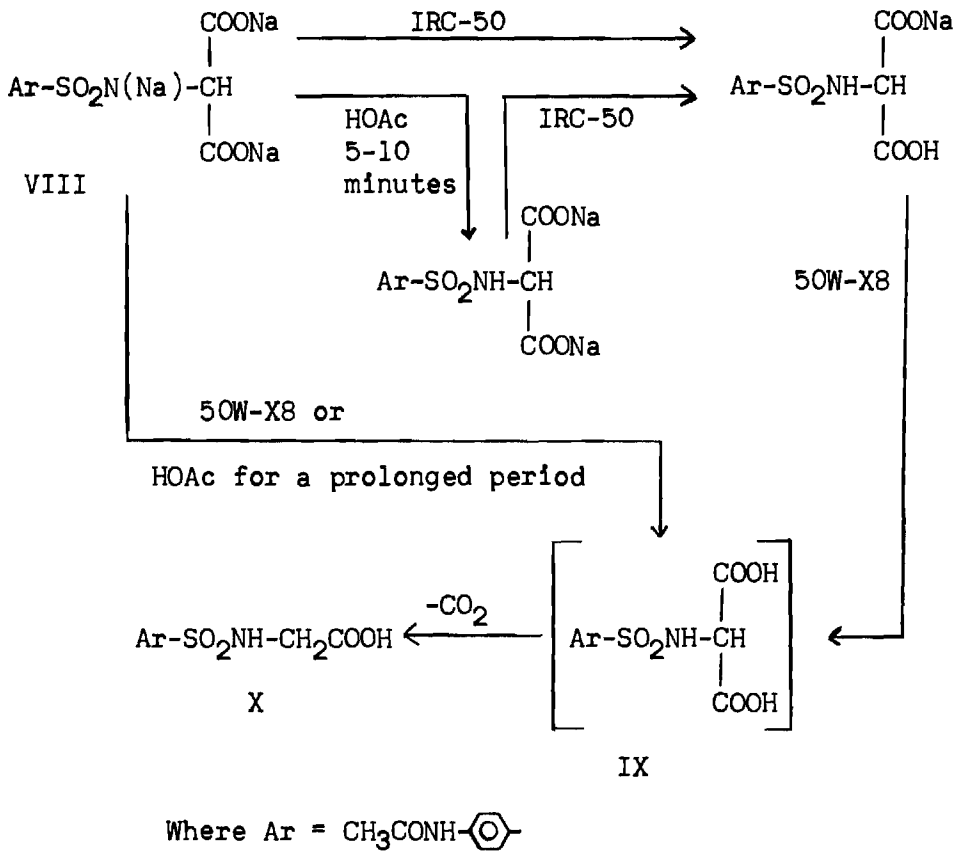


Figure 16. Acidification of Trisodium N-Acetyl-sulfanilamidomalonate

acid. This unexpected lack of stability of the required N-acetyl-sulfanilamidomalonic acid likewise spelled disaster for the third proposed path to the synthesis of 5-sulfanilamidobarbituric acid.

At this point, all hope for the successful preparation of 5-sulfanilamidobarbituric acid, itself, was abandoned and a closer investigation of uramil and alkylated uramils was commenced. Due to the anomalous physical and chemical properties of uramil, it was decided that such an investigation would be informative. Purification of uramil was finally accomplished by recrystallization from boiling concentrated hydrochloric acid. What is of singular importance is that no evidence whatsoever was obtained for the formation of a hydrochloride salt. This is in agreement with the report of Stein,

et al. (43) concerning the salt formation of 1-alkyl uramils, but in disagreement with that of Singh and Berlingoet (40) who reported hydrochloride salt formation of 5-alkyl uramils. The significance of this shall be considered at the end of the discussion. The infrared (IR) spectrum of the purified uramil did not show clear or sharp peaks in the regions of N-H or C = O stretchings (see Appendix). Instead, quite broad, poorly defined absorptions appeared. This may indicate that ring enolizations are occurring to some extent. Some such possibilities are shown in Figure 17. Contrary to popular representations, X-ray studies (26) of the solid have shown that

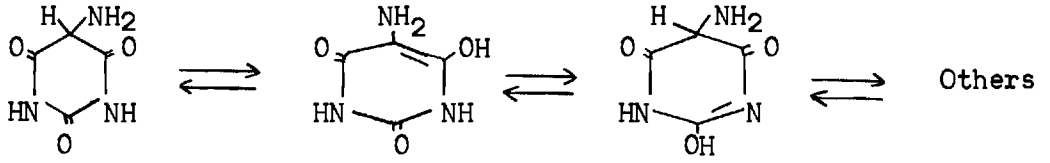
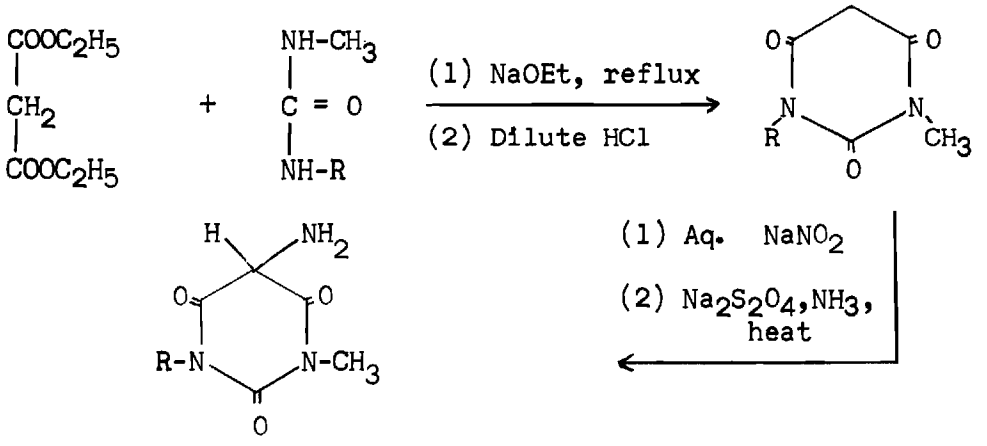


Figure 17. Possible Tautomers of Uramil

barbituric acid itself exists in its triketo form, but no such study of uramil has been undertaken. Some of the questions concerning the type and extent of enolization seemed to be answered by this present investigation, but this was by no means a complete study of the problem. Other spectral information was desired, but all attempts at obtaining a suitable nuclear magnetic resonance (NMR) spectrum of uramil failed completely due to its insolubility in inert NMR solvents. Dimethyl-sulfoxide, concentrated sulfuric acid, and 70 per cent perchloric acid were the only solvents found to dissolve enough uramil to obtain a spectrum. It was found that not only were these spectra quite different from each other, but also they were completely uninterpretable.

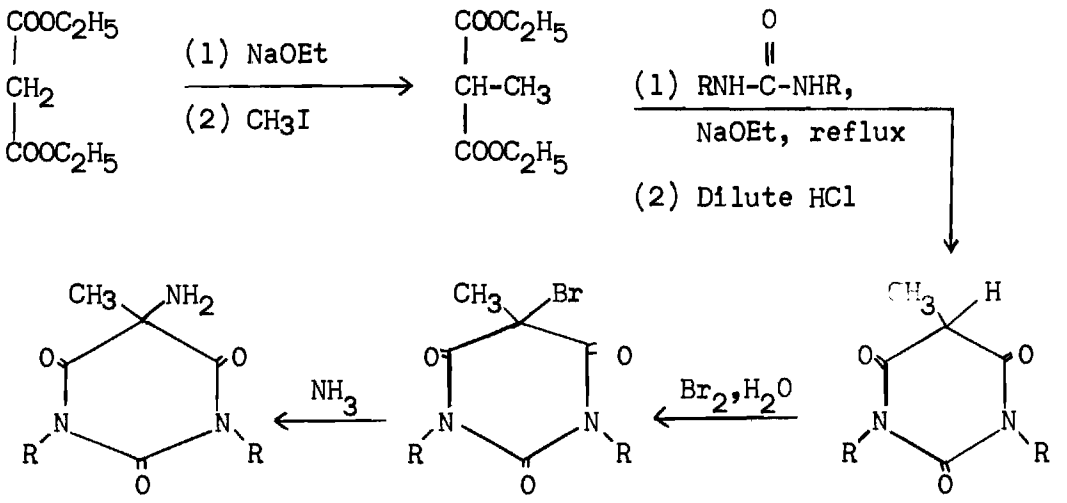
In fact, apparent identical preparations of samples occasionally resulted in non-reproducible spectra. Finally, it was concluded that a reaction was occurring with these solvents. It is thought that uramil in concentrated sulfuric acid was being protonated only, since it was recovered unchanged upon dilution. Such was probably the case in perchloric acid also, but the fate of the uramil in dimethylsulfoxide is obscure.

It was at this point that the investigation of various methylated uramils was begun, solely for the purpose of obtaining spectral information. Actually, this approach proved to be very fruitful. For the synthesis of the methyluramils, it was found that the same method was not applicable to all of them. Those containing a 5-methyl group required a different approach than had been used previously for the conversion of barbituric acid to uramil. These two paths are outlined in Figures 18 and 19. Of the five possible methylated



Where R = H or CH_3

Figure 18. Synthesis of Methyluramils Not Alkylated at the 5-Position



Where R = H or CH_3

Figure 19. Synthesis of Methyluramils Alkylated at the 5-Position

uramils, four of them, as shown in Table 1, were successfully prepared and characterized.

Concerning the IR spectra of these uramils and comparing them with that of the parent compound, there was found to be a definite increase in the sharpness of the N-H and C=O stretching regions, with increasing number of methyl groups present (see Appendix, Figs. 33-37). The uramils, in increasing order of spectral clarity in the above mentioned regions were: uramil, 1-methyluramil, 5-methyluramil, 1,3-dimethyluramil, and 1,3,5-trimethyluramil. Only in the case of 1,3,5-trimethyluramil, did the IR spectrum show sharp N-H and C=O stretches, two absorptions being observed, as expected, in the latter region. Since the introduction of each successive methyl group eliminates enolization possibilities, it seems justified in suggesting that uramil, itself, does not exist predominately in its triketo tautomer as is the case for barbituric acid. Additional work also substantiating this view shall be discussed shortly.

Table 1. Methyluramils

Uramil	Melting Point* Observed	Literature	
1-Methyluramil	254-258(d.)	253-256(d.)	(43)
5-Methyluramil **	233.0-234.5	237	(23)
1,3-Dimethyluramil	283-285	about 300	(6)
1,3,5-Trimethyluramil ***	92.5-94.0	105-106	(28)

* All melting points are in degrees Centigrade and were determined using a Mel-Temp melting point apparatus and are uncorrected.

** Calculated for $C_5H_7N_3O_3$: C = 38.22 per cent
H = 4.49 per cent
N = 26.74 per cent

Found: C = 38.25 per cent
H = 4.48 per cent
N = 27.11 per cent

*** Purification of this uramil was never successfully accomplished.

Like uramil itself, the lack of solubility in common NMR solvents of any of these methylated uramils precluded obtaining suitable NMR spectra. Again, only by using dimethylsulfoxide, concentrated sulfuric acid, or 70 per cent perchloric acid were any spectra obtained. For the most part, these spectra were uninterpretable with the sole exception that all methyl groups were always intelligible, regardless of

the solvent. Unfortunately, this did not help elucidate further the actual structure of uramil, since it was the hydrogens rather than the methyl groups that were of interest. Also, it is quite possible that even an interpretable spectrum may be meaningless when extrapolated to the pure solid, since it seemed likely that the uramils were reacting with these solvents.

Meanwhile, as spectral data of the various methyluramils were being gathered, a reaction of each was attempted with N-acetylsulfanilyl chloride, analogous to that of uramil shown in Figure 9. Even though all hope for the successful preparation of 5-sulfanilamidobarbituric acid, itself, had been abandoned, such was not the case for the alkylated 5-sulfanilamidobarbituric acids. However, when reactions of 1-methyluramil and 1,3-dimethyluramil with N-acetylsulfanilyl chloride were tried, they all, not unexpectedly, failed as had uramil. This same reaction was next attempted with 1,3,5-trimethyluramil, and astonishingly enough, this condensation was found to proceed in good yield to give 1,3,5-trimethyl-5-(N-acetylsulfanilamido)barbituric acid, Figure 20.

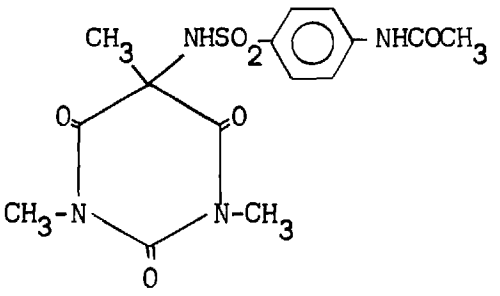
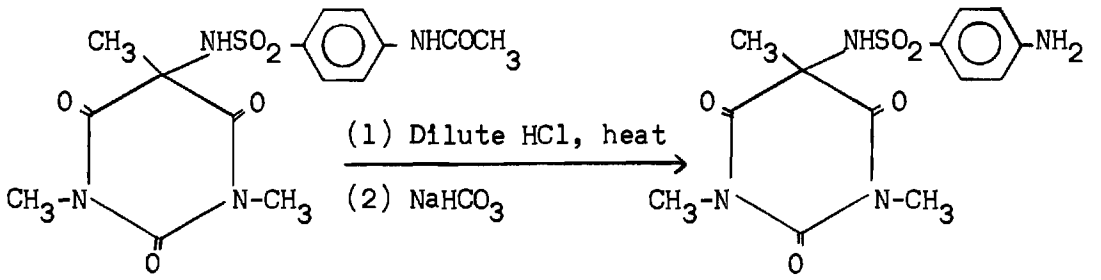


Figure 20. 1,3,5-Trimethyl-5-(N-acetylsulfanilamido)barbituric Acid

For the purpose of possible physiological activity studies, the hydrolysis of the acetyl group was desired. This was found to be accomplished

selectively, as is outlined in Figure 21, to give 1,3,5-trimethyl-5-sulfanilamidobarbituric acid, XIII.



XIII

Figure 21. Hydrolysis of 1,3,5-trimethyl-5-(N-acetylsulfanilamido)barbituric acid

Despite all the past failures, it was considered advantageous that this 5-sulfanilamidobarbituric acid did contain 5-alkyl substituent. This is due to the fact that of the barbituric acid derivatives which have been reported to have pronounced hypnotic activity, all are di-substituted in the 5-position(15). In fact, some 1,3,5,5-tetraalkyl derivatives are known to produce action of transient character (12).

At this point, it would be desirable to have a better understanding of why 1,3,5-trimethyluramil reacted with N-acetylsulfanilyl chloride while the other uramils failed completely to do so. It is noted that the only difference was the presence of a 5-methyl substituent and thus, it is this difference alone which must account for the observed facts. As had previously been discussed, it was suspected from IR spectra, that the triketo form of uramil was not its best representation. Additional support for this was supplied by Cox, Macbeth, and Pennycuick (16) who studied the 5-halobarbituric acids. After noting the inertness of these compounds and observing their spectra, these workers concluded that the

5-halo derivatives of barbituric acid exist in the enolic modification shown in Figure 22. In this enol form, being analogous to a vinyl

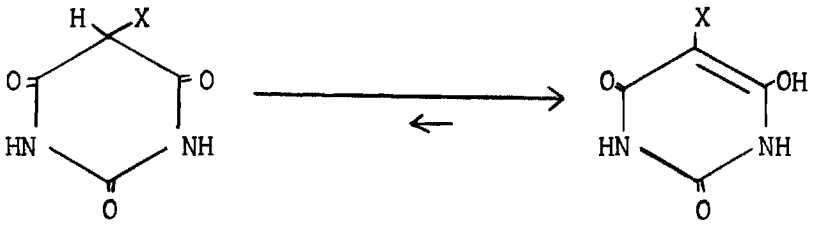
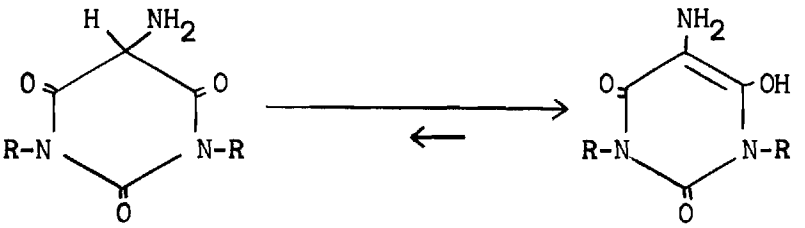


Figure 22. Enolization of 5-Halobarbituric Acids

halide, the lack of reactivity is explained. Cox, et al. also suggests that in the 5-halo-5-alkyl barbituric acids, the existance of the enolic form is excluded and the reactivity of the halogen atom is to be expected as was confirmed.

It is most likely that the same phenomenon is also responsible for the nucleophilic behavior of 1,3,5-trimethyluramil, whereas none was observed for uramil, 1-methyluramil, and 1,3-dimethyluramil. Therefore, it seems most justified to suggest that 5-unsubstituted uramils exist in the enolic modification of Figure 23. Due to resonance of the type shown



XIV

Figure 23. Enolization of Uramils Unsubstituted in the 5-Position

in Figure 24, it can be argued that the enol structure, XIV, would account not only for the loss of nucleophilicity as supported by

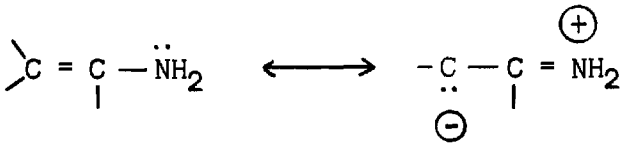
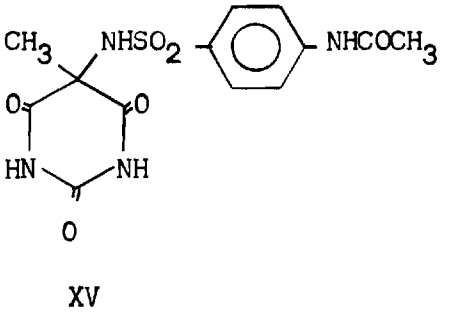


Figure 24. Resonance of Vinyl Amines

experiment, but also the lack of expected basicity of a primary amine. It has previously been pointed out that a hydrochloride salt of uramil could not be obtained, which also agreed with that reported for 1-alkyl uramils (43). What had originally seemed paradoxical, the salt formation of 5-alkyl uramils (40), can now be explained by noting that the enolic form is excluded and normal amine behavior should be expected.

If this theory is correct in that only the presence of a 5-alkyl group is demanded to impart normal nucleophilic behavior to the uramils, then the absence of alkyl groups on the 1- and 3- positions should make no difference. To test this hypothesis, the last remaining uramil, 5-methyluramil, was next allowed to react with N-acetylsulfanilyl chloride. It appears, from incomplete evidence, that the desired product, 5-methyl-5-(N-acetylsulfanilamido)barbituric acid, XV, was obtained. However, the conditions required to bring the reaction about were more drastic than those for 1,3,5-trimethyluramil and, as a result,



XV

Figure 25. 5-Methyl-5-(N-acetylsulfanilamido)barbituric Acid

the yield of XV plunged drastically due to decomposition products. The fact that the reaction did occur, even to some extent, while all of the 5-unsubstituted uramils failed to react supports the hypothesis. However, no explanation is given for the difference in reactivity of 5-methyluramil and 1,3,5-trimethyluramil under the same conditions. Because of this difference, all attention was then shifted solely to the trialkyl uramils.

Even as convincing as the above argument may appear, there exists analogies from which it could be concluded that this may not be the complete explanation. The following is total speculation, but it presents a problem that should be considered at this time. It is noted that in all of the "sulfa" drugs listed in Figure 2, the amine from which the drug was produced is a vinyl amine, exactly analogous to that proposed for the 5-unsubstituted uramils in Figure 23. The fact that each of these heterocyclic amines do react with aromatic chlorides, whereas the uramils fail to react, is a point not to be taken lightly. As an example, one possible answer for this dilemma comes from a closer look into the preparation of sulfathiazole. It is a fact (13) that in the reaction of 2-aminothiazole with N-acetylsulfanilyl chloride, the major side product is the sulfonamide shown in Figure 26. Cason and Rapoport state (13) that

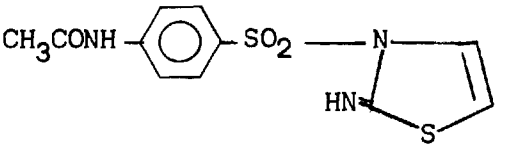


Figure 26. Side Product of the Reaction of N-Acetylsulfanilyl Chloride with 2-Aminothiazole

this is a result of the tautomerism of the amino hydrogen between the exocyclic nitrogen and the ring nitrogen, Figure 27. If such tautomerism is indeed so, such reasoning may also be applied to the 5-unsubstituted

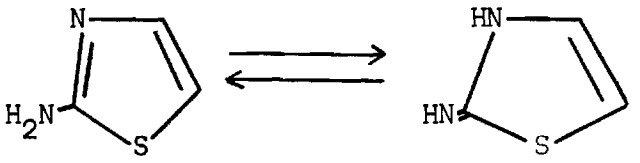
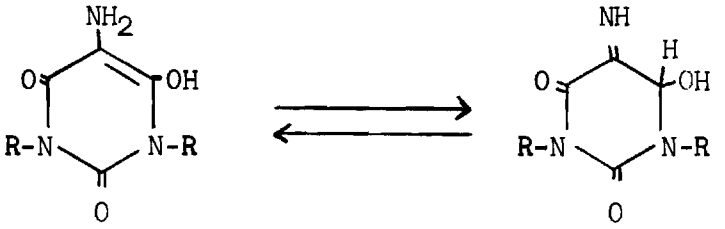


Figure 27. Possible Amine Tautomerism of 2-Aminothiazole

uramils as shown in Figure 28. Complete lack of nucleophilicity



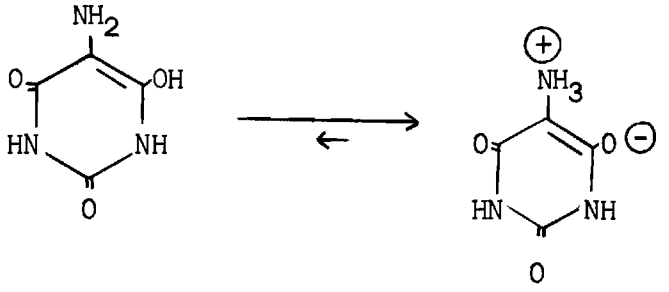
XIV XVI

Figure 28. Possible Amine Tautomerism of Uramils Unsubstituted in the 5-Position

as judged by attempted reactions of such uramils with sulfonyl chlorides and total inability to function as bases as determined by their lack of hydrochloride salt formation and probable protonation only under the most acidic conditions would be better explained by structure XVI.

As was mentioned earlier, this proposal is complete speculation. It would be expected that a structure such as XVI, being an imine, would very easily undergo hydrolysis and such has not been observed. It is worthwhile to point out that it is conceivable that structure XIV may well not be the complete answer to the anomolous behavior of uramil.

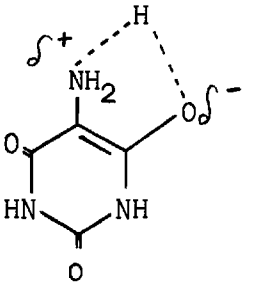
Other proposals are also possible. Because uramil does not melt below 400°, a zwitterionic structure such as XVII, resulting from an intramolecular proton transfer, would also be conceivable.



XIV XVII

Figure 29. Possible Zwitterionic Structure of Uramil

Structure XVIII could even be written as an alternative (Figure 30).



XVIII

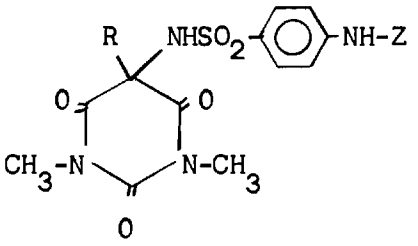
Figure 30. Alternate Possible Structure of Uramil

However, since zwitterionic compounds are frequently soluble in perfluoro solvents, uramil's lack of solubility in trifluoroacetic acid tends to shed doubt upon this proposal, also. Obviously, only by a more thorough study than was undertaken here, will the nature of the actual structure of uramil be solved.

The observation that placement of an alkyl group at the 5-

position prevented enolization or tautomerism was important to the success of this investigation. Only by this procedure was it possible to synthesize 5-sulfanilamidobarbituric acids.

The remaining work was concerned primarily with obtaining various sulfanilamidobarbituric acids whose structures most resembled those of barbiturates and "sulfa" drugs known to possess unique physiological activity. Such compounds of interest are summarized by Figure 31.



Where R = C_2H_5 as in barbital

R = C_6H_5 as in phenobarbital

Z = H as in most of the "sulfa" drugs

Z = $COCH_2CH_2COOH$ as in sulfasuxidine

Figure 31. Various Trialkyl 5-Sulfanilamidobarbituric Acids

In the synthesis of 1,3,5-trimethyl-5-(N-succinoylsulfanilamido)barbituric acids, the procedure previously used to succinoylate a primary aromatic amine (aniline) failed (14). It was thought that loss of the nucleophilicity of the amino group was due to resonance interaction as shown in Figure 32. In this case, the solvent, water, competed much better for the succinic anhydride than could the sulfanilamide. Such was also the case when methanol was used as the solvent. A successful method was arrived at by using a large excess of succinic anhydride in the non-nucleophilic solvent, chloroform. This was the

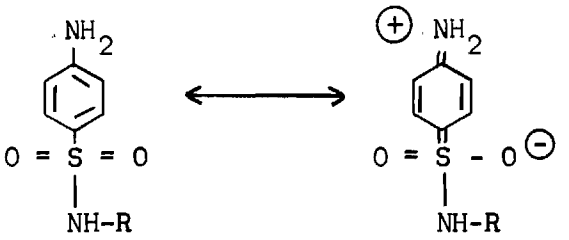


Figure 32. Resonance of Sulfanilamides

only succinoylated "sulfa" drug prepared in this investigation, but it was thought that additional ones could also be synthesized by applying the same method to the other trialkyl-5-sulfanilamidobarbituric acids next to be discussed.

Starting with diethyl ethylmalonate and diethyl phenylmalonate, 5-ethyl-1,3-dimethyluramil and 1,3-dimethyl-5-phenyluramil, respectively, were synthesized by the route shown in Figure 19. By condensing each with N-acetylsulfanilyl chloride, and following with acid catalyzed hydrolysis, 5-ethyl-1,3-dimethyl-5-sulfanilamidobarbituric acid and 1,3-dimethyl-5-phenyl-5-sulfanilamidobarbituric acid were also successfully prepared. Although of no consequence to the syntheses, it was interesting to note a marked difference in the rates of hydrolyses of the three trialkyl-5-(N-acetylsulfanilamido)barbituric acids. The hydrolysis rates of their N-acetyl groups decreased in the order: methyl, ethyl, phenyl, as the 5-substituent of the barbituric acid. Since resonance interaction of these groups with the hydrolysis site is not possible in these molecules, it was conceived that steric crowding about the N-acetyl group, as a result of the increased bulk of the 5-substituent, was responsible for the observed rate variations.

In Table 2, are summarized all of the compounds, previously unreported, which were obtained during this investigation. Spectra of

most of them are contained in the Appendix as indicated. Four of these compounds, 1,3,5-trimethyl-5-sulfanilamidobarbituric acid, 5-ethyl-1,3-dimethyl-5-sulfanilamidobarbituric acid, 1,3-dimethyl-5-phenyl-5-sulfanilamidobarbituric acid, and 1,3,5-trimethyl-5-(N-succinoylsulfanilamido)-barbituric acid are to be screened for possible physiological activity.

Table 2. New Compounds

Compound	M. P. (C°)	Spectra Figure
Pyridinium N-Acetylsulfanilate	181-183	38
Diethyl N-Acetylsulfanilamidomalonate	163.5-164.5	39,53
Diethyl N-Succinoylsulfanilamidomalonate	166.0-167.5	40
Trisodium N-Acetylsulfanilamidomalonate	281-284(d.)	41,54
N-Acetylsulfanilamidoacetic Acid	239-241	42,55
N,N'-Diacetylsulfanilamidoacetic Acid	183-184	43,56
5-Bromo-1,3,5-trimethylbarbituric Acid	112.5-113.0	--
5-Bromo-5-ethyl-1,3-dimethylbarbituric Acid	57.5-59.0	--
5-Ethyl-1,3-dimethyluramil	*	44
1,3-Dimethyl-5-phenyluramil	*	--
5-Methyl-5-(N-acetylsulfanilamido)barbituric Acid	*	45
1,3,5-Trimethyl-5-(N-acetylsulfanilamido)barbituric Acid	274.0-275.5	46
1,3,5-Trimethyl-5-sulfanilamidobarbituric Acid	261.0-263.0	47
1,3,5-Trimethyl-5-(N-succinoylsulfanilamido)barbituric Acid	274-276	48
5-Ethyl-1,3-dimethyl-5-(N-acetylsulfanilamido)barbituric Acid	277.5-278.5	49
5-Ethyl-1,3-dimethyl-5-sulfanilamidobarbituric Acid	199.0-199.5	50
1,3-Dimethyl-5-phenyl-5-(N-acetylsulfanilamido)barbituric Acid	265.5-266.5(d.)	51
1,3-Dimethyl-5-phenyl-5-sulfanilamidobarbituric Acid	239.5-241.0	52

*Sample was not able to be purified successfully.

CHAPTER III

EXPERIMENTAL

All melting points and boiling points are in degrees Centigrade and are uncorrected. Melting points were determined in capillary tubes using a Mel-Temp melting point apparatus. Elemental microanalyses were performed by either Dr. Alfred Bernhardt, Mulheim, West Germany or Galbraith Laboratories, Knoxville, Tennessee. Molecular weights were determined with a Mechrolab Vapor Pressure Osmometer, Model 301A. Infrared spectra employing potassium bromide pellets were recorded using a Perkin-Elmer Infracord Model 137 spectrophotometer. Nuclear magnetic resonance spectra were obtained with a Varian Associates Model A-60 spectrometer. Spectral data are occasionally reported throughout the experimental section, but the Appendix contains the complete spectra of a number of compounds whose preparations have herein been described.

Attempted Preparation of 5-(N-Acetylsulfanilamido)-barbituric Acid by Direct Condensation

Uramil

The method of Davidson and Epstein (17) was followed in preparing this compound. Multiple preparations resulted in yields of crude uramil from 58 per cent to 85 per cent. Uramil did not melt below 400°. In all of the following experiments, unpurified uramil was used unless otherwise indicated. Uramil purification was accomplished by crystallization from boiling concentrated hydrochloric acid (29). However, uramil became pink when exposed to the atmosphere and, therefore, was stored in the refriger-

ator under concentrated hydrochloric acid.

Attempted Reaction of Uramil with N-Acetylsulfanilyl Chloride

This reaction was tried a total of thirteen times, but due to the similarity of conditions, only a complete description of a few trials shall be given. A typical experiment was performed as follows. In a three-necked flask fitted with a stirrer, condenser, thermometer, and heating mantle were introduced 1.00 g. (0.0070 mole) of uramil and 200 ml. of N,N'-dimethylformamide. The mixture was refluxed for 15 minutes in a futile attempt to dissolve completely the uramil. It was then cooled to 75° after which 560 mg. (0.0070 mole) of pyridine and 1.63 g. (0.0070 mole) of N-acetylsulfanilyl chloride were added. The mixture was stirred for three hours while maintaining the temperature at 75°. Upon cooling, the resulting solid was removed by filtration and was found to be unreacted uramil. Work with the filtrate failed to result in the isolation of any identifiable product.

Very similar reactions to the one described above were also performed, the major differences being only in the solvents chosen. Other solvent systems used were aqueous sodium carbonate, alcoholic sodium carbonate, ethanol, and butanol. Procedures for very similar reactions suggested by Schwarzenbach, et al. (39) and Desai and Mehta (18) utilizing five normal sodium hydroxide and chloroform, respectively, were also tried. In all cases, however, unreacted uramil was again the only identifiable product. The use of dimethylsulfoxide in the presence of a stoichiometric quantity of quinoline at 150°, resulted in destruction of both reactants.

Attempts at heating a mixture of the two reactants under nitrogen at the melting point of N-acetylsulfanilyl chloride also failed to give

the desired condensation. Only unreacted starting materials, along with degradation products of the aromatic sulfonyl chloride, were obtained.

In another attempt, to 100 g. of pyridine was added 2.86 g. (0.020 mole) of uramil and 4.67 g (0.020 mole) of N-acetylsulfanilyl chloride. The mixture was warmed for 30 minutes and then stirring of the mixture at 25° was continued overnight. After filtering off the unchanged uramil, 81 per cent recovery, the filtrate was stirred for 16 hours with 35 g. of Amberlite IRC-50 ion exchange resin in 100 ml. of absolute ethanol. After resin removal, the solution was treated with decolorizing carbon, thoroughly filtered, and stripped under vacuum to a volume of 30 ml. To this was added 500 ml. of benzene and the orange oil which separated, solidified upon scratching the sides of the flask. After removal by filtration, the orange solid was dissolved in a minimum quantity of absolute ethanol, benzene was added until turbidity occurred, and the solution was placed under vacuum. Shortly thereafter, an off-white solid precipitated, which was filtered off and washed with acetone. This solid was subjected to two more ethanol and benzene treatments, as described above, to give 240 mg. (4 per cent yield) of a slightly off white solid with m. p. 181-183°. The product was found to be water soluble and to liberate pyridine in the presence of aqueous sodium hydroxide. This information, coupled with physical data of the compound, led to the conclusion that it was a pyridinium salt, namely pyridinium N-acetylsulfanilate. Its IR spectrum showed major absorptions at 3.03, 3.22, 5.90, and 12.05 microns, the last peak being characteristic of a <u>para</u>-substituted benzene ring (20).

Calculated for $C_{13}H_{14}N_2O_4S$: molecular weight, 294;

N, 9.52; S, 10.90.

Found: molecular weight, 284;

N, 9.25; S, 11.59.

Obviously, this product was the result of using undried pyridine as the solvent. Some of the N-acetylsulfanilyl chloride was hydrolyzed to N-acetylsulfanilic acid which then formed the salt with the solvent.

Attempted Preparation of 5-(N-Acetylsulfanilamido)-barbituric Acid Under Basic Conditions

Diethyl Isonitrosomalonate

Synthesis of this compound utilized the method described by Zambito and Howe (48). Typical crude yields were on the order of 75 per cent. Attempted purification by vacuum distillation resulted in rapid decomposition of near explosive proportions. The ester was, therefore, always used in its crude form.

Diethyl Aminomalonate

This compound was prepared by the reduction of diethyl isonitrosomalonate. However, the methods of Johnson and Nicolet (31) using hydrogen sulfide in base and Putochin (37) using platinum oxide catalyzed hydrogenation in ethanol gave but very low yields. The procedure of Hartung, et al. (30) using palladium catalyzed hydrogenation in dry ether was found to be superior. The resulting diethyl aminomalonate was isolated and characterized by conversion to its hydrochloride salt followed by purification.

Diethyl Aminomalonate Hydrochloride

The method of Hartung, et al. (30) was followed for the synthesis of this compound; however, much better purity and recrystallization recovery was realized if the solvent used was acetone rather than the mixed

solvent system reported. Typical overall yields, based upon diethyl malonate, were on the order of 20 per cent. The pure solid was found to melt at 166.0-166.5° (lit. (30) m. p. 163-164°).

Calculated for $C_7H_{14}ClNO_4$: C, 39.72; H, 6.68;
N, 6.62; Cl, 16.75.

Found: C, 40.20; H, 6.76
N, 6.63; Cl, 16.66.

Diethyl N-Acetylsulfanilamidomalonate

To 85 ml. of pyridine was added 21.2 g. (0.10 mole) of diethyl aminomalonate hydrochloride and stirring commenced. To the flask, immersed in an ice bath, was slowly added 24.6 g. (0.105 mole) of N-acetylsulfanilyl chloride. Upon complete solution, the contents were stirred for 24 hours at 40°. This was first filtered then slowly poured into a mixture of 450 ml. of ice and water with vigorous stirring. A solid formed. After the ice had melted, the light tan solid was filtered off and was washed with two 50 ml. portions of ice water. After drying, the product was crystallized from toluene in better than 95 per cent recovery to give 20.4 g. (55 per cent yield) of a white, very fluffy solid, m. p. 163.5-164.5°. Principal diagnostic IR absorptions were at 3.00, 3.31, 5.73, 5.97, 7.47, 8.63, and 12.14 microns. The NMR spectrum will be found in the Appendix.

Calculated for $C_{15}H_{20}N_2O_7S$: N, 7.52; S, 8.59.

Found: N, 7.53; S, 8.35.

Attempted Condensation of Diethyl N-Acetylsulfanilamidomalonate with Urea

This procedure is based on that of Dickey and Gray (19) who reported the condensation of diethyl malonate with urea. In a 250 ml. round-bottomed flask equipped with a heating mantle, magnetic stirrer, and a reflux condenser, were placed 35 ml. of absolute ethanol and 253

mg. (0.011 mole) of freshly cut sodium. As soon as the sodium had completely reacted, 3.724 g. (0.010 mole) of diethyl-N-acetylsulfanilamidomalonate was added followed by 600 mg. (0.010 mole) of dry urea in ten ml. of hot absolute ethanol and refluxing commenced. Shortly thereafter, the solution became dark red in color. Refluxing was continued for seven hours. To this red solution was added 25 g. of Amberlite IRC-50 ion exchange resin and the mixture mechanically stirred overnight. After filtering off the resin, decolorizing carbon was added to the filtrate and the mixture was stirred overnight. The filtrate, following removal of the carbon by filtration through both paper and sintered-glass filters, was now pale yellow in color. To this filtrate was added 400 ml. of benzene whereupon a colorless gelatinous mass formed. After filtration and drying, 467 mg. of product was recovered. Recrystallization from 1-butanol gave 133 mg. (28 per cent recovery) of a white amorphous solid, m. p. 333-335° (d.). Analysis of this compound failed to support the desired structure. The IR spectrum showed important absorptions at 3.01, 3.20, 6.02, and 12.04 microns; however, the lack of two strong absorptions in the vicinity of 7.7 and 8.7 microns, tended to indicate that the sulfur-nitrogen bond of the sulfonamide had been cleaved.

Several other attempts, following the same general procedure with differences being only in the isolation techniques, also seemed to support this conclusion. Analyses continually indicated that the desired condensation had failed and infrared spectra were void in the S = O stretching regions of a sulfonamide. The actual structure of the product obtained, as described above, was never conclusively determined; however, IR and NMR spectra indicate that it was a derivative of N-acetylsulfanilic acid.

In two attempts, one utilizing aqueous acid in the work-up and the other using potassium tert-butoxide as the base and Dowex 50W-X8 as the exchange resin, acetic acid and sulfanilic acid were the only products identified. It was thus concluded that the conditions of strong base required to prepare the barbituric acid were disasterous to the sulfonamide portion of the molecule. All hope of obtaining 5-(N-acetylsulfanilamido)barbituric acid by the base catalyzed reaction was abandoned. A proposed method utilizing acidic catalysis shall be described shortly.

Attempted Preparation of 5-(N-Succinoylsulfanilamido)-barbituric Acid

Succinic Acid Monoanilide

A method very similar to that described by Cason and Rapoport (14) for the preparation of acetanilide was used. To a solution of 24 ml. of concentrated hydrochloric acid in 700 ml. of water was added 26.0 g. (0.28 mole) of aniline. The aniline was brought into solution with stirring. Since the aniline used was old and discolored, several grams of decolorizing carbon was added and the mixture stirred for three hours. The mixture was first filtered by gravity and then again through a sintered-glass filter to assure complete carbon removal. The aniline hydrochloride solution was then warmed to 75° and 35.0 g. (0.35 mole) of succinic anhydride was added and dissolved by stirring very briefly. This was followed by the immediate addition of a solution of 44 g. of sodium acetate in 150 ml. of water. The hot solution was then suction filtered and chilled thoroughly in an ice bath. The crystallized product was collected, washed with a small quantity of ice water, and dried. The dried crystals, being slightly off-white in color, weighed 42.5 g. (79 per cent yield), m. p. 145.0-146.0° (lit. (2) m.p. 144.5-145.5°). The

succinic acid monoanilide was used without further purification.

Yields of other preparations ranged from 71 to 83 per cent, the highest being obtained on a three molar scale.

N-Succinoylsulfanilyl Chloride

A method adapted from that of Cason and Rapoport (14) for N-acetylsulfanilyl chloride was used. In a 500 ml. round-bottomed flask was placed 9.65 g. (0.050 mole) of dry succinic acid monoanilide. It was melted by gently heating with a flame and permitted to solidify as a solid cake on the lower walls of the flask by moderate swirling as it cooled. The entire flask was then gently flamed in order to remove completely any water within the flask. The flask was fitted with a gas trap and, after thorough cooling in an ice bath, 29.2 g. (0.25 mole) of chlorosulfonic acid was added in one portion. The flask was then removed from the ice bath and the reaction allowed to proceed with occasional swirling. After no more solid reactant was visible, the mixture was heated on a steam bath for two hours to complete the reaction. This was then poured slowly, with stirring, into a mixture of 100 g. of ice and 100 ml. of water. A gummy mass resulted, which, after stirring in the presence of the solvent, became solid. The product was filtered with suction and washed with ice water. The dried, yellow solid of crude N-succinoylsulfanilyl chloride weighed 5.15 g. (35 per cent yield), m.p. 192-193°.

Crystallization of this compound from chloroform was attempted, but due to the huge loss of product and inefficient purification, future preparations of N-succinoylsulfanilyl chloride were always used in their crude form. It was also observed that if less than a five-fold excess of chlorosulfonic acid was used, the yields dropped drastically, being but 16 per cent when three equivalents were used. It is, therefore, advisable

to use at least a five-fold excess of the acid.

Diethyl N-Succinoylsulfanilamidomalonate

To 50 ml. of pyridine was added 3.75 g. (0.018 mole) of diethyl aminomalonate hydrochloride and stirring commenced. To the solution was slowly added 5.15 g. (0.018 mole) of crude N-succinoylsulfanilyl chloride. The solution was stirred at 45° for six hours, filtered, slowly poured into 450 ml. of water, and chilled overnight in a refrigerator. The product that had formed was filtered, washed once with cold water, and purified from boiling toluene. The dried diethyl N-succinoylsulfanilamidomalonate, a fluffy white solid, weighed 2.92 g. (38 per cent yield), m. p. 165.5-167.0°. Diagnostic IR absorptions were at 3.00, 3.32, 5.68, 5.75, 5.85, 7.47, 8.50, and 11.95 microns. An analytical sample, m. p. 166.0-167.5°, was prepared by recrystallization from toluene.

Calculated for $C_{17}H_{22}N_2O_9S$: N, 6.51; S, 7.45.

Found (Galbraith): N, 6.82; S, 8.19.

Found (Bernhardt): N, 6.50; S, 7.14.

Found (Average): N, 6.66; S, 7.66.

It was originally planned to condense the diethyl N-succinoylsulfanilamidomalonate with urea in sodium ethoxide. However, after discovering that these conditions led to sulfur-nitrogen bond cleavage (see attempted condensation of diethyl N-acetylsulfanilamidomalonate with urea), the reaction was not even performed since it appeared very probable that this sulfonamide would fragment in the same fashion.

Attempted Reaction of Uramil with N-Succinoylsulfanilyl Chloride

To 100 ml. of pyridine was added 4.0 g. (0.028 mole) of uramil, very little of which dissolved. An excess of N-succinoylsulfanilyl chloride was introduced to this suspension, the mixture was warmed on a steam bath for one hour, and then stirred overnight at 25°. Addition

of 100 ml. of absolute ethanol to the mixture was then made followed by warming on a steam bath for one hour. The solid still present at this time was removed by filtration and found to be unchanged uramil recovered in 76 per cent yield. Further work with the filtrate failed to result in the isolation of any identifiable product.

Attempted Preparation of 5-(N-Acetylsulfanilamido)-barbituric Acid Under Acidic Conditions

Introduction

Since it was obvious that the desired barbituric acid could not be synthesized using strong base, other possible paths were investigated. A method of general applicability, reported by Biltz and Wittek (9), utilized only acidic conditions. In this report, urea was condensed with malonic acid in the presence of hot glacial acetic acid and acetic anhydride to give barbituric acid. To verify this 45 year old publication, the procedure was followed precisely as reported and found to give a 66 per cent yield of barbituric acid.

Model Compound Studies

Two such studies were first conducted before any further work with diethyl N-acetylsulfanilamidomalonate was undertaken. In the first, it was desired to learn if the amide and the sulfonamide bonds of diethyl N-acetylsulfanilamidomalonate would be stable to these acidic conditions. Thus, N-acetylsulfanilamide, whose synthesis is given in the following section, was chosen as the model and subjected to glacial acetic acid and acetic anhydride at 90° for six hours. After cooling, the solid that separated was found to be unchanged N-acetylsulfanilamide. This indicated that both types of amide bonds were of sufficient stability to withstand the required reaction conditions.

Since N-acetylsulfanilamidomalonic acid was not yet available, but rather its diethyl ester, it would be expedient if the diester, itself, would react with urea under these conditions. To test this, diethyl malonate was chosen as the second model compound and its condensation with urea under these anhydrous acidic conditions was also tried. Unfortunately, no barbituric acid was produced at all. The only product obtained, other than unreacted diethyl malonate, was found to be N,N'-diacetylurea, m. p. 150-152° (lit. (44) m. p. 154-155°). This indicates that the desired barbituric acid could not be synthesized from the diester, but would necessitate its saponification and the intermediate preparation of N-acetylsulfanilamidomalonic acid.

N-Acetylsulfanilamide

The method of Cason and Rapoport (14) was followed in preparing this compound. A preparation on a 0.05 molar scale, after crystallizing the crude product from 95 per cent ethanol, resulted in a 43 per cent yield, m. p. 218-219° (lit (25) m. p. 219°).

Trisodium N-Acetylsulfanilamidomalonate

A modified procedure of that reported by Beaujon (3) for the saponification of a substituted aminomalonic ester was used. In a typical preparation of this salt, a mixture of 50 ml. of 65 per cent aqueous ethanol and 1.80 g. (0.045 mole) of sodium hydroxide was prepared in an Erlenmeyer flask and cooled. To this was added 5.59 g. (0.015 mole) of diethyl N-acetylsulfanilamidomalonate, the flask immersed in an ice bath, and the cold solution was stirred for five hours. After about two hours, a white precipitate was observed, the quantity of which increased with time. Afterwards, the mixture was allowed to stand in a refrigerator overnight. To this was next added, with vigorous stirring, 150 ml. of cold absolute ethanol. The white solid was filtered off and

washed with 100 ml. of 95 per cent ethanol. Since it was later shown that this trisodium salt crystallized from the aqueous ethanolic solution as a trihydrate, the resultant 5.30 g. of dried trisodium N-acetylsulfanilamidomalonate trihydrate represented an 81 per cent yield. Its melting point was 281-284° (d.). It was found that the three molecules of water of crystallization could be removed by prolonged drying in an Abderhalden drying pistol utilizing boiling toluene.

Significant IR absorptions were found at 3.03, 6.00-6.30 (broad), 7.34, 7.56, 8.70, and 12.00 microns. Usual absorptions of carboxylate anions appear around 6.3 and 7.3 microns (20). The NMR spectrum showed all the expected proton absorptions, that of the amide being absent due to its exchange with the deuterium oxide solvent.

Calculated for $C_{11}H_9N_2O_7SNa_3 \cdot 3H_2O$: C, 30.28; H, 3.47;
N, 6.42; S, 7.35; Na, 15.81.

Found: C, 30.48; H, 3.30;
N, 6.23; S, 6.91; Na, 15.45.

Concerning this preparation, the procedure as given above was found to be the best of many variations tried. Three major problems, worthy of note, were encountered during the saponification. The first of these resulted when an excess of sodium hydroxide (more than three equivalents) was used. Due to the very similar solubility characteristics of the product and sodium hydroxide, a completely successful method of removing the excess base was never found. The use of column chromatography, utilizing Sephadex G-15 as the packing, resulted in partial purification, but analysis of this product still showed the presence of sodium hydroxide. The second difficulty arose if insufficient base was used. In this case, an orange tar of unknown structure resulted. This was quite unexpected,

but it could always be circumvented by using at least three equivalents of sodium hydroxide. The third problem was solved by keeping the reaction at 0°. It was found that temperatures greater than 20° sometimes resulted in cleavage of the acetyl group by the aqueous base. This was verified by the disappearance of the NMR absorption of the acetyl singlet.

Attempted Preparation of N-Acetylsulfanilamidomalonic Acid

In three ml. of glacial acetic acid was dissolved 0.50 g. (0.0011 mole) of trisodium N-acetylsulfanilamidomalonate trihydrate. Stirring of the solution was commenced and in about ten minutes the solution became viscous and practically gelled. Filtration followed by washing with absolute ethanol left behind a white solid which was originally thought to be the desired acid. Addition of ethyl ether to the filtrate and characterization of the resulting sodium acetate also supported this. However, inspection of an IR spectrum failed to detect the presence of a carboxyl group, but absorptions of the carboxylate anion at about 6.3 and 7.2 microns were obvious. The compound was found to be stable to decarboxylation and to leave a basic residue upon ignition. Also, as has been implied, the IR spectrum was different from that of the reactant as was its melting point of about 245° (d.). These data strongly suggested that the isolated product was only partially acidified, being actually disodium N-acetylsulfanilamidomalonate.

It became apparent that either more severe conditions or longer reaction time would be necessary to replace all three sodium atoms and the latter approach was found to be successful. To 14.3 g. (0.033 mole) of trisodium N-acetylsulfanilamidomalonate trihydrate was added 10.0 ml. of glacial acetic acid and the solution stirred at 25° for 65 hours. The mixture was then filtered and washed with glacial acetic acid followed

by ethyl ether. Again, the expected sodium acetate was isolated from the filtrate. The dried white product weighed 6.6 g., m. p. 239-241°, and was crystallized from glacial acetic acid in 93 per cent recovery. Ignition of a sample indicated that sodium was absent. The IR spectrum, with diagnostic absorptions at 2.97, 3.05, 3.41, 3.92, 5.86, 6.15, 7.69, 8.68, and 12.02 also supported the temporary conclusion that this was the desired substituted malonic acid. However, analysis proved this not to be the case. The product was actually found to be the decarboxylated compound, N-acetylsulfanilamidoacetic acid.

Calculated for $C_{10}H_{12}N_2O_5S$: C, 44.11;
H, 4.44; N, 10.29.

Found: C, 44.02;
H, 4.55; N, 10.24.

A doublet at 6.38γ in the NMR spectrum (in DMSO-d_6), integrating for two hydrogens, also support this assigned structure.

It was now obvious that either the above conditions of prolonged treatment with glacial acetic acid were too severe or else N-acetylsulfanilamidomalonic acid is inherently unstable. Thus, acidification of the trisodium salt using ion exchange resins was investigated. Into a mixture of 75 ml. of ethanol and 100 ml. of water was introduced 3.00 g. (0.0069 mole) of trisodium N-acetylsulfanilamidomalonate trihydrate. This was followed by addition of 25 g. of Amberlite IRC-50 cation exchange resin and the mixture mechanically stirred at 25° for 24 hours. After removing the exchanged resin, the filtrate was stripped to dryness to leave behind a cream colored solid. All available chemical and physical evidence, though incomplete, indicated that this compound was monosodium N-acetylsulfanilamidohydrogenmalonate. Apparently, this weak resin, being a carboxylic acid resin, successfully exchanged two of the sodium atoms

but was incapable of removing the third sodium atom. A sulfonic acid resin, Dowex 50W-X8, was then employed in hopes of exchanging the last sodium atom without resulting in decarboxylation. The suspected monosodium N-acetylsulfanilamidohydrogenmalonate was dissolved in 150 ml. of 33 per cent ethanol to which was added 20 g. of Dowex 50W-X8 (20-50 mesh, H^+ form). The mixture was mechanically stirred for 21 hours at 25°. After resin removal, the filtrate was stripped to dryness to give a solid whose physical characteristics were identical with those of N-acetylsulfanilamidoacetic acid. Thus, since the desired N-acetylsulfanilamidomalonic acid was not produced even under mild conditions, it was concluded that the compound is quite unstable.

Attempted Condensation of Trisodium N-Acetylsulfanilamidomalonate with Urea

It was also considered that 5-(N-acetylsulfanilamido)barbituric acid might result if, in the presence of urea, the trisodium salt were subjected to the Biltz and Wittek method of condensation (9). If the substituted malonic acid would condense with urea at a rate faster than it would decarboxylate, then a barbituric acid could possibly be realized. To test this, 3.91 g. (0.0102 mole) of trisodium N-acetylsulfanilamidomalonate (water of hydration was removed by thorough drying) was added to 20 ml. of glacial acetic acid followed by addition of 900 mg. (0.0150 mole) of urea. The temperature was brought to 60° whereupon the disodium salt began separating. To this was next added 15 ml. of acetic anhydride over a 30 minute period. Immediately upon the initial addition of acetic anhydride, a solution was formed and voluminous quantities of gas, later found to be carbon dioxide, were given off. The temperature was raised to 90° and stirring was continued for five hours. Upon cooling of the solution, a white solid resulted that was removed by filtration and washed

with 50 ml. of ethyl ether. It was soon discovered that this product was not the desired barbituric acid, but rather N,N'-diacetylsulfanilamidoacetic acid, formed by decarboxylation and by N-acylation. Thus, the 3.13 g. of product, m. p. 183-184°, represented a 98 per cent yield based upon the starting trisodium salt. From the filtrate of the reaction were isolated the expected sodium acetate and N,N'-diacetylurea, which accounts for the fate of the urea. An analytical sample of the acid was prepared by crystallization from glacial acetic acid.

Calculated for $C_{12}H_{14}N_2O_6S$: C, 45.85; H, 4.49; N, 8.91.

Found: C, 45.84; H, 4.52; N, 9.00.

Originally it was not known which nitrogen atom of the N-acetylsulfanilamidoacetic acid had been acylated, but a singlet in its NMR spectrum (in DMSO-d_6) at 5.48τ integrating for two hydrogens resolved any speculation. Its IR spectrum showed strong absorptions at 2.99, 3.30, 3.84, 5.75, 5.95, 6.05, 7.60, 8.60, and 11.96 microns.

Alkylated Uramil Preparations

Introduction

All of the uramils synthesized were found to turn pink slowly upon air exposure. To prevent this, it was found necessary to store them under nitrogen or, even better, under vacuum.

Synthesis of 1-Methyluramil

1-Methylbarbituric acid. A procedure adapted from that of Dickey and Gray (19) was found not to be applicable. The method of Stein, Gregor, and Spoerri (43) was, therefore, followed. A reaction utilizing 0.38 mole of malonic acid, 0.34 mole of methylurea, and 0.69 mole of acetic anhydride produced 24.9 g. (52 per cent yield) of impure 1-methylbarbituric acid, m. p. 124-126° (lit. (43) m.p. 125-129°; lit. (5)

m.p. 132°), after repeated crystallizations.

1-Methyluramil. The procedure used was that for uramil reported by Davidson and Epstein (17). In a four liter beaker were mixed 24.9 g. (0.175 mole) of 1-methylbarbituric acid, 13.1 g. (0.191 mole) of sodium nitrite, and 850 ml. of water. The mixture which almost immediately became purple, was warmed and then filtered. After the filtrate was brought to a boil, a filtered solution of 105 g. (0.60 mole) of sodium hydrosulfite in 530 ml. of water and 180 ml. of concentrated ammonium hydroxide was added and boiling continued for one hour. The now yellow solution was chilled thoroughly in an ice bath and the solid which had formed was filtered off. Purification was accomplished by crystallization from water containing several grams of sodium hydrosulfite and a little ammonium hydroxide. The dried 1-methyluramil weighed 8.14 g. (30 per cent yield) and melted at 254-258° (d.) (lit. (43) m. p. 253-256°). Its IR spectrum is contained in the Appendix.

Synthesis of 5-Methyluramil

Diethyl methylmalonate. The method of Weiner (47) was followed with but two exceptions. Methyliodide, rather than methylbromide, was used as the alkylating agent and the product was washed with a three per cent sodium bisulfite solution prior to sodium hydroxide treatment in order to destroy the iodine that was present. The diethyl methylmalonate was purified by vacuum distillation, b. p. 93°/16 mm. (lit. (47) b. p. 96°/ 16 mm.). Repeated preparations gave yields of 70 to 80 per cent.

5-Methylbarbituric acid. The general procedure of Dickey and Gray (19) was used with modifications. In a three-necked, two liter round-bottomed flask fitted with a dropping funnel, a condenser to which was affixed a calcium chloride drying tube, a mechanical stirrer, and a

heating mantle, 7.0 g. (0.31 mole) of freshly cut sodium was reacted with 500 ml. of absolute ethanol. To the ethoxide solution was slowly added, over a period of 20 minutes, 51.2 g. (0.29 mole) of diethyl methylmalonate and the mixture then allowed to cool to room temperature. In several portions was added a hot solution of 18.1 g. (0.30 mole) of urea dissolved in 650 ml. of boiling absolute ethanol. Vigorous stirring was commenced and the reaction was allowed to proceed, without applied heat, for one hour. A solid had now formed and the mixture was then refluxed, with continued stirring, for eight hours. Afterwards, 250 ml. of hot water and 70 ml. of concentrated hydrochloric acid were added to dissolve the resultant solid. This permitted removal of the ethanol without violent bumping. Most of the ethanol was distilled from the solution and while still hot the solution was quickly filtered and then thoroughly chilled. The 5-methylbarbituric acid was collected and recrystallized from water containing a small amount of hydrochloric acid to give 11.6 g. (28 per cent yield) of slightly yellow needles, m. p. 203-204° (lit. (22) m.p. 202-203°).

It should be pointed out that vigorous stirring and the use of a large quantity of ethanol during the refluxing period was found necessary in order to control the viscosity and to prevent bumping.

5-Bromo-5-methylbarbituric acid. This procedure was based upon that of Cox, et al. (16) who had reported the synthesis of various 5-bromobarbituric acids. In a typical experiment, 11.6 g. (0.082 mole) of 5-methylbarbituric acid was dissolved in 100 ml. of boiling water. With stirring and continued heating, 4.4 ml. (0.082 mole) of bromine was added slowly. The solution was sufficiently chilled and filtered and the solid was dried to give 9.7 g. (54 per cent yield) of white needles. The 5-bromo-5-methylbarbituric acid was found to melt at 191-

192° (lit. (16) m. p. 190°; lit. (23) m. p. 193.5°).

Initial attempts at this reaction were unsuccessful due to the use of excess bromine. Those barbituric acids brominated in the Cox publication (16) also contained substituents on the 1- and 3- positions and thus the addition of bromine until its color persisted would be sufficient to indicate a stoichiometric quantity. However, it was found that this was not satisfactory for barbituric acids other than the trialkylated ones and only one equivalent of bromine must be added.

5-Methyluramil. In 85 ml. of absolute ethanol, contained in a heavy walled bottle, was dissolved 23.6 g. (0.107 mole) of 5-bromo-5-methylbarbituric acid. The solution was chilled to below 0° in a salt-ice-water mixture and gaseous ammonia was passed through the solution for 15 minutes. Afterwards, the bottle was securely sealed and allowed to come to room temperature. After standing for 12 days, the solid was removed by filtration and the crude product was crystallized from absolute ethanol to give 6.14 g. (37 per cent yield) of 5-methyluramil, m. p. 229-231° (lit. (23) m. p. 237°). An analytical sample was prepared by recrystallization from absolute ethanol, m. p. 233.0-234.5°.

Calculated for $C_5H_7N_3O_3$: C, 38.22; H, 4.49; N, 26.74.

Found: C, 38.25; H. 4.48; N, 27.11.

It was observed that recovery from ethanol during purification was poor, about half of the product being lost with each successive crystallization. The IR spectrum of 5-methyluramil is contained in the Appendix.

Synthesis of 1,3-Dimethyluramil

1,3-Dimethylbarbituric acid. For the synthesis of this compound, again, the somewhat altered general procedure of Dickey and Gray (19) was used. In a three-necked, 500 ml. round-bottomed flask fitted with a

dropping funnel, a condenser to which was attached a calcium chloride drying tube, a mechanical stirrer, and a heating mantle, 5.75 g. (0.25 mole) of freshly cut sodium was reacted in 125 ml. of absolute ethanol. To this solution was added 40.0 g. (0.25 mole) of diethyl malonate followed by 22.0 g. (0.25 mole) of dimethylurea dissolved in 125 ml. of hot absolute ethanol. The mixture, with continuous stirring, was refluxed for six hours. Next was added 250 ml. of 50° water to effect solution and just enough concentrated hydrochloric acid to make the solution acidic. Most of the ethanol was then removed by distillation, the hot mixture filtered, and the filtrate thoroughly chilled. The crystallized 1,3-dimethylbarbituric acid was collected by filtration and recrystallized twice from absolute ethanol to give 12.9 g. (33 per cent yield) of long white needles, m. p. 122.5-123.5° (lit. (33, 45) m. p. 123°).

1,3-Dimethyluramil. The procedure used was again that reported by Davidson and Epstein (17) for uramil. In a two liter beaker were mixed 12.9 g. (0.083 mole) of 1,3-dimethylbarbituric acid, 6.3 g. (0.091 mole) of sodium nitrite, and 400 ml. of water. The mixture was heated, at which time it became purple, and then filtered. After the filtrate was brought to a boil, a filtered solution of 49 g. (0.28 mole) of sodium hydrosulfite in 250 ml. of water and 85 ml. of concentrated ammonium hydroxide was added and boiling continued for one hour. The now yellow solution was chilled in an ice bath and the white product filtered off. After drying, the 1,3-dimethyluramil weighed 6.7 g. (47 per cent yield) and melted at 283-285° (lit. (6) m. p. about 300°). The product was recrystallized twice from water to give 3.3 g. (24 per cent yield) of white needles of purified 1,3-dimethyluramil, m. p. 283-285°. It was observed that this uramil rather quickly became pink upon air exposure

and hence was kept under nitrogen during purification as much as possible. See the Appendix for the IR spectrum of 1,3-dimethyluramil.

Attempted Synthesis of 1,5-Dimethyluramil

1,5-Dimethylbarbituric acid. The altered method of Dickey and Gray (19) for barbituric acid was followed. Mechanical stirring and much larger amounts of ethanol were used to prevent violent bumping as had occurred previously with similar preparations. In a three-necked, two liter round-bottomed flask fitted with a mechanical stirrer, a heating mantle, a dropping funnel, and a condenser to which was affixed a calcium chloride drying tube, 7.8 g. (0.34 mole) of cut sodium was added to 500 ml. of absolute ethanol. The solution, after reaction subsided, was cooled to 25° and 55.5 g. (0.32 mole) of diethyl methylmalonate was added followed by slow addition of 23.7 g. (0.32 mole) of methylurea dissolved in 500 ml. of boiling absolute ethanol. Refluxing of the solution was then commenced and continued for seven hours. To this was next introduced 250 ml. of hot water and 50 ml. of concentrated hydrochloric acid to dissolve the solid salt. All of the ethanol was removed by distillation. The remaining hot solution was quickly filtered and chilled. After filtering off the solid which had formed, the dried crude 1,5-dimethylbarbituric acid was found to weigh 27.5 g. (55 per cent yield) and to melt at 163-164° (lit. (46) m. p. 169-170°; lit. (32) m. p. 173°). The crude product was immediately brominated without further purification.

5-Bromo-1,5-dimethylbarbituric acid. The procedure followed was based upon that of Cox, et al. (16). In 300 ml. of boiling water was dissolved 27.5 g. (0.18 mole) of 1,5-dimethylbarbituric acid. With stirring and continued heating, 8.4 ml. (0.18 mole) of bromine was added slowly. The solution was chilled and filtered to give, after drying, 38.5 g. (93 per cent yield) of long needles of 5-bromo-1,5-dimethylbarbituric acid,

m. p. 119-120°.

Attempted reaction of 5-bromo-1,5-dimethylbarbituric acid with ammonia. The procedure of Fischer and Dilthey (23) for the preparation of 5-methyluramil from 5-bromo-5-methylbarbituric acid was explicitly followed without success. It appeared that the reaction itself proceeded (as evidenced by the usual pink color which developed), but that the product, 1,5-dimethyluramil, was destroyed by the heat used to remove the solvent. It was thought that a successful preparation of 1,5-dimethyluramil would be realized if the same procedure for the synthesis of 5-methyluramil were followed. However, experiments with some of the other uramils proved quite successful and, as a result, this reaction was not again performed.

Synthesis of 1,3,5-Trimethyluramil

Anhydrous ethanol. Commercial absolute ethanol was still found to contain some water. In order to obtain it completely free of water, the commercial absolute ethanol was re-dried by treatment with sodium and diethyl phthalate according to the method of Smith (42). In future sections, ethanol dried by this procedure shall be referred to as "anhydrous," whereas the term "absolute" ethanol shall be used to designate the commercial product.

1,3,5-Trimethylbarbituric acid. A procedure adapted from Dickey and Gray (19) was used in this synthesis. One of the large scale preparations proceeded as follows. In a three-necked, five liter round-bottomed flask equipped with a dropping funnel, a condenser to which was attached a calcium chloride drying tube, a mechanical stirrer, and a heating mantle, 64.0 g. (2.78 mole) of cut sodium was added to 1.5 l. of anhydrous ethanol. To this solution, after reaction subsided, was added 463 g. (2.66 mole) of diethyl methylmalonate over a period of 30 minutes.

This was followed by slow addition, with vigorous stirring, of 234 g. (2.66 mole) of N,N'-dimethylurea dissolved in 1.0 l. of hot anhydrous ethanol. The solution was refluxed for seven hours. It was acidified with 275 ml. of concentrated hydrochloric acid and then distilled. Simultaneously with the removal of 2.2 l. of ethanol, 900 ml of water was slowly added to the mixture in order to prevent settling of the solid and possible bumping. After rapid filtration, the solution was allowed to crystallize by thorough cooling. The product was then filtered off and a second crop was also obtained by concentrating the filtrate to about one-fifth its volume. The combined crops of 1,3,5-trimethylbarbituric acid weighed 320 g. (70 per cent yield) and melted at 85-87° (lit. (36) m. p. 88°; lit. (15) m. p. 89.5-90.0°). This product was then brominated without further purification.

In a preparation identical to the one described above, the sole difference being that absolute ethanol was employed, the yield was only 46 per cent. Thus, the advantage of using anhydrous ethanol is obvious.

5-Bromo-1,3,5-trimethylbarbituric acid. Again, a method similar to that of Cox, et al. (16) was used. In a typical bromination, 21.7 g. (0.13 mole) of 1,3,5-trimethylbarbituric acid was first dissolved in 200 ml. of boiling water. To this solution was then slowly added 6.7 ml. (0.13 mole) of bromine, with stirring, at which time the bromine color just persisted. A few drops of dilute sodium bisulfite was added to destroy the residual bromine. Since some product had separated, an additional 700 ml. of boiling water was added in order to dissolve it. The hot solution was immediately filtered and chilled overnight. The 5-bromo-1,3,5-trimethylbarbituric acid was obtained as long white needles by filtration and after drying weighed 18.8 g. (59 per cent yield), m. p. 112.5-113.0°. An analytical sample was prepared by recrystalli-

zation from water.

Calculated for $C_7H_9BrN_2O_3$: C, 33.76; H, 3.64; Br, 32.08.

Found: C, 33.99; H, 3.72; Br, 31.94.

A minor problem was encountered during preparations of this compound on a large scale. The huge quantity of water necessary for purification made for difficult handling since its solubility was less than 20 g. per liter.

1,3,5-Trimethyluramil. While this compound had been previously reported by Goldhahn (28), no exact procedure was given for its preparation. After several initial failures, a successful method was found as described below. In 60 ml. of chloroform contained in a heavy walled pyrex bottle, was dissolved 22.1 g. (0.089 mole) of 5-bromo-1,3,5-trimethylbarbituric acid. The solution was chilled to below 0° in a brine bath and gaseous ammonia was passed through for 20 minutes. Afterwards, the bottle was securely sealed, allowed to come to room temperature, and permitted to stand for 26 hours. Following removal of the chloroform under vacuum, the residual pink solid was extracted eight times with 25 ml. portions of room-temperature benzene. The benzene was stripped from the combined extracts to leave a pink solid which still contained some unreacted starting material. The product was removed by extraction with 150 ml. of water followed by filtration, since only it was water soluble. Removal of the water at reduced pressure resulted in the recovery of 13.4 g. (82 per cent yield) of crude 1,3,5-trimethyluramil, now deep red in color. The melting point of the crude product was found to be 92.5-94.0° (lit. (28) m. p. 105-106). All attempts at further purification were in vain and an analysis was, therefore, not performed. That this was the expected 1,3,5-trimethyluramil was later confirmed by a correct analysis of a product derived from this uramil.

It is worthy of note to point out several precautions or improvements concerning the above synthesis. First, heat could not be applied to aid the removal of solvents, since some form of decomposition always resulted. Second, it was found that insufficient extraction with benzene resulted in a significant decrease in yield. Extraction should be repeated until the residual ammonium bromide is but faintly pink. Third, as a major improvement in the above procedure, the use of water to extract the product from unreacted starting material was abandoned. It was discovered that extended contact of 1,3,5-trimethyluramil with water resulted in its hydrolysis. Pyridine was found to accomplish satisfactorily the desired separation by dissolving the uramil only. In addition, pyridine was found to be the most suitable solvent for the next reaction utilizing 1,3,5-trimethyluramil. This eliminated the need for a third solvent removal. The IR spectrum of the impure 1,3,5-trimethyluramil is contained in the Appendix.

Synthesis of 5-Ethyl-1,3-dimethyluramil

5-Ethyl-1,3-dimethylbarbituric acid. The publication of Cope, et al. (15) suggested this synthesis. With modifications, considerable increased yields were obtained. In a three-necked, five liter round-bottomed flask equipped with a dropping funnel, a condenser to which was affixed a calcium chloride drying tube, a magnetic stirrer, and a heating mantle, 32.2 g. (1.40 mole) of cut sodium was added to 1.0 l. of anhydrous ethanol. To this solution, after reaction subsided, was slowly added 254 g. (1.35 mole) of commercial diethyl ethylmalonate. This was followed by slow addition, with vigorous stirring, of 119 g. (1.35 mole) of N,N'-dimethylurea dissolved in 1.0 l. of hot anhydrous ethanol. The

The solution was refluxed for 12 hours. Afterwards, 1.0 l. of ethanol was removed by distillation at which time the solution was acidified by addition of 450 ml. of water containing 150 ml. of concentrated hydrochloric acid. Distillation was continued and another 1.0 l. of ethanol was removed. The solution was filtered and the two phases which had formed were separated. The aqueous layer was then extracted with 100 ml. of ethyl ether, the ether layer combined with the organic phase, and the mixture dried over calcium chloride. After filtering, the 5-ethyl-1,3-dimethylbarbituric acid was vacuum distilled, b. p. 130°/6 mm. (lit. (15) b. p. 130-132°/6 mm.), to give 166 g. (67 per cent yield) of a viscous colorless liquid.

5-Bromo-5-ethyl-1,3-dimethylbarbituric acid. Since the general method of Cox, et al. (16) had been successful in the past for similar brominations, it was also used for this preparation. In 1.7 l. of boiling water was added 166 g. (0.90 mole) of 5-ethyl-1,3-dimethylbarbituric acid. It appeared that not all of the acid had dissolved, but bromination was commenced anyway. To the mixture was slowly added, with stirring, 54.8 ml. (1.0 mole) of bromine at which time the bromine color persisted. A small quantity of dilute sodium bisulfite was then added to destroy the residual bromine. Upon cooling, the product solidified and after drying, was found to weigh 224 g. (95 per cent yield), m. p. 57.5-59.0°. The product was crystallized from water, but due to its low melting point, about half of the material oiled out and froze, only the remaining quantity actually crystallizing. The total product now weighed 186 g. (82 per cent recovery). An analysis was performed on a sample of 5-bromo-5-ethyl-1,3-dimethylbarbituric acid which had crystallized in long white

needles, m. p. 57.5-59.0°.

Calculated for $C_8H_{11}BrN_2O_3$: C, 36.53; H, 4.21; Br, 30.37.

Found: C, 36.34; H, 4.29; Br, 30.58.

Because of the difficulty encountered in crystallizing the product and because the melting point was not affected by further purification, crystallization was omitted in later preparations and the 5-bromo-5-ethyl-1,3-dimethylbarbituric acid was used in crude form.

5-Ethyl-1,3-dimethyluramil. In 200 ml. of cold chloroform contained in a heavy walled bottle was dissolved 186 g. (0.71 mole) of 5-bromo-5-ethyl-1,3-dimethylbarbituric acid. The solution was chilled to below 0° in a brine bath and gaseous ammonia was passed through for 30 minutes. Afterwards, the bottle was securely sealed and allowed to come to room temperature standing for 50 hours, at which time a yellow precipitate had formed. The contents were then placed under vacuum and the chloroform removed. The residual solid, now pink, was repeatedly extracted with approximately 75 ml. portions of room-temperature benzene until the remaining ammonium bromide was practically colorless. The benzene was stripped off and the solid was extracted with pyridine and filtered to remove insoluble impurities. By weighing the pyridine before and after the extraction, it was determined that the crude 5-ethyl-1,3-dimethyluramil weighed a minimum of 112 g. (80 per cent yield). As was true with 1,3,5-trimethyluramil, all attempts to obtain a pure sample of 5-ethyl-1,3-dimethyluramil failed. That this was the desired uramil was later confirmed by a correct analysis of a product derived from 5-ethyl-1,3-dimethyluramil. The crude product was kept in pyridine since pyridine

was found to be a suitable solvent for its next reaction.

In a later preparation of 5-ethyl-1,3-dimethyluramil, it appeared that even the benzene extraction could be eliminated. Not only was pyridine found to dissolve only the uramil, but also extraction from the residual solids was found to be much more efficient.

Synthesis of 1,3-Dimethyl-5-phenyluramil

1,3-Dimethyl-5-phenylbarbituric acid from diethyl phenylmalonate. The method of Dickey and Gray (19) was used, but this time with poor success. In a three-necked, five liter round-bottomed flask fitted with a dropping funnel, a magnetic stirrer, a condenser to which was attached a calcium chloride drying tube, and a heating mantle, 50.6 g. (2.20 mole) of cut sodium was added to 1.6 l. of anhydrous ethanol. To this solution, after reaction, was slowly added 506 g. (2.14 mole) of commercial diethyl phenylmalonate over a period of one hour. This was followed by slow addition, with vigorous stirring, of 184 g. (2.14 mole) of N,N'-dimethylurea dissolved in 1.0 l. of hot anhydrous ethanol. The solution was refluxed for 12 hours. Afterwards, 1.2 l. of ethanol was removed by distillation at which time the solution was acidified by addition of 550 ml. of water containing 230 ml. of concentrated hydrochloric acid. Distillation was continued and an additional 1.1 l. of ethanol was removed. The solution was immediately filtered and placed in a refrigerator for several days. At this time, two distinct liquid layers had formed, but no solid as was anticipated. However, agitation of the liquids resulted in the formation of crystals which were collected by filtration. Again the filtrate was chilled, agitated to give a second crop, and filtered. After obtaining several crops by this method, further attempts at securing additional

product were futile. The combined crops weighed but 60 g. (12 per cent yield), which was considerable lower than anticipated. A small sample of the crude 1,3-dimethyl-5-phenylbarbituric acid was recrystallized from absolute ethanol to give a white solid, m. p. 139.5-140.5° (lit. (15) m. p. 140.0-140.5°).

Due to the poor yield and the length of time involved in preparing the 1,3-dimethyl-5-phenylbarbituric acid *via* this method, another route was investigated which was found to be somewhat of an improvement.

Phenylmalonic acid. A solution of 80.0 g. (2.00 mole) of sodium hydroxide in 650 ml. of 65 per cent aqueous ethanol was first prepared. To this was slowly added 236 g. (1.00 mole) of diethyl phenylmalonate, with stirring. The now hot solution was allowed to cool to room temperature and stirring continued for 1(hours. The mixture was then poured into 1.5 l. of absolute ethanol and the resulting thick suspension was filtered. The dried white disodium phenylmalonate weighed 220 g. (98 per cent yield). To it was added 200 ml. of water, enough to dissolve the sodium chloride formed upon acidification, and the slurry was frozen in dry ice. Likewise, 185 ml. of concentrated hydrochloric acid was chilled just to its freezing point. Then, in five ml. portions, the acid was added to the frozen sodium salt and the mixture allowed to warm slowly with manual stirring as it thawed. The aqueous suspension was refrozen and the process was repeated until all of the acid had been added. After allowing the mixture to warm to room temperature, the phenylmalonic acid was filtered off, dried, and found to weigh 156 g. (87 per cent yield from diethyl phenylmalonate), m. p. 147-148° (lit. (38) m. p. 150.5°).

1,3-Dimethyl-5-phenylbarbituric acid from phenylmalonic acid. The fundamental reference for this type of condensation is that of Biltz and Wittek (9); however, the modification suggested by Stein, et al. (43) was employed. To 156 g. (0.87 mole) of phenylmalonic acid in a one liter round-bottomed flask fitted with a dropping funnel, a magnetic stirrer, a condenser to which was affixed a calcium chloride drying tube, and a heating mantle, was added 76.3 g. (0.87 mole) of N,N'-dimethylurea dissolved in 350 ml. of glacial acetic acid. This mixture was brought to 60°, and, with stirring, 200 ml. (2.11 mole) of acetic anhydride was added over a period of 45 minutes, maintaining the temperature at 60-65°. The temperature was then rapidly raised to 90° and stirring continued for an additional six hours. From the mixture was vacuum distilled 520 ml. of acetic acid and acetic anhydride. The residue was filtered and the filtrate thoroughly cooled; however, crystallization was realized only by agitation. The product was collected by suction filtration and dried to give 49 g. (24 per cent yield) of crude 1,3-dimethyl-5-phenylbarbituric acid. A portion of the crude material was recrystallized from absolute ethanol to give long white needles, m. p. 139.0-140.5° (lit. (15) m. p. 140.0-140.5°).

5-Bromo-1,3-dimethyl-5-phenylbarbituric acid. The two preparations of 1,3-dimethyl-5-phenylbarbituric acid were combined, to give a total weight of 108 g. (0.47 mole), and added to 1.8 l. of boiling water. It appeared that very little of the acid dissolved, but bromination was commenced anyway. Since the rate of this bromination was found to be considerably slower than any encountered thus far, the bromine had to be added quite slowly. A pasty semi-solid formed initially, but by the time all the bromine was added, this became a viscous liquid. A total of

20.7 ml. (0.39 mole) of bromine had been consumed when the bromine color persisted. The small excess was destroyed by addition of aqueous sodium bisulfite. The mixture was then chilled thoroughly. After decanting the water and drying the product under vacuum, it was found to weigh 95 g. (66 per cent yield). However, the impure 5-bromo-1,3-dimethyl-5-phenylbarbituric acid was not a solid as were all the previous bromobarbituric acids, but rather an amazingly sticky substance with a melting point apparently well below 0°. Due to this unexpected physical behavior, an analysis was not performed and the product was immediately converted into its corresponding uramil.

1,3-Dimethyl-5-phenyluramil. In 125 ml. of chloroform contained in a heavy walled bottle, was dissolved 95 g. (0.31 mole) of 5-bromo-1,3-dimethyl-5-phenylbarbituric acid. The solution was chilled to well below 0° in dry ice whereupon gaseous ammonia was passed through for 30 minutes while maintaining the temperature at 0 ± 10°. Afterwards, the bottle was securely sealed and allowed to come to room temperature standing for five days, at which time a yellow precipitate had formed. The residual solid had become slightly pink, which in the past has always been a reliable test for the presence of a uramil. The solid was slurried twice with pyridine and filtered to remove ammonium bromide and any remaining reactant. By weighing the pyridine before and after the extraction, the weight of the crude 1,3-dimethyl-5-phenyluramil was determined to be 67 g. (89 per cent yield). Again, as with other trialkyluramils, purification attempts were in vain. That this was the desired uramil was again later confirmed by a correct analysis of a product derived from 1,3-dimethyl-5-phenyluramil. This also confirmed the structure of the uramil's precursor, 5-bromo-1,3-dimethyl-5-

phenylbarbituric acid.

Sulfanilamidobarbituric Acids From Alkylated Uramils

Attempted Preparation of 1-Methyl-5-(N-acetylsulfanilamido)barbituric Acid

This reaction of 1-methyluramil with N-acetylsulfanilyl chloride was tried three times, but as was the case with uramil, all of them resulted in failure. The first attempt utilized refluxing aqueous alcoholic sodium hydroxide and after acidification, resulted in the isolation of what was thought to be N-acetylsulfanilic acid. The second, using refluxing aqueous pyridine, yielded only pyridine hydrochloride after acidification. The third employed hot dry pyridine for 30 minutes, but no identifiable product was obtained.

Attempted Preparation of 1,3-Dimethyl-5-(N-acetylsulfanilamido)barbituric Acid

The reaction of 1,3-dimethyluramil with N-acetylsulfanilyl chloride was tried in dry pyridine at 100° for one hour. Upon adding the reaction mixture to ice water and filtering, only a small amount of solid was obtained. It was concluded from the IR spectrum and the melting point that this solid was recovered impure 1,3-dimethyluramil. The necessary S=O stretching frequencies of a sulfonamide were definitely absent in its IR spectrum indicating that the desired condensation had failed.

Preparation of 5-Methyl-5-(N-acetylsulfanilamido)barbituric Acid

An initial attempt using pyridine at room temperature failed. However, use of somewhat more vigorous conditions seemed to result in

the desired reaction. In 75 ml. of pyridine was dissolved 3.71 g. (0.024 mole) of 5-methyluramil. To this was added 5.6 g. (0.024 mole) of N-acetylsulfanilyl chloride and the solution was warmed to 70° and maintained at this temperature, with stirring, for 20 hours. Afterwards, this was poured into 300 ml. of ice and water, but when no solid resulted the solution was placed under vacuum and stripped to dryness. The resultant green solid was washed twice with absolute ethanol, but further purification by crystallization from absolute ethanol was only mildly successful. Only 163 mg. of a yellow-green solid, m. p. 220-230°, was recovered, which was obviously quite impure. However, the IR spectrum of this compound showed sulfonamide S=O stretching absorptions at 7.59 and 8.70 microns indicating that the desired condensation had taken place. It is probable that the reaction conditions were too severe accounting for the poor yield. Much more promising reactions were soon encountered utilizing the trialkyluramils and as a result, the reaction with 5-methyluramil was not further pursued.

Preparation of 1,3,5-Trimethyl-5-(N-acetylsulfanilamido)barbituric Acid

In 40 ml. of pyridine was dissolved 4.4 g. (0.024 mole) of impure 1,3,5-trimethyluramil. Stirring was commenced and 5.6 g. (0.024 mole) of N-acetylsulfanilyl chloride was slowly added with occasional cooling in an ice bath. The solution was stirred at 40° for seven hours after which it was slowly poured into a mixture of 200 g. of ice and water. A solid had formed and after thorough chilling was filtered off and washed twice with cold water. The dried crude 1,3,5-trimethyl-5-(N-acetylsulfanilamido)barbituric acid weighed 4.1 g. (45 per cent yield), m. p. 274-275°. The product was purified by two crystallizations from absolute ethanol to give 1.4 g. (15 per cent yield overall), m. p. 274.0-275.5°.

Its IR spectrum showed important absorptions at 2.90, 3.02, 3.47 (weak), 5.92, 7.59, 8.72, 12.00, and 13.27 microns. During the course of this investigation, it was discovered that an absorption in the infrared region in the vicinity of 13.3 microns was diagnostic of a 5-substituted barbituric acid.

Calculated for: $C_{15}H_{18}N_4O_6S$: C, 47.12; H, 4.74
N, 14.65; S, 8.38.
Found: C, 47.29; H, 4.95;
N, 14.48; S, 8.53.

In a later reaction, it was found that the yield could be vastly improved by a slight alteration in the procedure. By stirring for 21 hours followed by addition of another half equivalent of N-acetylsulfanilyl chloride and stirring continued for ten more hours, a 73 per cent yield of crude 1,3,5-trimethyl-5-(N-acetylsulfanilamido)barbituric acid was obtained.

Preparation of 1,3,5-Trimethyl-5-sulfanilamidobarbituric Acid

An adaptation of the procedure of Cason and Rapoport (14) for the N-acetyl cleavage of sulfanilamides was used. In one of the large scale preparations, 77.9 g. (0.204 mole) of 1,3,5-trimethyl-5-(N-acetyl-sulfanilamido)barbituric acid was placed in a two liter round-bottomed flask, which was fitted with a reflux condenser, a magnetic stirrer, and a heating mantle. One and one-half liters of water and 125 ml. of concentrated hydrochloric acid was added through the condenser and refluxing was commenced. Refluxing was continued until all the reactant had hydrolyzed, as indicated by total solution. This required three hours. (Less time was found necessary when less reactant was used.) The hot solution was immediately filtered and then neutralized to a

pH of approximately eight using solid sodium bicarbonate. Due to the amphoteric nature of sulfanilamides, it was important that sodium bicarbonate be used, rather than a stronger base. The solid product then precipitated, the mixture was thoroughly chilled, suction filtered, and the precipitate washed with 50 ml. of portions of water. Upon drying, the crude 1,3,5-trimethyl-5-sulfanilamidobarbituric acid weighed 49.2 g. (71 per cent yield), m.p. 240-245°. Purification by crystallization from 12 l. of methanol gave 38.1 g. (55 per cent yield overall), m. p. 259.5-262.5°, of small, slightly tan crystals. Diagnostic absorptions in its IR spectrum were at 2.90, 3.03, 3.42 (weak), 5.92, 7.65, 8.76, 12.04, and 13.35 microns. An analytical sample was prepared by recrystallizing a portion from methanol, m. p. 261.0-263.0°.

Calculated for $C_{13}H_{16}N_4O_5S$: C, 45.87; H, 4.74;
N, 16.46; S, 9.42.

Found: C, 45.77; H, 4.76;
N, 16.39; S, 9.23.

Preparation of 1,3,5-Trimethyl-5-(N-succinoylsulfanilamido)barbituric Acid

The procedure previously used for the succinoylation of aniline (14), resulted in complete failure. In a modification of this procedure, using methanol as the solvent, only the starting sulfanilamide was recovered in 63 per cent. Finally, success was realized by utilizing a method of Patki and Shirsat (35) in which various "sulfa" drugs were acylated. To a mixture of 3.40 g. (0.010 mole) of 1,3,5-trimethyl-5-sulfanilamidobarbituric acid and 15.0 g. (0.150 mole) of succinic anhydride in a 100 ml. round-bottomed flask were added 50 ml. of chloroform and ten ml. of pyridine. A condenser was attached and the mixture refluxed, with

stirring, for eight hours. A solid was filtered from the mixture and found to be 10.1 g. of unreacted succinic anhydride. From the filtrate was then distilled the 50 ml. of chloroform. The residue, which had partially solidified upon cooling, was slurried with 75 ml. of water. Shortly thereafter, a solid began forming which was removed by filtration. After drying, this crude 1,3,5-trimethyl-5-(N-succinoylsulfanilamido)-barbituric acid weighed 3.92 g. (89 per cent yield), m. p. 260-263°. The product was crystallized from methanol in 72 per cent recovery m. p. 262.5-263.5°, but it still was very tan colored. Therefore, the product was again dissolved in boiling methanol, treated with decolorizing carbon, filtered well, and recrystallized three times to give 0.91 g. (30 per cent yield overall) of small white crystals, m. p. 266.5-268.0°. The IR spectrum showed the necessary absorptions at 2.92 (weak), 3.18, 3.42 (weak), 5.89-6.01 (broad), 7.56, 8.69, 11.93, and 13.30 microns. An analytical sample was prepared by twice recrystallizing the 1,3,5-trimethyl-5-(N-succinoylsulfanilamido)barbituric acid from methanol, m. p. 274.0-276.0°, in a concerted effort to rid the sample completely of decolorizing carbon.

Calculated for $C_{17}H_{20}N_4O_8S$: C, 46.35; H, 4.58;
N, 12.72; S, 7.28.

Found: C, 48.07; H, 4.52;
N, 13.02; S, 7.61.

From this analysis, apparently all of the decolorizing carbon was not able to be removed completely, in spite of rigorous attempts. All other chemical and physical evidence, including IR spectrum and mixed melting point with the reactant, support the assigned structure.

Preparation of 5-Ethyl-1,3-dimethyl-5-(N-acetylsulfanilamido)barbituric Acid

To 9.0 g. (0.045 mole) of impure 5-ethyl-1,3-dimethyluramil contained in 75 ml. of pyridine was slowly added 11.7 g. (0.050 mole) of N-acetylsulfanilyl chloride with stirring and occasional cooling. The solution was stirred at 40° for eight hours, to which one liter of water was then added. After overnight refrigeration, the mixture was filtered and washed with water to give an orange crystalline solid. After drying, the crude 5-ethyl-1,3-dimethyl-5-(N-acetylsulfanilamido)barbituric acid weighed 7.7 g. (43 per cent yield), m. p. 245-257° (d.). From two successive 95 per cent ethanol crystallizations, 1.8 g. were recovered, m.p. 274.0-274.5°, but the crystals were still highly colored. Methanol was found to be a better purification solvent, from which the still impure product was recrystallized four times. This treatment gave 410 mg. of an almost pure white crystalline solid, m.p. 277.5-278.5° (d.). Major IR absorptions were at 2.99, 3.17, 3.38, 5.92, 7.60, 8.72, 12.00, and 13.36 microns.

Calculated for $C_{16}H_{20}N_4O_6S$: C, 48.48; H, 5.09;
N, 14.13; S, 8.09.

Found: C, 48.70; H, 4.93;
N, 14.17; S, 8.27.

In later preparations, methanol was used as the sole recrystallization solvent resulting in much better overall recovery of purified product.

Preparation of 5-Ethyl-1,3-dimethyl-5-sulfanilamidobarbituric Acid

In a 500 ml. round-bottomed flask fitted with a condenser, a magnetic stirrer, and a heating mantle, was added 2.97 g. (0.0075 mole) of purified 5-ethyl-1,3-dimethyl-5-(N-acetylsulfanilamido)barbituric acid. To this was introduced, through the condenser, 225 ml. of water and 15

ml. of concentrated hydrochloric acid. Refluxing was commenced and continued until all of the reactant had hydrolyzed. Complete hydrolysis, as indicated by total solution, required one and one-half hours. The hot solution was immediately filtered and then neutralized to a pH of approximately eight using solid sodium bicarbonate. At this point, a solid product had precipitated. The mixture was thoroughly chilled, the product was removed by suction filtration, and then washed with water. Upon drying, the crude 5-ethyl-1,3-dimethyl-5-sulfanilamidobarbituric acid weighed 2.52 g. (95 per cent yield), m.p. 183-185°. Purification was accomplished by three recrystallizations from minimum quantities of methanol to give 360 mg. (14 per cent yield overall), m.p. 199.0-199.5°, of very small, slightly off-white crystals. All of the necessary absorptions were present in its IR spectrum.

Calculated for $C_{14}H_{18}N_4O_5S$: C, 47.45; H, 5.12;
N, 15.81; S, 9.05.
Found: C, 47.58; H, 5.18;
N, 15.66; S, 9.30.

Preparation of 1,3-Dimethyl-5-phenyl-5-(N-acetylsulfanilamido)barbituric Acid

To 11.9 g. (0.048 mole) of impure 1,3-dimethyl-5-phenyluramil contained in 75 ml. of pyridine was slowly added, with stirring, 11.7 g. (0.050 mole) of N-acetylsulfanilyl chloride. The solution was stirred at 40° for six hours and then slowly poured, with vigorous shaking after each addition, into a mixture of 800 ml. of ice and water. At first, a somewhat gummy substance resulted, but it became solid with continued shaking. After the ice had melted, the mixture was filtered and washed with water to give an off-white solid. Upon drying, the crude 1,3-di-

methyl-5-phenyl-5-(N-acetylsulfanilamido)barbituric acid weighed 17.4 g. (81 per cent yield), m.p. 252-254°. An analytical sample was prepared by three recrystallizations from minimum quantities of absolute ethanol. This gave a 25 per cent recovery of a white crystalline solid, whose melting point was 265.5-266.5°. Its IR spectrum showed important absorptions at 2.99, 3.23, 3.51 (weak), 5.94, 7.62, 8.75, 11.98, 13.31, and 14.48 microns. The last absorption must be present if the compound contains a monosubstituted benzene ring (20), as was the case here.

Calculated for $C_{20}H_{20}N_4O_6S$: C, 54.05; H, 4.54;
N, 12.61; S, 7.21.

Found: C, 54.27; H, 4.72;
N, 12.49; S, 7.40.

Preparation of 1,3-Dimethyl-5-phenyl-5-sulfanilamidobarbituric Acid

In a 500 ml. round-bottomed flask equipped with a condenser, a magnetic stirrer, and a heating mantle, was introduced 2.14 g. (0.0048 mole) of once recrystallized 1,3-dimethyl-5-phenyl-5-(N-acetylsulfanilamido)barbituric acid. This was followed by addition, through the condenser, of 200 ml. of water and 20 ml. of concentrated hydrochloric acid. Refluxing was commenced and continued until all of the reactant had hydrolyzed. Complete hydrolysis, as indicated by total solution, required about seven hours. The hot solution was immediately filtered and then neutralized with solid sodium bicarbonate to a pH of approximately eight. A solid product precipitated. The mixture was then chilled thoroughly, the product was removed by suction filtration, and then washed with water. After drying, the crude 1,3-dimethyl-5-phenyl-5-sulfanilamidobarbituric acid weighed 1.73 g. (89 per cent yield), m. p. 232-234°. This crude product was recrystallized first from absolute ethanol, but very little

purification resulted as indicated by its tan color and lack of increased melting point. Purification was successfully accomplished by two successive recrystallizations from 50 per cent aqueous methanol to give 570 mg. (29 per cent yield overall) of slightly off-white crystals, m. p. 239.5-241.0°. Major IR absorptions of this compound were at 2.93, 3.04, 3.37 (weak), 5.92, 7.73, 8.82, 12.04, 13.35, and 14.49 microns.

Calculated for $C_{18}H_{18}N_4O_5S$: C, 53.72; H, 4.51;
N, 13.92; S, 7.97.

Found: C, 53.53; H, 4.51;
N, 14.02; S, 8.06.

Infrared Spectra

The infrared spectra of solid compounds were determined in potassium bromide pellets and recorded using a Perkin-Elmer Model 137 spectrophotometer. The pellets were prepared by adding 1.5 mg. of the solid to 150 mg. of dry potassium bromide. The mixture was intimately mixed by grinding in an agate morter. The sample was compressed into a half-inch diameter disc by application of about 25,000 pounds per square inch pressure for one to two minutes in a briqueting press (Applied Research Laboratories). The spectra of liquid samples were recorded using thin films of the liquids between sodium chloride plates. The sharp polystyrene absorption band at 6.24 microns was recorded on all spectra to serve as a reference point. The infrared spectra of most of the new compounds prepared in this investigation are reproduced in the Appendix (Figures 33-52).

Nuclear Magnetic Resonance Spectra

All nuclear magnetic resonance spectra were obtained with a Varian

Associates Model A-60 spectrometer. The spectra of solid compounds were obtained by dissolving them in suitable aprotic or deuterated solvents. The use of tetramethylsilane was employed as an external standard. Its single absorption at zero parts per million served as a reference point in calibrating the spectra of the samples. The nuclear magnetic resonance spectra of some of the new compounds prepared in this investigation are reproduced in the Appendix (Figures 53-56).

CHAPTER IV

CONCLUSIONS

Three methods that originally appeared feasible for preparing 5-N-acetylsulfanilamidobarbituric acid, from which 5-sulfanilamidobarbituric acid could be obtained by hydrolysis, have been unsuccessfully investigated: direct condensation of uramil with N-acetylsulfanilyl chloride; base catalyzed cyclization of diethyl N-acetylsulfanilamidomalonate with urea; and acid catalyzed cyclization of N-acetylsulfanilamidomalonic acid with urea.

Suitable procedures for the reaction of trialkyl uramils with N-acetylsulfanilyl chloride to give various alkylated 5-sulfanilamidobarbituric acids and an alkylated 5-(N-acetylsulfanilamido)barbituric acid have been developed.

Spectra have been recorded for the new barbituric acids as well as for some new intermediates and by-products; IR absorptions from an S=O stretch of a sulfonamide at approximately 7.7 and 8.7 microns and at about 13.3 microns from the presence of a six membered barbituric acid ring were extremely useful in elucidating structures.

Attempts at procuring meaningful NMR spectra of sundry uramils have been without success due to their insolubility in common NMR solvents; they appeared to react with dimethylsulfoxide, concentrated sulfuric acid, and 70 per cent perchloric acid, the only media in which spectra were obtained at all.

The classical structure of uramil as 5-amino-2,4,6-trioxohexahydropyrimidine, depicted as a primary amine, has been found, based on

its chemical behavior, including its lack of basicity and nucleophilicity, to be a very poor representation of its actual structure.

CHAPTER V

RECOMMENDATIONS

By application of the effective procedures developed during this investigation, it is felt that additional potential "sulfa" drugs could be successfully synthesized. It is predicted that those containing the N-succinoyl group could be produced by a method involving two fewer steps. By analogy with the reactions of trialkyluramils with N-acetylsulfanilyl chloride, the use of N-succinoylsulfanilyl chloride should directly result in the synthesis of these desired compounds.

Because all of the common barbiturates do not contain 1,3-dialkyl substituents, it would be of interest to develop a satisfactory method for the condensation of just 5-substituted uramils with appropriate sulfanilyl chlorides. One such reaction involving 5-methyluramil has been described in Chapter III, but suitable conditions were not vigorously pursued.

Conceivably, one of the most significant revelations of this investigation concerned the obvious disagreement between the classical structure and chemical behavior of uramil. Because, from this work, an answer to the quandary was not produced, it is recommended that a complete investigation of the actual structure of uramil, employing neutron diffraction, be undertaken.

It would be of great interest to obtain data regarding the physiological activities of the new potential therapeutic agents that were successfully synthesized during this investigation.

APPENDIX

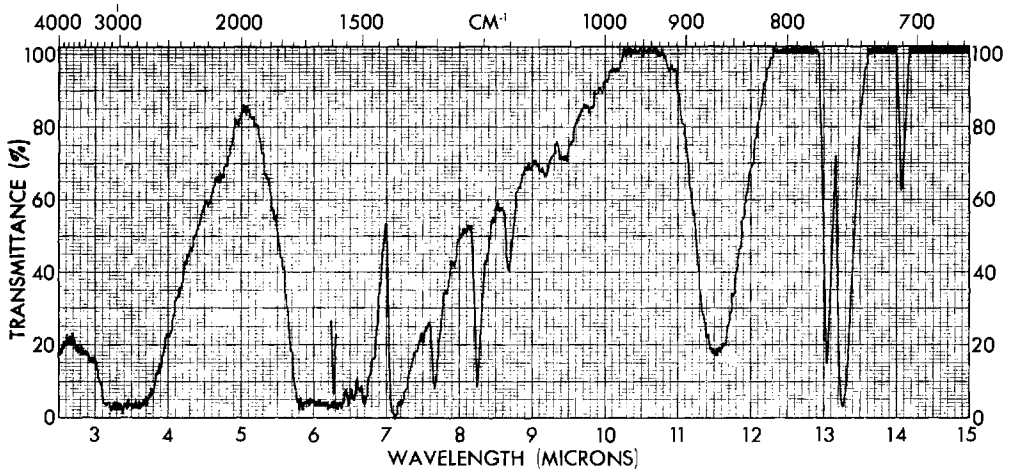


Figure 33. Infrared Spectrum of Uramil.

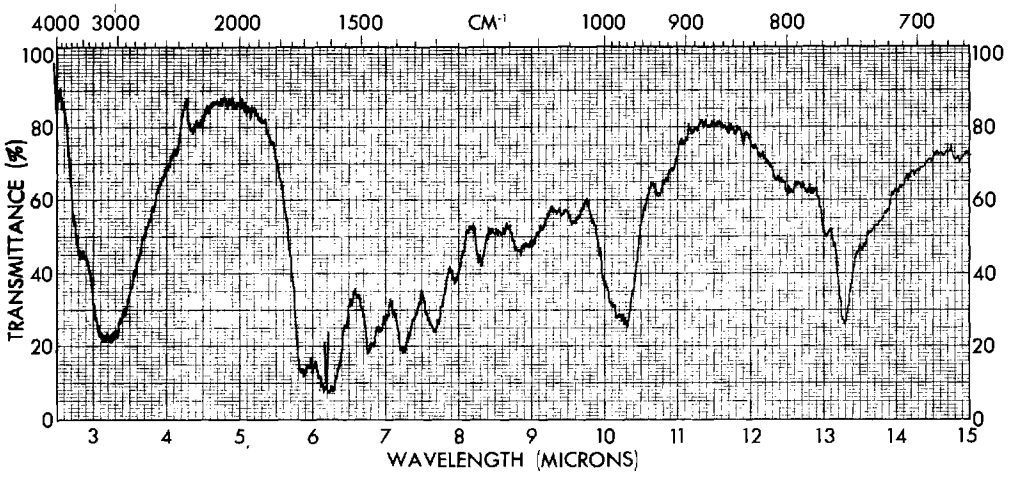


Figure 34. Infrared Spectrum of 1-Methyluramil.

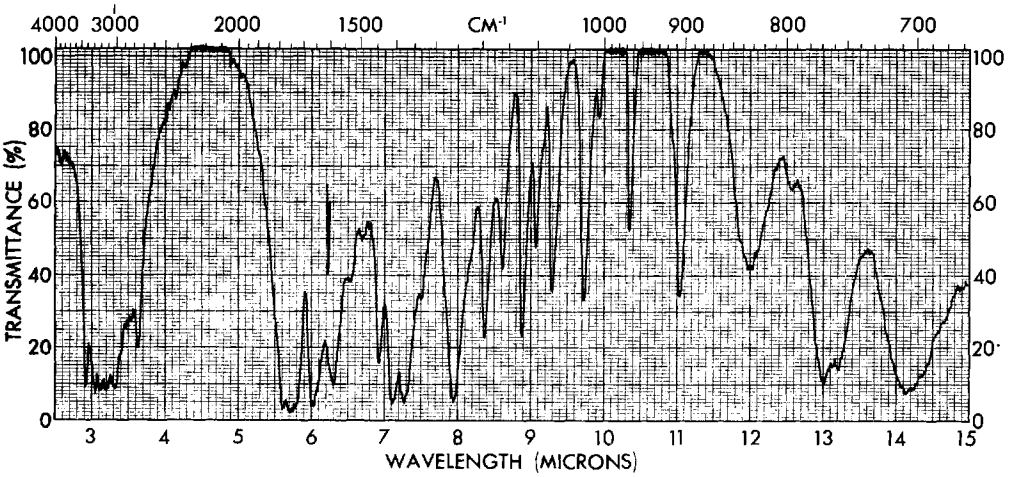


Figure 35. Infrared Spectrum of 5-Methyluramil.

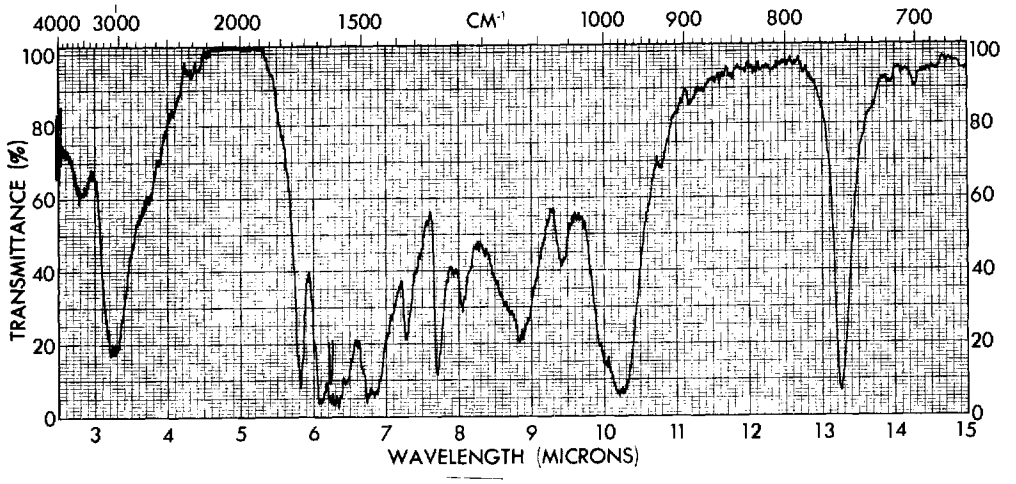


Figure 36. Infrared Spectrum of 1,3-Dimethyluramil.

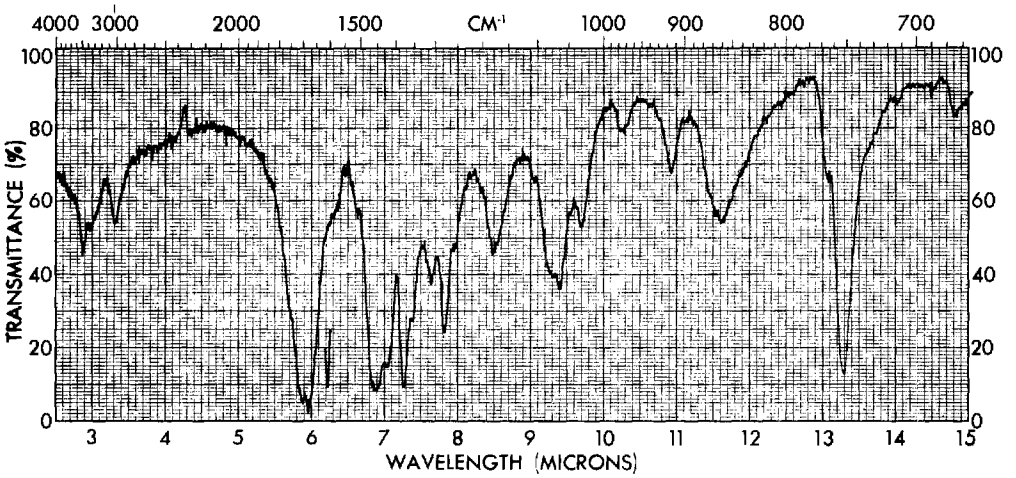


Figure 37. Infrared Spectrum of 1,3,5-Trimethyluramil (impure).

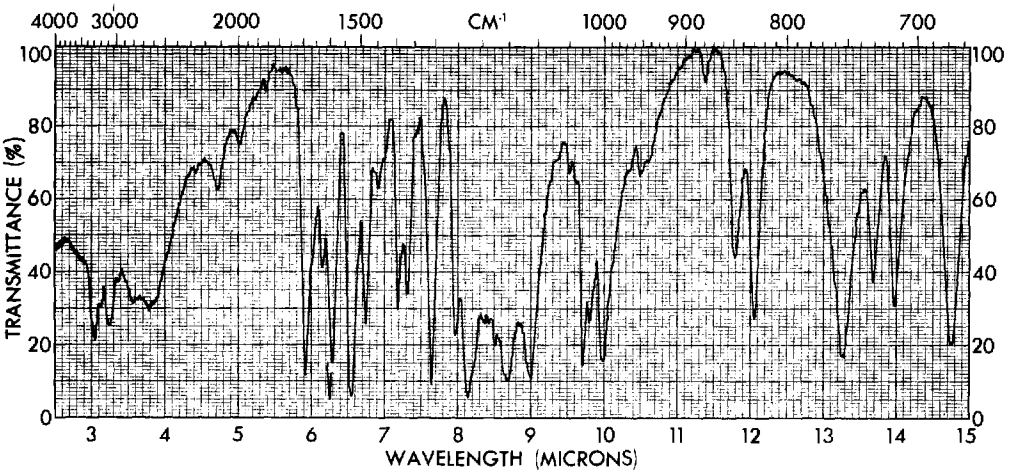


Figure 38. Infrared Spectrum of Pyridinium N-Acetylsulfanilate.

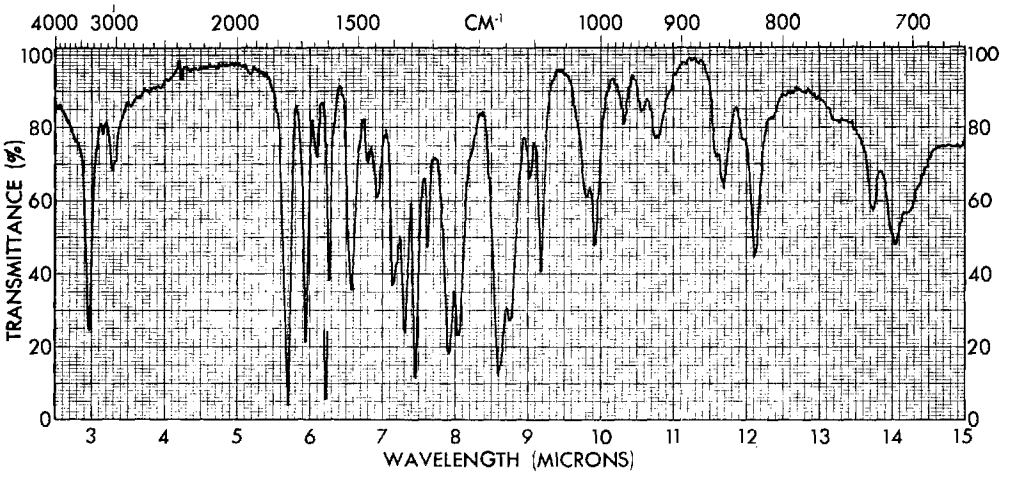


Figure 39. Infrared Spectrum of Diethyl N-Acetyl-sulfanilamidomalonate.

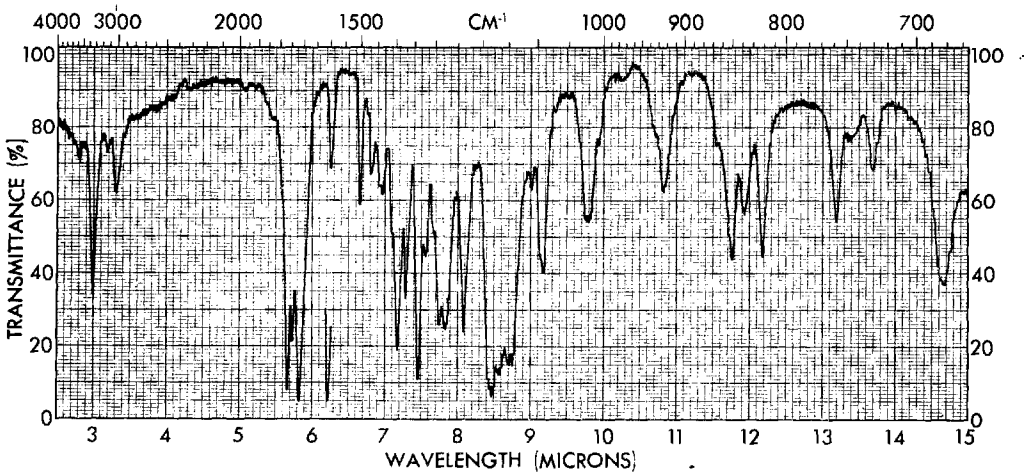


Figure 40. Infrared Spectrum of Diethyl N-Succinoyl-sulfanilamidomalonate.

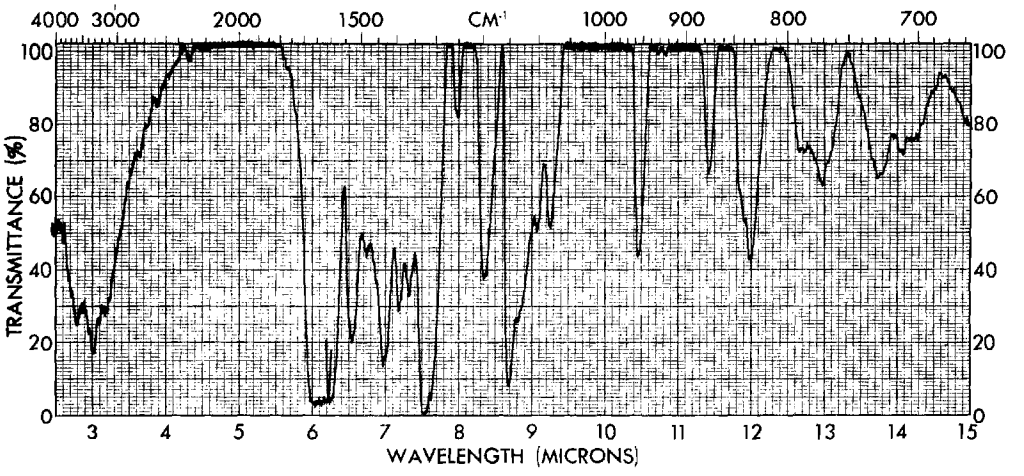


Figure 41. Infrared Spectrum of Trisodium N-Acetyl-sulfanilamidomalonate.

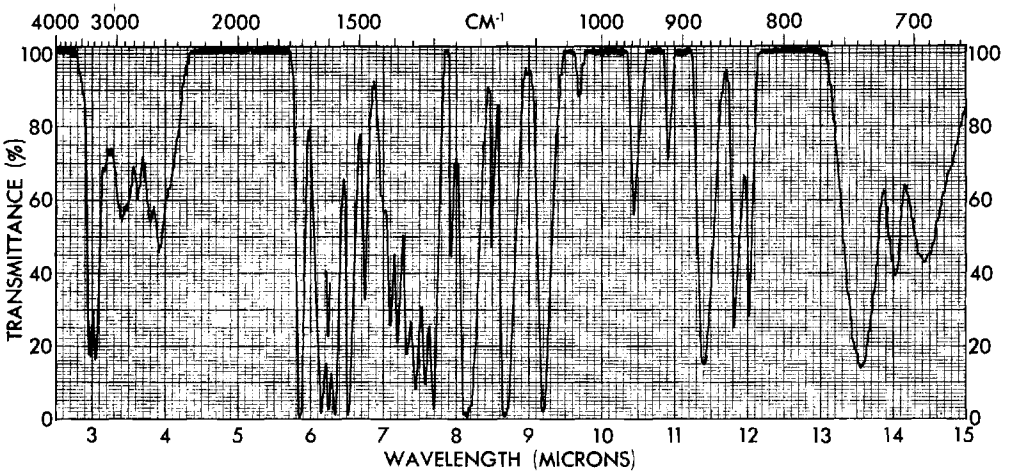


Figure 42. Infrared Spectrum of N-Acetylsulfanilamidoacetic Acid.

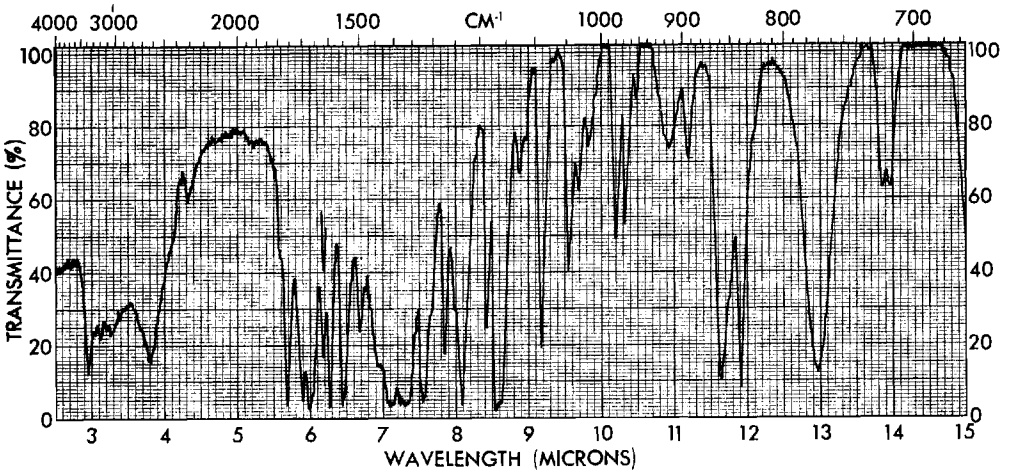


Figure 43. Infrared Spectrum of N,N'-Diacetylsulfanamidoacetic Acid.

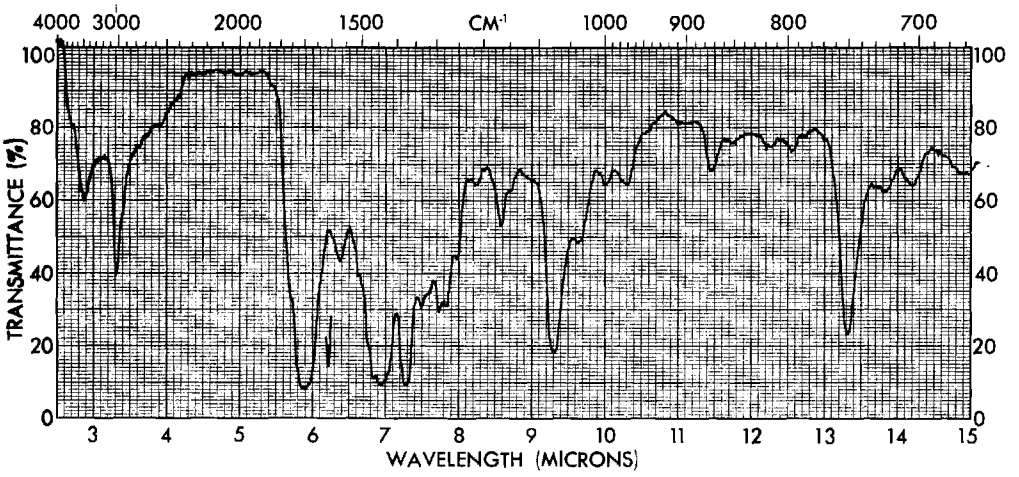


Figure 44. Infrared Spectrum of 5-Ethyl-1,3-dimethyluramil (impure).

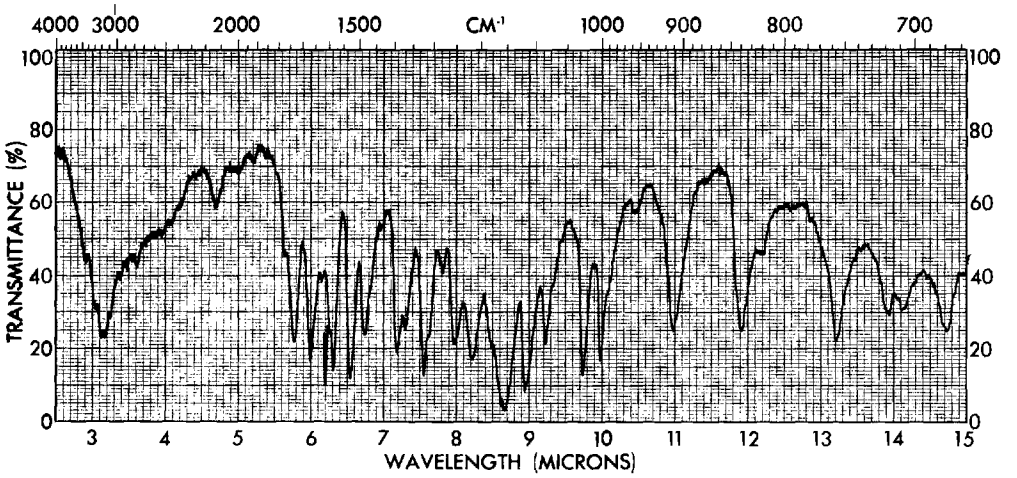


Figure 45. Infrared Spectrum of 5-Methyl-5-(N-acetylsulfanilamido)barbituric Acid (impure).

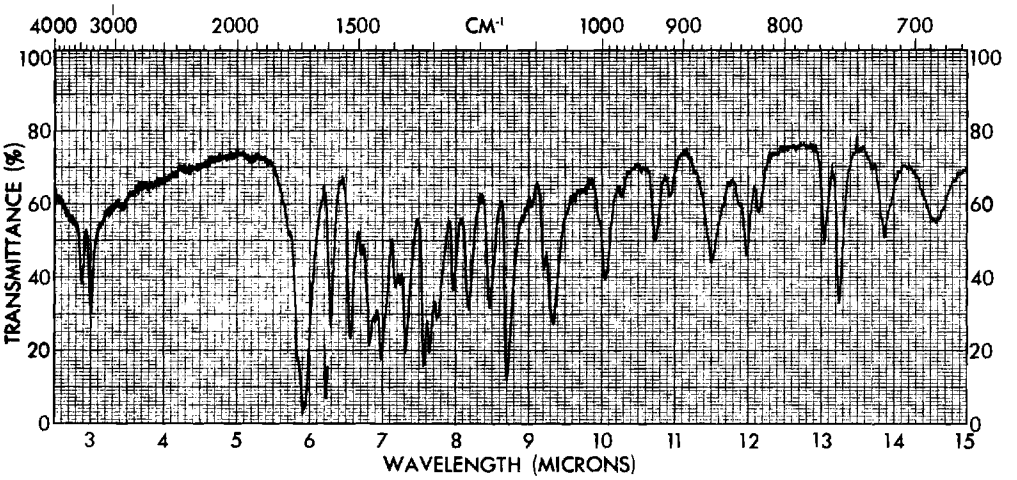


Figure 46. Infrared Spectrum of 1,3,5-Trimethyl-5-(N-acetylsulfanilamido)barbituric Acid.

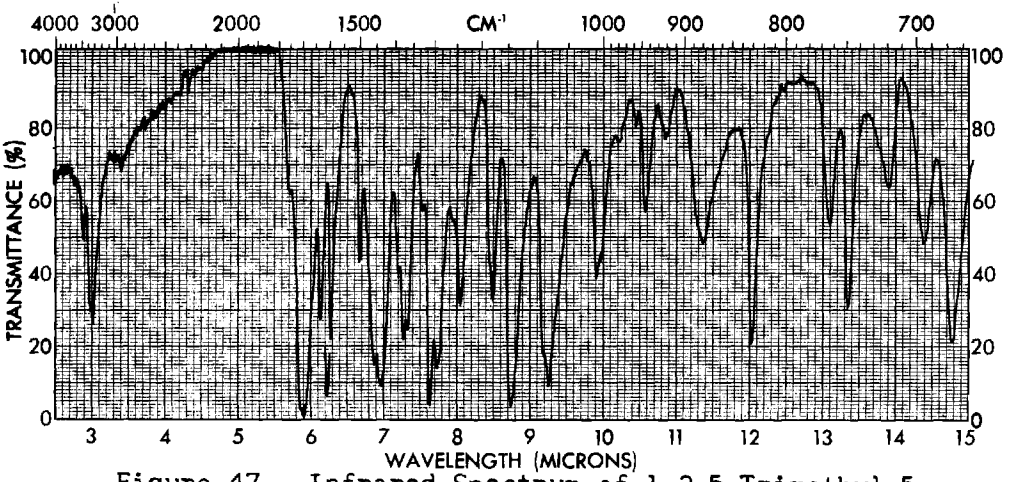


Figure 47. Infrared Spectrum of 1,3,5-Trimethyl-5-sulfanilamidobarbituric Acid.

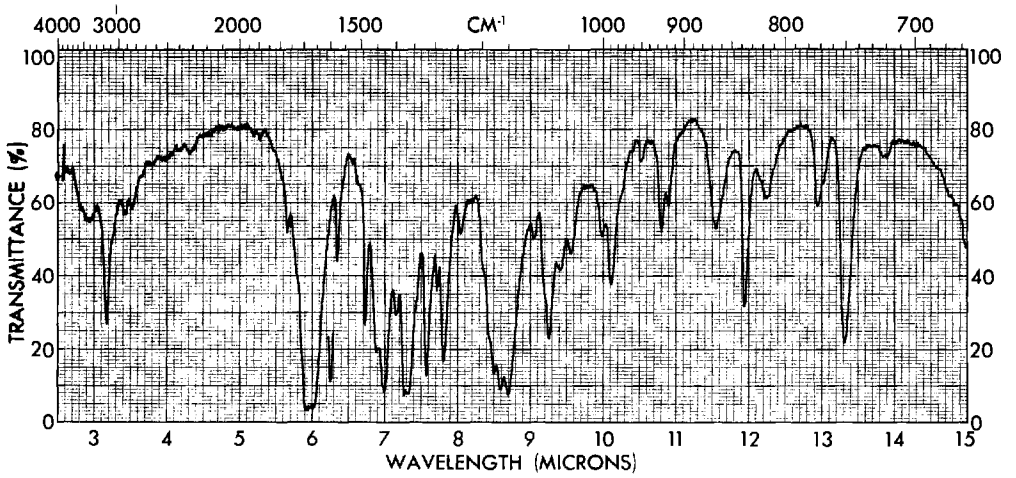


Figure 48. Infrared Spectrum of 1,3,5-Trimethyl-5-(N-succinoylsulfanilamido)barbituric Acid.

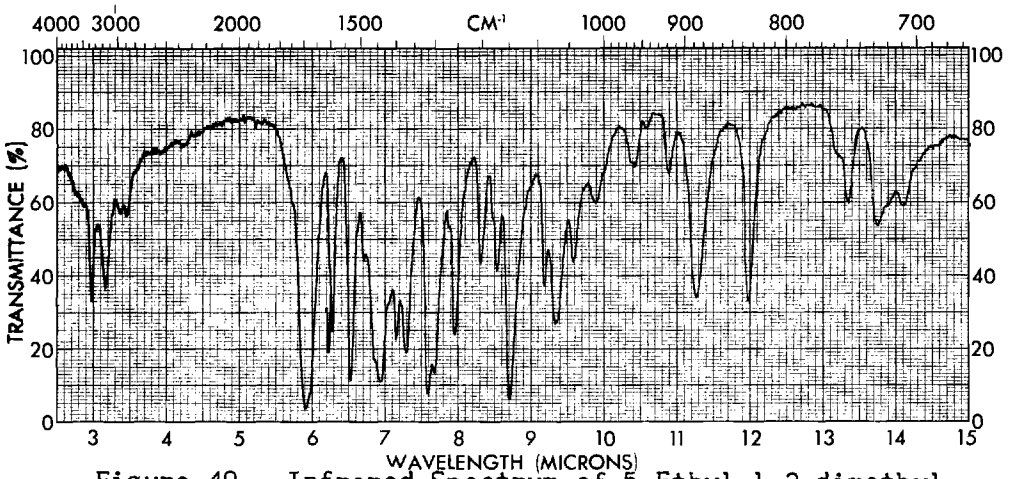


Figure 49. Infrared Spectrum of 5-Ethyl-1,3-dimethyl-5-(N-acetylsulfanilamido)barbituric Acid.

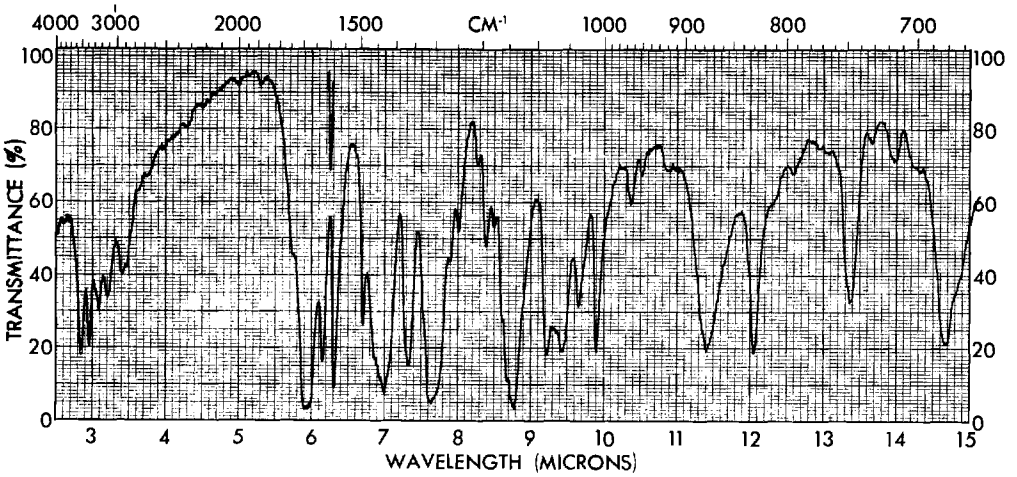


Figure 50. Infrared Spectrum of 5-Ethyl-1,3-dimethyl-5-sulfanilamidobarbituric Acid.

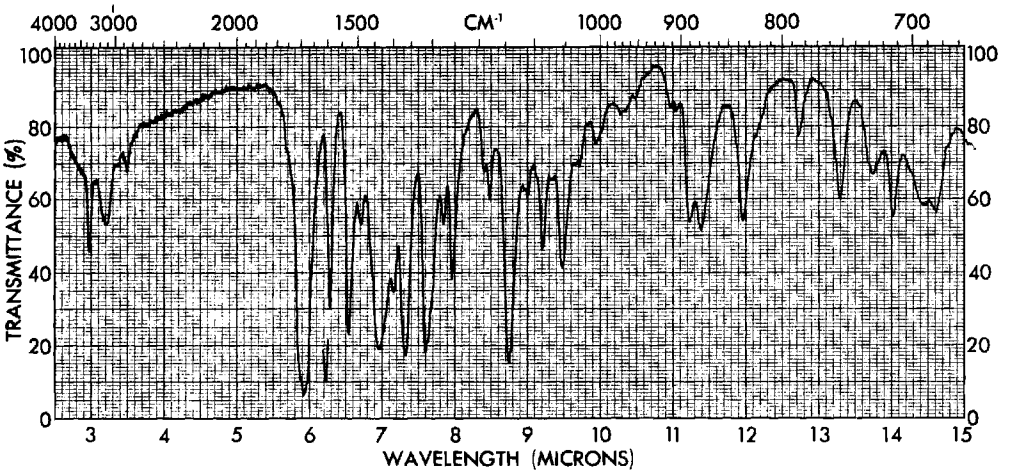


Figure 51. Infrared Spectrum of 1,3-Dimethyl-5-phenyl-5-(N-acetylsulfanilamido)barbituric Acid.

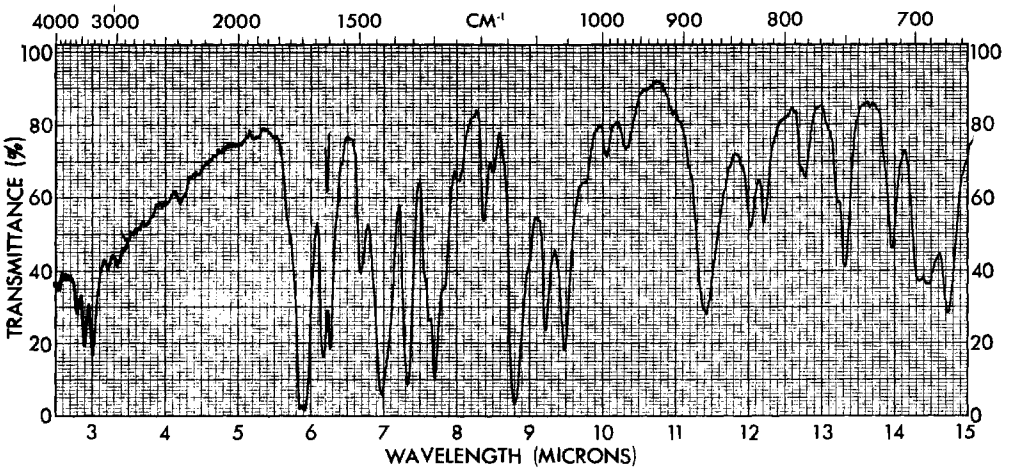


Figure 52. Infrared Spectrum of 1,3-Dimethyl-5-phenyl-5-sulfanilamidobarbituric Acid.

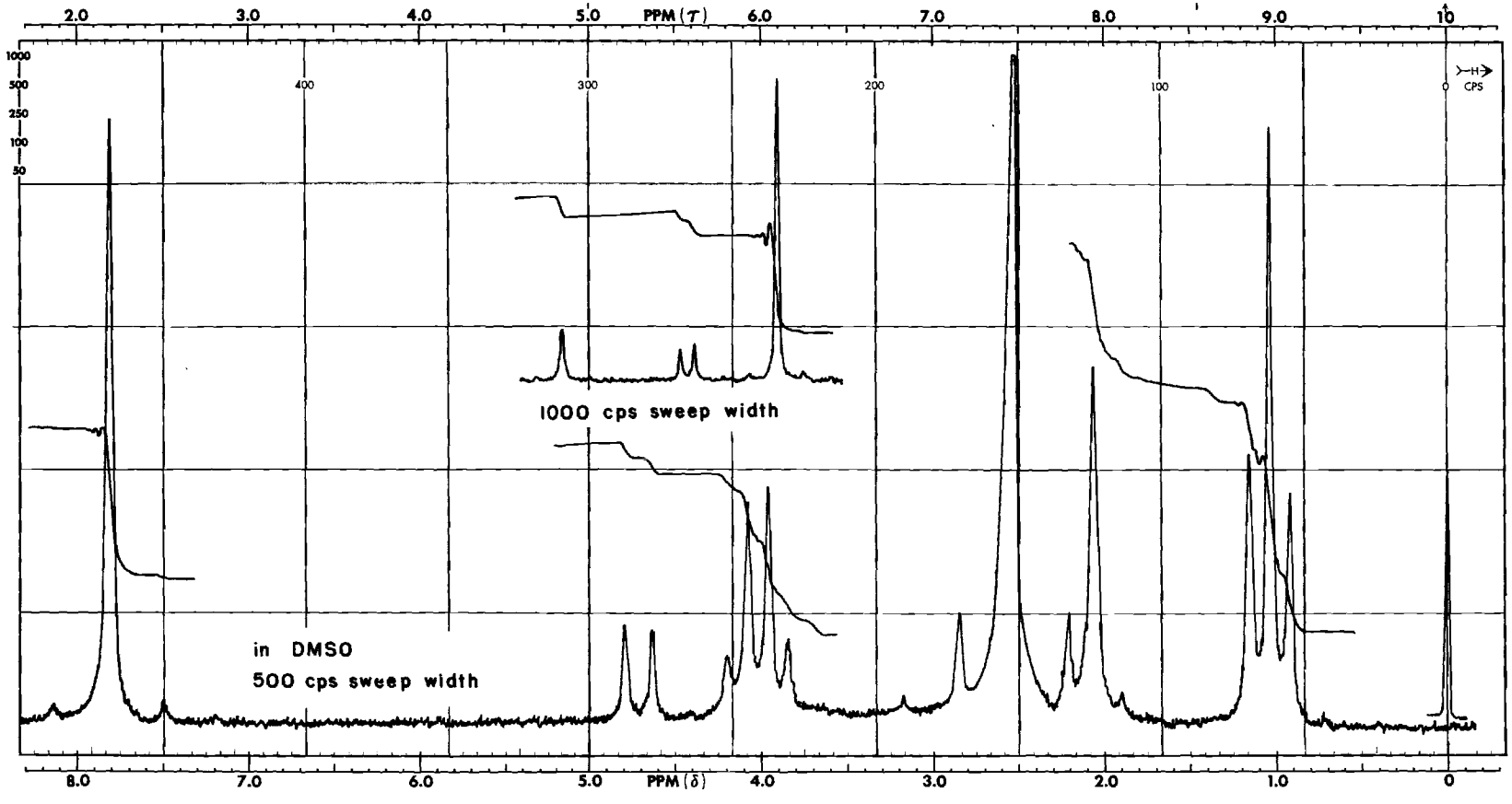


Figure 53. Nuclear Magnetic Resonance Spectrum of Diethyl N-Acetylsulfanilamidomalonate.

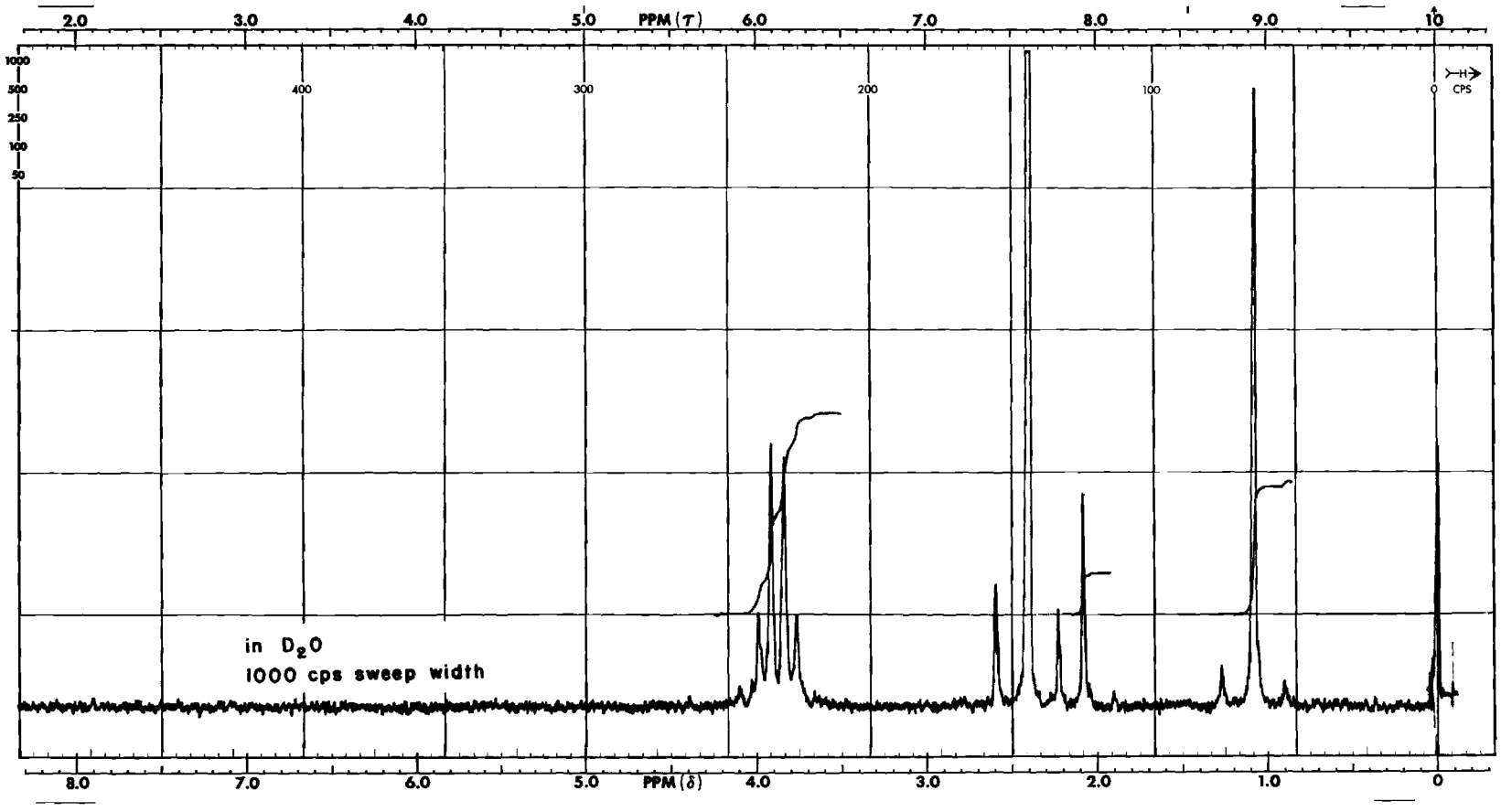


Figure 54. Nuclear Magnetic Resonance Spectrum of Trisodium N-Acetylsulfanilamidomalonate.

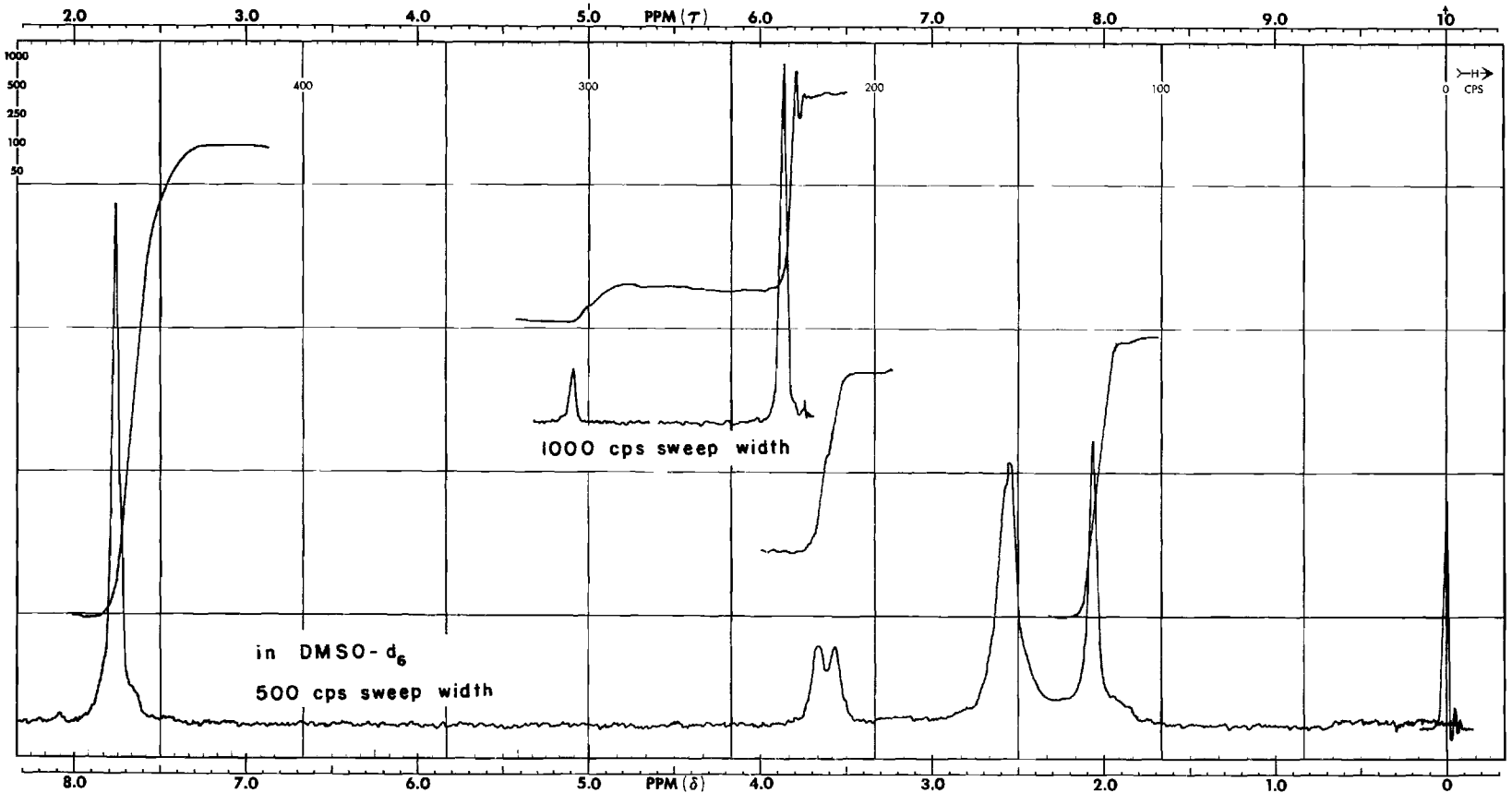


Figure 55. Nuclear Magnetic Resonance Spectrum of N-Acetylsulfanilamidoacetic Acid.

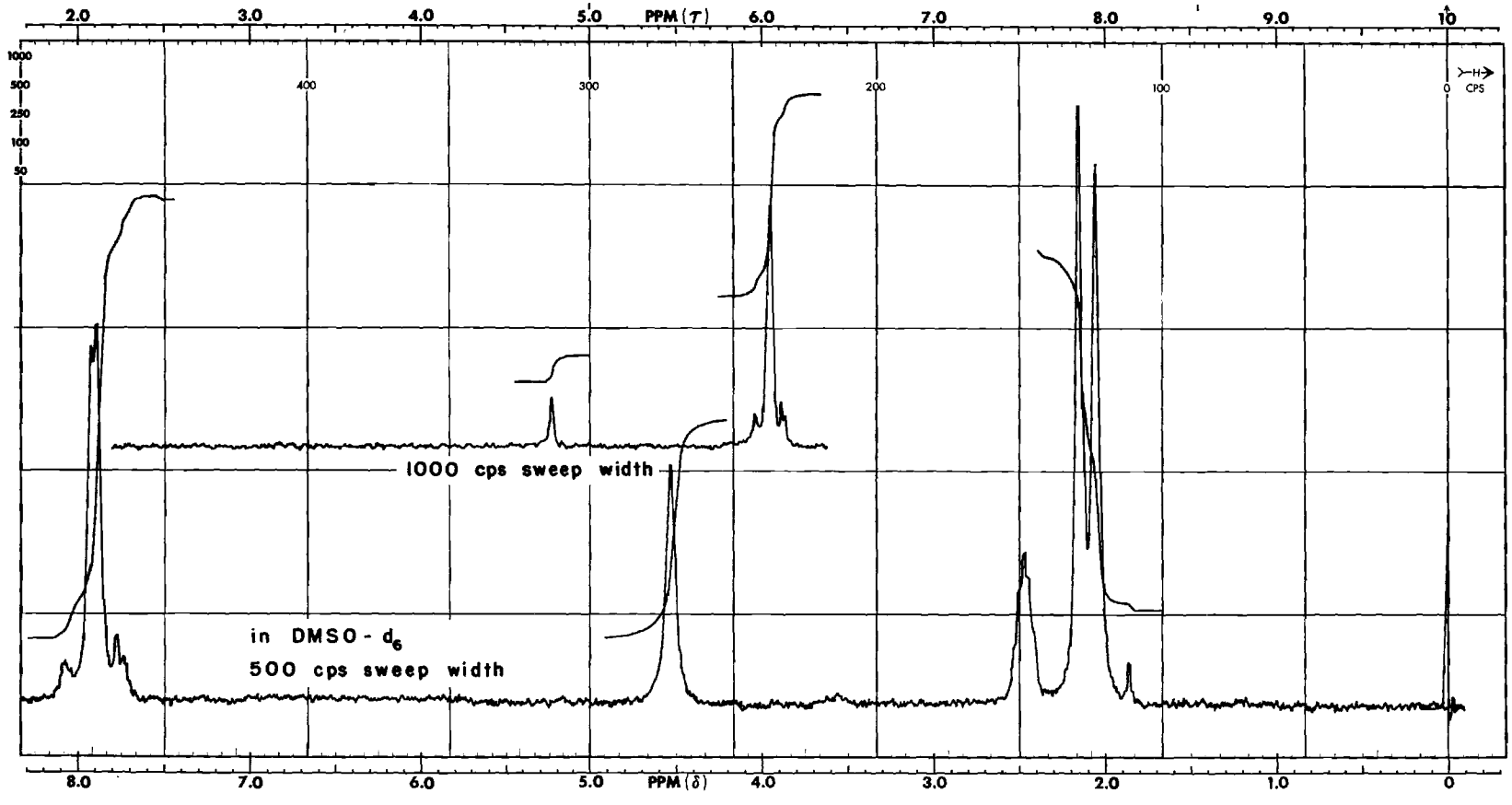


Figure 56. Nuclear Magnetic Resonance Spectrum of N,N'-Diacetylsulfanilamidoacetic Acid.

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VITA

VITA

Marvin L. Doerr was born October 16, 1939 in Oklahoma City, Oklahoma to Evelyn Freda and Elmer Christian Doerr. He has one brother, Robert Chris Doerr, seven years his junior. He attended public schools in Oklahoma City, Oklahoma, St. Louis, Missouri, and was graduated from Webster Groves High School, Webster Groves, Missouri in 1957. In 1961, he received the Artium Baccalaurei degree in Chemistry from Washington University, St. Louis, Missouri, during which time he was an active member of Tau Kappa Epsilon social fraternity. Upon graduation, he was employed as an Associate Development Chemist by the A. E. Staley Manufacturing Company in Decatur, Illinois. After 15 months, he enrolled in the Graduate Division, School of Chemistry, at Georgia Institute of Technology. While at Georgia Tech, he held a teaching assistantship in the School of Chemistry for five years and was the recipient of the Du Pont Graduate Teaching Assistant Award during the acedemic year 1966-1967. In September, 1963, he married the former Miss Jean Carole Rahmeier. They have one son, Robert Marvin.

He is a member of Sigma Xi Professional Honorary and the American Guild of Organists. He has accepted a position of Senior Research and Development Chemist with Fiber Industries, Incorporated, Charlotte, North Carolina, a subsidiary of the Celanese Corporation of America.