REACTION OF 5-BROMO-5-ALKYLBARBITURIC ACIDS WITH AMINES

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REACTION OF 5-BROMO-5-ALKYLBARBITURIC

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TABLE OF CONTENTS

Page

ACKNOWLEDGMENTS. ii

LIST OF ILLUSTRATIONS. v

SUMMARY. vii

CHAPTER

I. INTRODUCTION. 1

II. DISCUSSION OF EXPERIMENTAL RESULTS AND TECHNIQUES 4

Infrared Spectra
Nuclear Magnetic Resonance Spectra
Mass Spectra

III. EXPERIMENTAL. 18

Preparation of 5-Butylbarbituric Acid
Preparation of 5-Bromo-5-butylbarbituric Acid
Preparation of 5-Ethylbarbituric Acid
Preparation of 5-Bromo-5-ethylbarbituric Acid
Preparation of 5-Butyl-5-(N-morpholino)-barbituric Acid
Preparation of 5-Butyl-(N-ethylisonipecotato)-barbituric Acid
Preparation of 5-Butyl-5-(N-pyrrolidino)-barbituric Acid
Preparation of 5-Butyl-5-[N-(2,6-dimethyl-morpholino)]-barbituric Acid
Preparation of 5-Butyl-5-[N-(3-methyl-piperidino)]-barbituric Acid
Preparation of 5-Butyl-5-(N-ethyl-N'-piperazinocarboxylato)-barbituric Acid
Preparation of 5-Butyl-5-[N-(1-methyl-piperazino)]-barbituric Acid
Preparation of 5-Butyl-5-(N-p-phenetidino) barbituric Acid
Preparation of 5-Butyl-5-(N-piperidino)-barbituric Acid
Preparation of 5-Butyl-5-[N-(4-benzyl-piperidino)]-barbituric Acid

Chapter Page

Preparation of 5-Butyl-5-[N-(1,2,3,4-tetrahydroisoquinolino)]-barbituric Acid
Preparation of 5-Butyl-5-[N-(4-methyl-piperidino)]-barbituric Acid
Preparation of 5-Ethyl-5-[N-(2,6-dimethyl-morpholino)]-barbituric Acid
Preparation of 5-Ethyl-5-[N-(3-methyl-piperidino)]-barbituric Acid
Reaction of 5-Bromo-5-butylbarbituric Acid with Benzylamine
Reaction of 5-Bromo-5-butylbarbituric Acid with 4-Hydroxypiperidine
Reaction of 5-Bromo-5-butylbarbituric Acid with Allylamine
Reaction of 5-Bromo-5-butylbarbituric Acid with 2-Aminopyrimidine

IV. CONCLUSIONS. 40

V. RECOMMENDATIONS. 41

APPENDIX A. 43

APPENDIX B. 44

APPENDIX C. 52

BIBLIOGRAPHY. 62

LIST OF ILLUSTRATIONS

Figure		Page
1.	Structures of Salts.	5
2.	Mechanism of Salt Formation.	7
3.	5-Butyl-5-aminobarbituric Acid	9
4.	Dissociation of Salt of 5-Bromo-5-butyl-barbituric Acid and 2-Aminopyrimidine in DMSO. .	11
5.	Amines That Give M-45 Peaks in Mass Spectrum . .	14
6.	Decomposition of Amine Salts	14
7.	McLafferty Rearrangement of 5-Butyl-barbituric Acid.	16
8.	Infrared Spectrum of 5-Butyl-5-[N-(piperidino)]-barbituric Acid.	53
9.	Infrared Spectrum of 5-Butyl-5-[N-(ethyl-isonipecotato)]-barbituric Acid.	53
10.	Infrared Spectrum of 5-Butyl-5-[N-(morpholino)]-barbituric Acid.	54
11.	Infrared Spectrum of 5-Butyl-5-(N-pyrrolidino)-barbituric Acid.	54
12.	Infrared Spectrum of 5-Butyl-5-[N-(3-methylpiperidino)]-barbituric Acid	55
13.	Infrared Spectrum of [5-Butyl-5-N-(2,6-dimethylmorpholino)]-barbituric Acid	55
14.	Infrared Spectrum of 5-Butyl-5-[N-(ethyl-N'-piperazino-carboxylato)]-barbituric Acid	56
15.	Infrared Spectrum of 5-Butyl-5-[N-(4-methyl-piperazino)]-barbituric Acid	56
16.	Infrared Spectrum of 5-Butyl-5-(N-p-phenetidino)-barbituric Acid	57

Figure Page

17. Infrared Spectrum of 5-Butyl-5-[N-(4-benzyl-piperidino)]-barbituric Acid. 57

18. Infrared Spectrum of 5-Butyl-5-[N-(1,2,3,4-tetrahydroisoquinolino)]-barbituric Acid. 58

19. Infrared Spectrum of 5-Butyl-5-[N-(4-methyl-piperidino)]-barbituric Acid. 58

20. Infrared Spectrum of 5-Ethyl-5-[N-(2,6-dimethylmorpholino)]-barbituric Acid. 59

21. Infrared Spectrum of 5-Ethyl-5-[N-(3-methyl-piperidino)]-barbituric Acid. 59

22. Infrared Spectrum of the Salt of 5-Butyl-5-bromobarbituric Acid and 2-Aminopyrimidine. . . . 60

23. Infrared Spectrum of the Salt of 5-Butylbarbituric Acid and Benzylamine. 60

24. Infrared Spectrum of the Salt of 5-Butylbarbituric Acid and 4-Hydroxypiperidine. 61

25. Infrared Spectrum of the Salt of 5-Butylbarbituric Acid and Allylamine 61

SUMMARY

The object of this research was to study the reaction of 5-bromo-5-alkylbarbituric acids with amines and to synthesize some new 5-(N-amino)-barbituric acid derivatives. It was considered that such 5-(N-amino) compounds might possess useful physiological activity.

The 5-alkylbarbituric acids were prepared by condensing urea with the appropriate malonic ester in sodium ethoxide solution. The 5-ethyl barbituric acid thus formed was brominated by treating it with liquid bromine in hot water. The 5-butylbarbituric acid was brominated in a dilute solution of sodium hydroxide by adding cold bromine water dropwise. The reaction of the 5-bromo-5-alkyl-barbituric acids with the amines was carried out in methanol, and the products were generally isolated after the reaction had proceeded for 24 hours at room temperature.

Infrared, nuclear magnetic resonance, and mass spectral data have been recorded for all compounds prepared. These data show that the reaction of the 5-bromo-5-alkylbarbituric acids with amines can result in two different products. One is the 5-(N-amino) adduct, and the other is an amine salt of either the brominated or non-brominated alkylbarbituric acid.

CHAPTER I

INTRODUCTION

Barbituric acid was first synthesized by Baeyer [1] in the early 1860's. From then until the end of the nineteenth century, many researchers studied barbituric acid and prepared a number of derivatives.

One of the derivatives synthesized was 5,5-diethyl-barbituric acid [2], now commonly called Barbital. Interest in barbituric acid studies accelerated considerably when it was discovered [3], in the early 1900's, that Barbital had hypnotic properties. Since that time numerous barbiturates have been prepared and many tested for physiological activity. Only a very few of these compounds, however, have been found to be useful physiologically [4]. These compounds are mostly the 5-ethyl-5-alkyl (or phenyl) substituted barbituric acids, such as the aforementioned Barbital.

In addition to their use as therapeutic agents, barbituric acids possess a number of other useful properties. They have been employed as anti-oxidants in photography, as catalysts in the polymerization of halogenated vinyl monomers and styrene, and as intermediates in the formation of azo dyes. In analytical chemistry they have found use as components of buffer solutions in the pH range of 6-9 and as

reagents for the determination of small quantities of Ag, Hg, Cu, Pd, Pt, Ir, In, and Au [5].

It has also been suggested that barbituric acids are involved in some biological processes. Desoxyribonucleic acids contain thymine groups which give barbituric acid on biological oxidation. It has also been found that certain microorganisms assimilate barbituric acid, using the energy of its decomposition to CO_2, NH_3, and malonic acid for their life processes [5].

The amine function has been known for a long time to be part of the biological processes, and in 1963 it was suggested at a symposium sponsored by the Division of Medicinal Chemistry at Harvard that barbituric acids substituted at the 5 position by certain amines might have a useful effect on the central nervous system [6].

The presence of amine functions in physiologically active alkaloids such as cocaine and in other drugs such as Demerol [7] also suggests that joining the barbituric acid molecule to an amine might possibly produce a useful molecule.

This probability also finds some support from the phenomenon of synergism. 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. Perhaps the most notable case of synergism involving barbiturates is that displayed by barbiturates and ethyl alcohol [8]. Many people have died from taking a barbiturate, whose dosage alone would have

caused no ill effects, while under the influence of ethyl alcohol. There are other examples of synergism involving barbiturates. Sulfathiazole and phenobarbital have been found [9] to exhibit synergism in tests on laboratory animals, and the combination of sulfanilamide and barbiturates was found [10] to be fatal in rats. Fornaroli and Koller [11] have reported that 5-hydroxytryptamine prolongs narcosis caused by pentothal administered to laboratory animals.

With this in mind, this research was begun in order to study reactions of amines with 5-bromo-5-alkylbarbituric acids with the hope of preparing some new barbiturates having the possibility of unusual physiological activity.

Gebauer [12] had reported in his patented process in 1937 that amines such as aniline, piperidine, and p-phenetidine could be reacted with 5-bromo-5-alkylbarbituric acids to form the 5-amino derivative. A different approach to the syntheses of these compounds had been tried by Guidicelli [13], who condensed urea with an aminomalonic ester, and Walker [14] reported the preparation of a series of 5-aminobarbituric acids in 1973.

In addition there have been a few reports [15,16] in the literature of reactions of barbituric acids, mostly 5,5-dialkyl derivatives, with a variety of organic bases to form salts. This work concerns the reaction of amines with 5-bromo-5-alkylbarbituric acids.

CHAPTER II

DISCUSSION OF EXPERIMENTAL RESULTS AND TECHNIQUES

During the course of this investigation a total of fourteen 5-alkyl-5-(N-amino)-barbituric acids were prepared. Twelve of these were 5-butyl derivatives; eleven of these have not previously been reported. Two new 5-ethyl derivatives were also reported. A series of 5-phenyl and 5-ethyl derivatives had already been prepared by Walker [14] using a different method of reaction. The reaction sequence used in all but two cases involved stirring two equivalents of amine with one equivalent of 5-bromo-5-alkylbarbituric acid in methanol at room temperature for 24 hours. The 5-butyl-5-(N-piperidino)-barbituric acid derivative was prepared by refluxing the reaction mixture for half an hour, and the 5-butyl-5-(N-p-phenetidino)-barbituric acid derivative was isolated after the reaction mixture had stirred for approximately two hours.

In several of the remaining reactions a product would precipitate after the 24 hour reaction time. In such cases, the reaction mixture was then cooled and the product was removed by filtration. For those reactions in which a precipitate did not form on completion of the 24 hours of stirring, it was necessary to remove solvent from the reaction

mixture until a thick tarry resin was formed. The resin was then shaken with water while small amounts of acetone were added until the resin was dissolved. In four of these cases a precipitate formed on further shaking, but in three instances a precipitate crystallized out only after the solution was thoroughly chilled in a refrigerator.

The products were found to be easily recrystallized from an acetone-water solution by placing a sample in hot water and adding acetone until it just dissolved and then cooling.

In several cases the attempt to prepare the 5-butyl-5-(N-amino) derivative resulted instead in the formation of a salt. Two different salts were found to be possible. One was the salt of 5-butylbarbituric acid in which the bromine atom has been eliminated from the molecule, and the other was the salt of the 5-butyl-5-bromobarbituric acid. Typical structures are shown below.

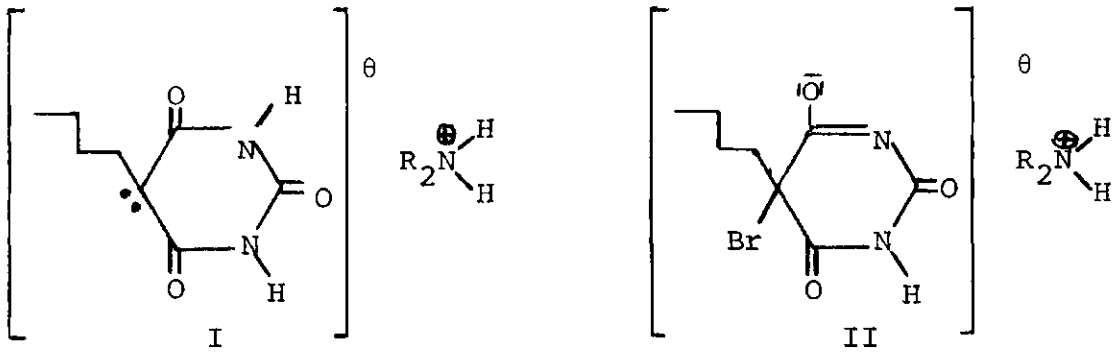


Figure 1. Structures of Salts

In either of these the negative charge on the barbituric acid ring could be located in any one of several places. Bromine is probably lost from the 5-bromo-5-butylbarbituric acid via an N-bromination reaction to give the N-bromoamine and 5-butylbarbituric acid which then forms the salt typically like I in Figure 1. These postulates are summarized in Figure 2. However, no N-bromoamine was isolated from the reaction mixtures.

The spectral data is in good agreement with the formation of a salt. The mass spectra of salt of type II definitely shows the presence of bromine and indicates that the bromine atom has remained attached to the barbituric acid ring. Further indication of the two salts was given by reprecipitation from a dilute acid solution. The salts, when reprecipitated, gave 5-butyl-barbituric acid in those cases where bromine was not present and 5-butyl-5-bromobarbituric acid in the case where bromine was present.

Infrared Spectra

The infrared spectra of the 5-alkyl-5-(N-amino)-barbituric acid derivatives are all very similar. Generally, two carbonyl absorptions appeared: one at approximately 1700 cm^{-1} and another, less intense absorption, at approximately 1760 cm^{-1}. Two other bands generally appeared in the spectra at approximately 1410 cm^{-1}, attributable to C-H bending, and approximately 1270 cm^{-1}, resulting from C-N

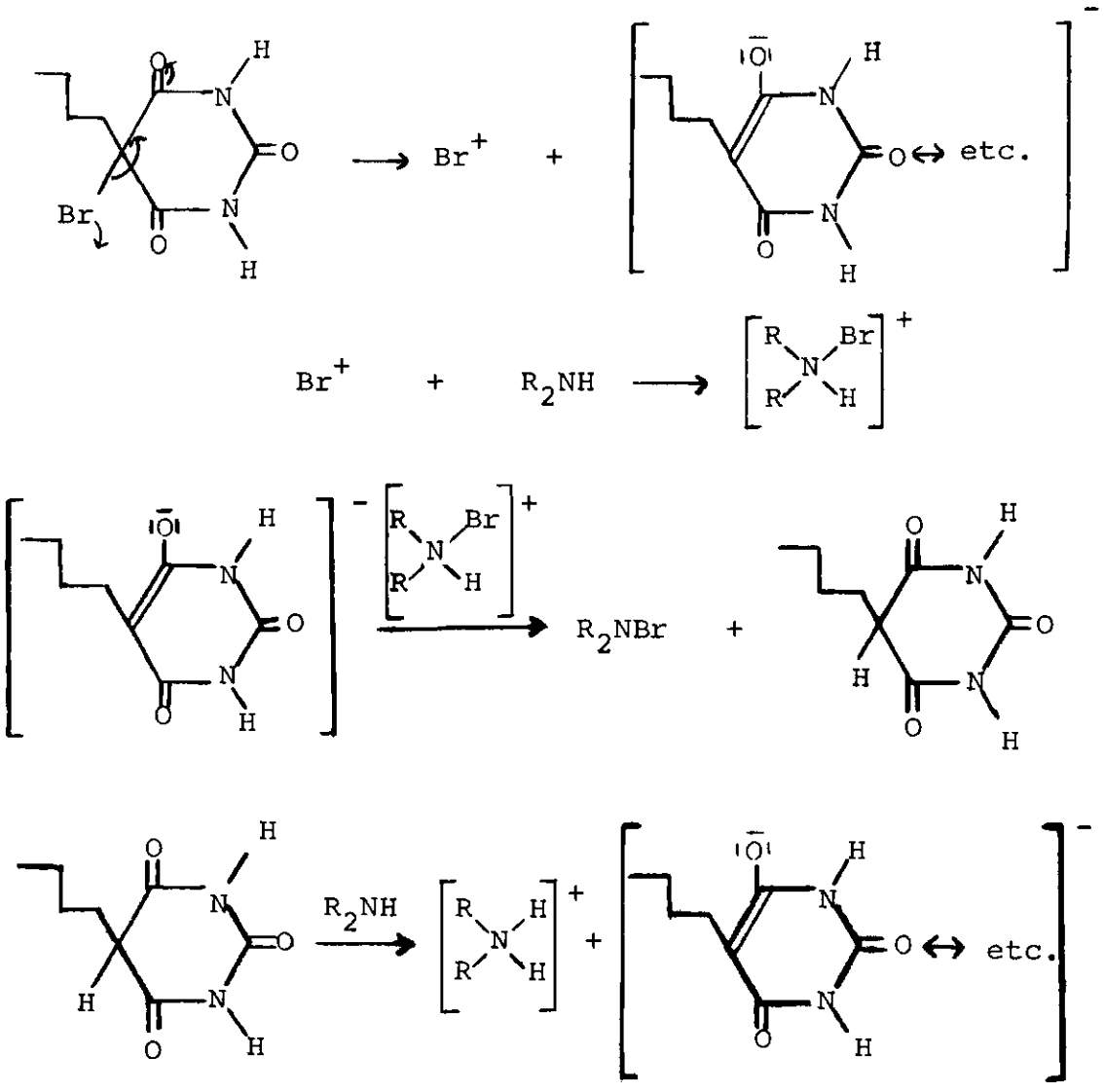


Figure 2. Mechanism of Salt Formation

stretching.

The infrared spectra of the salts of 5-butylbarbituric acid on the other hand gave an intense band at approximately 1570 cm^{-1}, due to N-H bending from the amine salt, and a less intense band at approximately 1380 cm^{-1}, which could result from either C-H or O-H bending. The IR spectrum of the salt containing bromine gave a sharp absorption at 1580 cm^{-1}. The bands at 1570 cm^{-1} and 1580 cm^{-1} are characteristic of amine salts [17]. The band at approximately 1380 cm^{-1} also appeared in the spectra of the 5-amino derivatives but was very weak and much less intense. The carbonyl absorption in the spectra of the salts generally occurred at approximately 1660-1700 cm^{-1}. The carbonyl band of the non-bromo salts generally did not show clear resolution of the carbonyl band into two distinct absorptions. On the other hand the bromo salt did show two distinct bands, one at 1700 cm^{-1} and the other at 1722 cm^{-1}.

Nuclear Magnetic Resonance Spectra

The NMR spectra of all the compounds were taken in either d_6-DMSO or d_5-pyridine. In several cases the absorption patterns were complicated by the fact that proton signals from the butyl group and the alkyl groups on the substituted amine overlapped and could not be resolved one from the other. Determinations of the spectra at lower sweep widths failed to improve the resolution of the signals

so as to enable one to distinguish the positions of the two types of groups. However, in most cases the spectra were not this complicated and the absorptions could be easily identified.

The most distinct feature of the spectra of the 5-(N-amino) derivatives was the occurrence in all cases of a singlet between 11.54δ and 13.52δ, depending on the solvent used. In d_6-DMSO this singlet appeared nearer to 11.54δ, and in d_5-pyridine it appeared closer to 13.52δ. This singlet always integrated for two protons and thus can be attributed to the imide hydrogens of the barbituric acid ring.

The butyl group at the 5 position on the ring gave three distinct absorptions. The protons labeled "a" in the

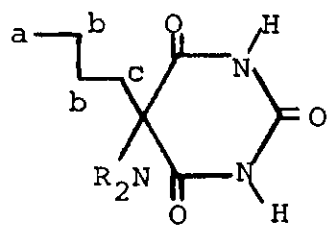


Figure 3. 5-Butyl-5-aminobarbituric acid

above figure appeared between 0.77δ and 0.96δ and were in the form of a triplet. The protons labeled "b" generally

appeared as a broad signal occurring between 1.20δ and 1.47δ, and the two protons labeled "c" also generally appeared as a broad signal centered between 1.98δ and 2.44δ.

Proton signals from the alkyl groups attached to the amines could not be fitted to a distinct pattern; however, one feature of special interest was noted. In the NMR spectra of 5-butyl-5-[N-(3-methypiperidino)]-barbituric acid, 5-ethyl-5-[N-(3-methylpiperidino)]-barbituric acid, and 5-butyl-5-[N-(4-methylpiperdino)]-barbituric acid, the methyl group on the piperidine ring hinders the interconversion of the equatorial and axial protons allowing one to differentiate between the α-equatorial and α-axial protons on the piperidine ring. The α-equatorial protons appear at higher δ values in the range of 3.16δ to 3.32δ as a doublet in all cases. The α-axial protons appear at lower δ values but in all cases are overlapped by other absorptions and can not be completely resolved. The doublet, resulting from the α-equatorial protons, is very similar in appearance and position to that reported for 3-methypiperidine and 4-methylpiperidine [18].

The NMR spectra of the amine salts of 5-butyl-barbituric acid gave three butyl absorptions at the expected locations. Those protons labeled "a" in Figure 3 appeared between 0.85δ and 1.00δ, those labeled "b" appeared between 1.22δ and 1.36δ, and those labeled "c" appeared between 2.09δ and 2.40δ. In all the spectra a very broad absorption occurred at high δ values in the position expected from ammonium ion protons.

The NMR spectrum in d_6-DMSO of the salt of 2-amino-pyrimidine and 5-bromo-5-butylbarbituric acid is of special interest. Apparently in DMSO the salt completely dissociates into its two components, as shown in Figure 4.

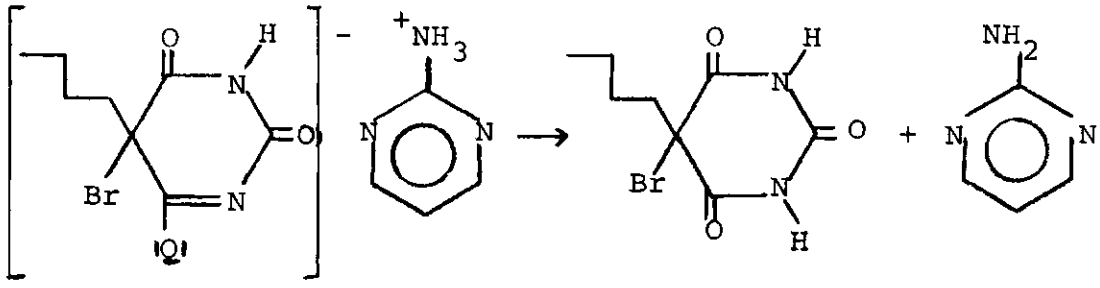


Figure 4. Dissociation of Salt of 5-Bromo-5-butyl-barbituric Acid and 2-Aminopyrimidine in DMSO

The NMR spectrum shows all the peaks typical of 5-bromo-5-butylbarbituric acid at the appropriate δ values, and all the peaks of 2-aminopyrimidine at the δ values observed in a spectrum of the free amine.

Mass Spectra

The mass spectra of the butyl derivatives were quite similar to one another. All but two of the compounds gave a molecular ion at the calculated point. The intensity of these peaks varied from 3 to 31% of the base peak. Those not giving a molecular ion were the ethyl isonipecotate derivative and the 1,2,3,4-tetrahydroisoquinoline derivative, which

gave an M-1 peak with 5% intensity of the base peak. All but one of the 5-butyl-5-(N-amino) derivatives gave peaks at M-57 which would correspond to either a loss of the butyl group from the five position or the loss of a NH-C(=O)-N fragment from the ring. An exact mass determination of the M-57 peak in the 5-butyl-5-(N-piperidino) derivative proved it to result from a loss of the butyl fragment. An experimental exact mass of 210.08494 atomic mass units was obtained with an instrument error of 3.9916 millimass units. The four possible fragments that would have a mass within this range are:

Calc. mass	deviation (in millimass units)	C	H	N	O
210.08519	.2	6	14	2	6
210.08787	2.9	9	12	3	3
210.08384	-1.1	4	12	5	5
210.08654	1.6	7	10	6	2

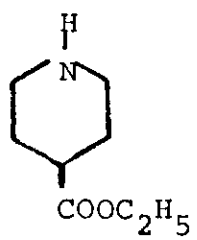
If the cleavage of M^+ is the result of a single bond cleavage only, then an odd M^+ will give an even fragment ion. Further the even fragment ion must contain all the nitrogens of M^+, i.e. three nitrogens in this case. On this basis fragments 1 and 4 above may be eliminated since they contain even numbers of nitrogen. Fragment 3 above may also be eliminated since it contains five nitrogens, while the M^+ contains only three. If NH-C(=O)-N is cleared, M-57 could result. One notes, however, this is not a simple cleavage. Rather it is

cleavage and proton migration. Fragment 1 thus cannot be eliminated by the above, but it can be eliminated since if an NH-C(=O)-N is lost, one nitrogen remains. Fragment 1 demands 2 nitrogens. Further, the fragment resulting from loss of an NH-C(=O)-N group did not fall within the error limits, its mass being 210.14940. It has also been reported [19] previously that 5-alkyl substituted barbiturates preferentially show fragmentation of the alkyl group prior to destruction of the ring.

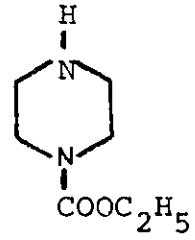
All but two of the butyl derivatives gave an M-85 peak which would correspond to a loss of a carbonyl group from the barbiturate ring after loss of the butyl group. These peaks ranged in intensity from 9 to 87% of the base peak. The two compounds not showing this peak were the derivatives of 4-methylpiperazine and ethyl isonipecotate.

All but two of the butyl derivatives showed as a base peak the mass of the amine involved minus one hydrogen. This would result from simple cleavage of the amine function from the ring. The two compounds in which the amine minus hydrogen peak was not the base peak were the 5-ethyl isonipecotato and 5-p-phenetidino derivatives but in both these cases this peak was significant, having a 48% intensity in the former and a 42% intensity in the latter.

Two of the butyl derivatives gave M-45 peaks. The two amines involved are shown below.



M-45 peak, 9% intensity



M-45 peak, 11% intensity

Figure 5. Amines that Give M-45 Peaks in Mass Spectrum

These peaks are a result of the loss of an O-Et group from the ester function on the two amines.

Both of the two 5-ethyl-5-amino derivatives gave as their base peak the mass of the amine minus one hydrogen. Both also gave M-29 peaks as a result of splitting off the ethyl group from the 5 position, as well as fragments corresponding to a breakdown in the ring and loss of NH-C(=O)-N. Both compounds gave peaks at the calculated point for a molecular ion.

Mass Spectrometry of the Salts

The mass spectra of the non-bromo salts were almost identical except in the regions where the respective amines from each compound gave prominent peaks.

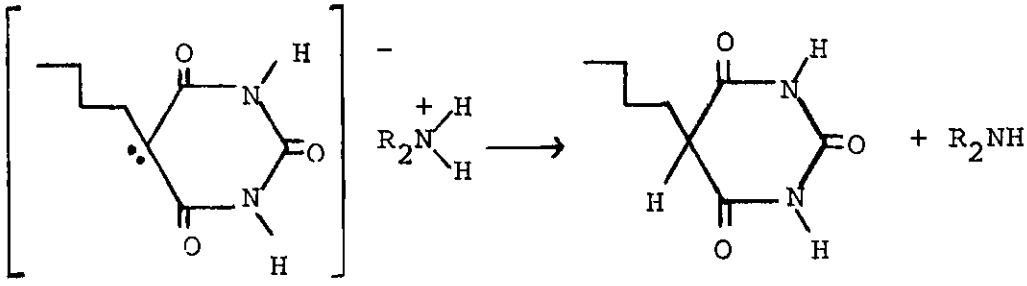


Figure 6. Decomposition of Amine Salts

Apparently the salt decomposes into its components in the instrument as shown above, and the spectra show peaks typical of 5-butylbarbituric acid and the amine involved. All the spectra gave a prominent peak at 155 ranging in intensity from 9-14% of the base peak. This peak resulted from a loss of CH_3-CH_2 from the butyl group and was also prominent in the spectrum of 5-butylbarbituric acid.

Peaks also appeared at 142 (intensity range 13-20%) and 141 (intensity range 21-33%). An exact mass determination of these two peaks proved them to result from fragmentation of the butyl group. The peak at 142 results from transfer of hydrogen to the carbonyl oxygen and loss of a CH_3-CH_2-CH fragment from the butyl group. The peak at 141 results from simple loss of a CH_3-CH_2-CH_2 fragment from the butyl group. These two peaks could also result from loss of N-C=O (m/e 142) and NH-C=O (m/e 141) from the ring, but, as has been mentioned previously [19] and has been proven in this work, in 5-alkylbarbituric acids fragmentation of the alkyl group occurs preferentially over rupture of the barbiturate ring.

The experimental exact mass determined for the 141 peak was 141.03075 atomic mass units with an instrument error of 2.6796 millimass units. The calculated exact mass of the fragment resulting from loss of a CH_3-CH_2-CH_2 group is 141.03002 and is in agreement with the experimental value. The fragment resulting from loss of an NH-C=O group did not fall within the error limits, its mass being 141.07898. The

experimental exact mass determined for the peak at 142 was 142.03600 atomic mass units with an instrument error of 2.6987 millimass units. The calculated exact mass of the fragment resulting from loss of a CH_3-CH_2-CH group is 142.03784 and is in agreement with the experimental value. The fragment resulting from loss of an N-C=O group did not fall within the error limits, its mass being 142.08680.

In two cases the base peak occurred at m/e 128 and in the other case this peak was 96% as abundant as the base peak. This peak corresponds to a McLafferty rearrangement involving the transfer of one hydrogen from the butyl group to a carbonyl oxygen and loss of the remainder of the butyl group [20].

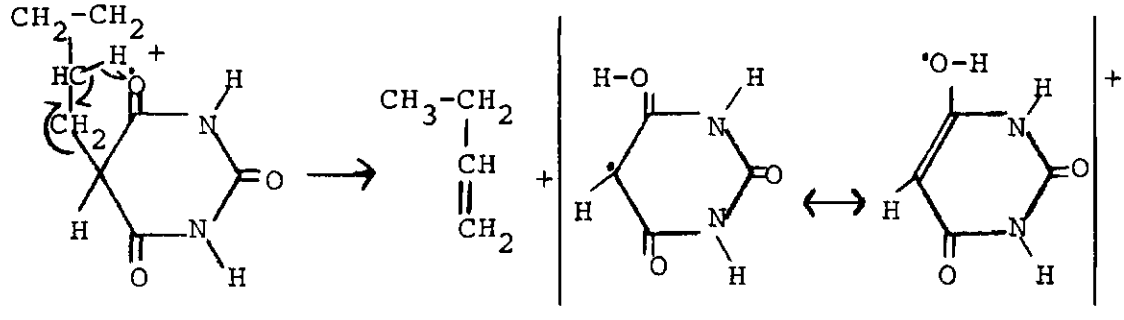


Figure 7. McLafferty Rearrangement of 5-Butyl-barbituric Acid

All the peaks discussed were prominent in the mass spectrum of 5-butylbarbituric acid. All of the spectra also showed prominent peaks for the amines involved at the calculated points.

The salt of 5-bromo-5-butylbarbituric acid and 2-aminopyrimidine gave a pair of prominent peaks at m/e 206 and m/e 208 corresponding to a McLafferty rearrangement involving the butyl group of 5-bromo-5-butylbarbituric acid. These two peaks also occurred prominently in the mass spectrum of 5-bromo-5-butylbarbituric acid, indicating the bromine atom remains attached to the barbituric acid ring in the salt. The only other prominent peaks occurring in the spectrum of the salt which did not appear in the spectrum of 5-bromo-5-butylbarbituric acid were at m/e 95 and m/e 68. The former is the calculated molecular weight for 2-aminopyrimidine, and the latter results from loss of the amine function (NH_2) from the pyrimidine ring system (calc. 68).

CHAPTER III

EXPERIMENTAL

All melting points are recorded in degrees Centigrade and are uncorrected. They were determined in capillary tubes using a Mel-Temp melting point apparatus. Infrared spectra were recorded with a Perkin-Elmer 700 spectrophotometer using potassium bromide pellets. Nuclear magnetic resonance spectra were taken with a Varian Associates Model A-60D spectrometer. Mass spectra were obtained with either a Varian Model M-66 mass spectrometer or a Hitachi Perkin-Elmer RMU-7L mass spectrometer.* All elemental Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia.

Preparation of 5-Butylbarbituric Acid

The general procedure used has been reported previously in the literature [21]. The reaction described below was repeated several times with good yields. A three-necked, three liter flask, containing one liter of absolute ethanol, was fitted with a condenser, protected from moisture by a calcium chloride drying tube and a dropping funnel. This flask was placed above a magnetic stirrer and arranged so that heat could be applied by using a heating mantle.

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*The purchase of this instrument was made possible by a grant from the National Science Foundation.

Fourteen grams (0.61 mole) of sodium was added over a period of ten minutes to the alcohol and stirred until it had completely reacted. To the above ethoxide solution was slowly added, through the attached dropping funnel, 130g(0.60 mole) of diethyl butylmalonate. After the malonate was added, 36g (0.60 mole) of urea was introduced. The reaction mixture was refluxed for 4.5 hours, then one-half liter of ethanol was removed by distillation at atmospheric pressure, and 500 ml of water containing 45 ml of concentrated HCl was added to the residue. Another one-half liter of ethanol was then removed by distillation, and the solution was cooled and filtered to remove the precipitated 5-butylbarbituric acid. In all cases the barbituric acid was contaminated with unreacted malonate which was removed by dissolving the acid in dilute base and extracting the malonate with ether. The barbituric acid was re-precipitated from the base solution with dilute HCl, filtered, washed with water, and vacuum dried. Yields averaged 75% with the best yield being 85%. A small sample was recrystallized from absolute ethanol and gave a melting point of 209.5-210.5°C (lit. 214°C)[22]. The IR spectrum gave an intense band at 1700 cm^{-1} (C=O stretch). Bands also appeared at 1450 cm^{-1} (N-H bend) and 1230 cm^{-1} (C-N stretch). The NMR (d_6-DMSO) gave peaks at 11.22δ (singlet,2H), 3.56δ (triplet, 1H), 1.92d (multiplet, 2H), 1.26δ (complex multiplet, 4H, and 0.88δ (triplet, 3H). The mass spectrum did not give a molecular ion, but prominent

peaks were observed at m/e 128 and m/e 141 as described in the literature [19].

Preparation of 5-Bromo-5-butylbarbituric Acid

Direct bromination of the sodium salt of 5-butylbarbituric acid gave rise to the desired 5-bromo derivative [23]. The reaction was repeated several times, usually resulting in good yields of product. Typically, 20.0g (0.11 mole) of 5-butylbarbituric acid was dissolved in 200 ml of 0.6 N NaOH. A cold* saturated solution of bromine in water was then added dropwise until a permanent bromine color persisted. Addition of solid sodium bisulfite achieved removal of excess bromine. The precipitate, which had formed during the bromination, was removed by filtration, washed with water, and dried under vacuum. The average yield was 78%, and the best yield obtained was 85%. This product was used without further purification. Recrystallization of a small sample gave a product with a melting point of 105-107°C (lit. 109°C) [24]. The IR showed bands at 1760 cm^{-1} and 1700 cm^{-1} (C=O stretch), and at 1430 cm^{-1} (C-H bend), and 1370 cm^{-1} (C-H bend). The NMR (d_6-DMSO) gave absorptions at 11.80δ (singlet, 2H), 2.12δ (broad multiplet, 2H), 1.20δ (broad multiplet, 4H), and 0.86δ (triplet, 3H). The mass spectrum gave no molecular ion but the presence of bromine

*Use of a room temperature bromine solution resulted often in the formation of an oil which was difficult to crystallize.

was indicated by a pair of peaks of approximately equal intensity at 206 and 208 resulting from a McLafferty rearrangement with the loss of C_4H_8.

Preparation of 5-Ethylbarbituric Acid

This compound was prepared in a manner analogous to that for the 5-butyl compound [21]. Into three liters of anhydrous ethanol contained in a 5 liter three-necked flask, fitted with a dropping funnel and a condenser and protected from atmospheric moisture by a calcium chloride drying tube, was placed 34.5g (1.5 mole) of sodium over a period of 20 minutes. This was mechanically stirred until all of the sodium had reacted. After formation of the ethoxide was complete, 282g (1.5 mole) of diethyl ethylmalonate was added to the flask dropwise over a period of thirty minutes. Before any heat was applied, 99g (1.6 moles) of urea was added to the flask and the mixture was mechanically stirred. A white precipitate appeared as heating was begun, and the reaction mixture was refluxed for 4.5 hours. After this time interval approximately 1.5 liters of ethanol was removed by distillation. Next 1.5 liters of water containing 130 ml of concentrated HCl was added to the flask. The remaining ethanol was then distilled off and the solution placed in the refrigerator to allow complete precipitation of the 5-ethylbarbituric acid. The solid was removed by filtration, washed twice with distilled water, and then partially dried

under vacuum. The melting point of the crude product was 185-189°C (lit. 189-190°C) [25]. No further characterization was done and the bromination, described below, was carried out with the crude product.

Preparation of 5-Bromo-5-ethylbarbituric Acid

The procedure used is that patterned after Cox [24]. The 5-ethylbarbituric acid, prepared as described above, was dissolved in one liter of water by heating and stirring. Bromine was slowly added to the solution until it had a permanent bromine color. As bromination proceeded the bromo product crystallized from solution. When the excess bromine had been destroyed with a small quantity of solid solium bisulfite, the solution was cooled and the precipitate filtered, washed with water, and dried under vacuum. The product weighed 265g (overall yield 75%) and had a melting point of 202-204°C (lit. 202°C) [24]. The IR gave absorptions at 1720 cm^{-1} (C=O stretch), 1440 cm^{-1} (C-H bend), and 1250 cm^{-1} (C-N stretch). The NMR showed absorptions at 11.80δ (singlet, 2H), 2.40δ (quartet, 2H), 0.90δ (triplet, 3H). In the mass spectrum a pair of peaks of approximately the same intensity at 206 and 208, resulting from a McLafferty rearrangement and loss of C_2H_4, indicate the presence of brominated compound.

Preparation of 5-Butyl-5-(N-morpholino)-barbituric Acid

Five grams (0.019 mole) of 5-bromo-5-butylbarbituric

acid was dissolved in 20 ml of methanol and stirred. To this solution was added, at one time, 3.3g (0.038 mole) of morpholine, and the mixture was stirred for 24 hours at room temperature. During stirring a precipitate formed. Following thorough chilling of the reaction mixture in a refrigerator, the precipitated product was filtered, washed with distilled water, and vacuum dried. The reaction gave 2.0g (40% yield) of product, m. p. 222-226°C.

After recrystallization from an acetone-water solution, the product melted at 226-227°C (lit. 229°C) [26]. The IR spectrum showed two carbonyl absorptions: at 1700 cm^{-1} and a shoulder at 1750 cm^{-1}. Also shown were significant absorptions at 1410 cm^{-1} (C-H bend), 1280 cm^{-1} (C-N stretch), and 1130 cm^{-1} (C-O stretch). The NMR spectrum in d_5-pyridine gave bands at 13.46δ (singlet, 2H), 3.76δ (triplet, 4H), 2.97δ (triplet, 4H), 2.30δ (multiplet, 2H), 1.32δ (multiplet, 4H), and 0.82δ (triplet, 3H). The mass spectrum gave an m/e at 269 (calc. for molecular ion 269).

Calculated, $C_{12}H_{19}N_3O_4$: C, 53.52; H, 7.11; N, 15.60.

Found: C, 53.69; H, 7.13; N, 15.63.

Preparation of 5-Butyl-5-(N-ethylisonipecotato)-barbituric Acid

To a solution of 5.0g (0.019 mole) of 5-bromo-5-butyl barbituric acid in 20 ml of methanol was added at one time 5.9 g (0.038 mole) of ethyl isonipecotate, and the mixture was stirred at room temperature for 24 hours. Since no

precipitate had appeared at the end of this time, the reaction mixture was rotovaped using a water aspirator at 40-50°C until a resin had formed. This resin was shaken with water, containing a small quantity of acetone, whereupon a precipitate appeared. The solution was cooled in a refrigerator, and the precipitate was removed by filtration, washed with distilled water, and dried under vacuum. The product weighed 2.0g (32% yield), m.p. 184-188°C.

Following recrystallization from an acetone-water solution, the product melted at 199.5-200.5°C. Two carbonyl absorptions appeared in the IR: one at 1700 cm^{-1} (C=O stretch) and a shoulder at 1730 cm^{-1} (C=O stretch). Other significant absorptions occurred at 1410 cm^{-1} (C-H bend) and 1280 cm^{-1} (C-N stretch). The NMR spectrum in d_5-pyridine showed absorptions at 12.94δ (singlet, 2H), 4.13δ (quartet, 2H), from 1.58-3.55δ (complex group of signals, 11H), 1.20δ (multiplet, 4H), 1.14δ (triplet, 3H), and 0.78δ (triplet, 3H). The mass spectrum did not show a molecular ion, but a peak occurred at 282 (M-57) which corresponds to a loss of the butyl group from the desired compound.

Calculated, $C_{16}H_{25}N_3O_5$: C, 56.62; H, 7.42; N, 12.38.

Found: C, 56.53; H, 7.47; N, 12.26.

Preparation of 5-Butyl-5-(N-pyrrolidino)-barbituric Acid

Into a solution of 5.0g (0.019 mole) of 5-bromo-5-butylbarbituric acid in 20 ml of methanol was introduced, at

one time, 2.7g (0.038 mole) of pyrrolidine. After stirring for 24 hours at room temperature a precipitate had formed in the reaction mixture. This precipitate was removed by filtration after the solution was cooled in the refrigerator. It was washed with distilled water and vacuum dried. The solid weighed one gram (22% yield), m.p. 242-244°C.

After recrystallization from an acetone-water solution the product melted at 243-244°C. The IR showed absorptions at 1760 cm^{-1} (C=O stretch), 1700 cm^{-1} (C=O stretch), 1410 cm^{-1} (C-H bend), and 1270 cm^{-1} (C-N stretch). The NMR spectrum (d_5-pyridine) gave bands at 13.14δ (singlet, 2H), 3.02δ (triplet, 4H), 2.44δ (multiplet, 2H), 1.64δ (multiplet, 4H), 1.34δ (multiplet, 4H), and 0.82δ (triplet, 3H). The mass spectrum gave an m/e at 253 (calculated for molecular ion, 253).

Calculated, $C_{12}H_{19}N_3O_3$: C, 56.90; H, 7.56; N, 16.59.

Found: C, 56.76; H, 7.62; N, 16.49.

Preparation of 5-Butyl-5-[N-(2,6-dimethylmorpholino)]-barbituric Acid

Five grams (0.019 mole) of 5-bromo-5-butylbarbituric acid was dissolved in 20 ml of methanol, and 4.4g (0.038 mole) of 2,6-dimethylmorpholine was added at one time. After stirring the solution at room temperature for 24 hours, the mixture was rotovaped, using a water aspirator at 40-50°C, until a resin was formed. Precipitation of the product was induced by shaking the resin in water and adding small

amounts of acetone until the resin just dissolved. Following filtration, washing with distilled water, and vacuum drying, the product weighed 2.0g (36% yield), m.p. 223.5-226.5°C.

Recrystallization from an acetone-water solution yielded a product, m.p. 227-228°C. The IR spectrum gave bands at 1760 cm^{-1} (C=O stretch), 1700 cm^{-1} (C=O stretch), 1410 cm^{-1} (C-H bend), and 1260 cm^{-1} (C-N stretch). The NMR spectrum (d_5-pyridine) gave bands at 12.74δ (singlet, 2H), 3.84δ (multiplet, 2H), 2.17-3.33δ (complex group of signals, 6H), 1.38δ (multiplet, 4H), 1.08δ (doublet, 6H), and 0.83δ (triplet, 3H). The mass spectrum gave an m/e at 297 (calc. for molecular ion, 297).

Calculated, $C_{14}H_{23}N_3O_4$: C, 56.55; H, 7.80; N, 14.13.

Found: C, 56.62; H, 7.87; N, 14.05.

Preparation of 5-Butyl-5-[N-(3-methylpiperidino)]-barbituric Acid

A solution was prepared by dissolving 5.0g (0.019 mole) of 5-butyl-5-bromobarbituric acid in 20 ml of methanol and then adding 3.8g (0.038 mole) of 3-methyl-piperidine at one time. After stirring for 24 hours, a precipitate had appeared. When the mixture had been chilled in a refrigerator, the precipitate removed by filtration, washed with distilled water, and vacuum dried, a yield of 1.0g (19% yield) of product, m.p. 233.5-235.5°C, was obtained.

Recrystallization was effected by placing some of the

product in hot water and adding just enough acetone to dissolve the solid. Upon cooling the recrystallized product gave a m.p. of 236-237°C. Significant absorptions occurring in the IR spectrum were located at 2950 cm^{-1} (C-H stretch), 1760 cm^{-1} (C=O stretch), 1700 cm^{-1} (C=O stretch), 1410 cm^{-1} (C-H bend), and 1260 cm^{-1} (C-N stretch). The NMR spectrum in d_5-pyridine gave bands at 12.84δ (singlet, 2H), 3.16δ (multiplet, 2H, α-equatorial), 2.39δ (multiplet, 4H), 1.47δ (broad complex multiplet, 8H), and 0.77δ (multiplet, 7H). The mass spectrum gave a molecular ion at 281.

Calculated, $C_{14}H_{23}N_3O_3$: C, 59.77; H, 8.24; N, 14.93.

Found: C, 59.85; H, 8.24; N, 14.84.

Preparation of 5-Butyl-5-(N-ethyl-N'-piperazinocarboxylato)-barbituric Acid

Ethyl N-piperazinocarboxylate (6.0g, 0.038 mole) was added at one time to 5-bromo-5-butylbarbituric acid (5.0g, 0.019 mole) in 20 ml of methanol, and the mixture allowed to stir for 24 hours at room temperature. No precipitate was visible after this time, so the mixture was rotovaped to remove solvent whereupon a resin remained. This was shaken in water while small amounts of acetone were added until the resin just dissolved. The solution was cooled to effect crystallization. A yield of 1.8g (28%), melting at 196-198°C, was obtained.

After recrystallization from an acetone-water solution,

a melting point of 196.5-197.5°C was observed. The IR spectrum of the compound showed absorptions at 1760 cm^{-1} (C=O stretch), 1700 cm^{-1} (C=O stretch), 1450 cm^{-1} (C-H bend), and 1260 cm^{-1} (C-N stretch). Bands occurred in the NMR spectrum (d_5-pyridine) at 13.52δ (broad singlet, 2H), 4.20δ (quartet, 2H), 3.60δ (multiplet, 4H), 2.95δ (multiplet, 4H), 2.30δ (multiplet, 2H), 1.25δ (broad multiplet, 4H), 1.16δ (triplet, 3H), and 0.81δ (triplet, 3H). The mass spectrum gave a molecular ion at 340.

Calculated, $C_{15}H_{24}N_4O_5$: C, 52.93; H, 7.11; N, 16.46.

Found: C, 52.95; H, 7.15; N, 16.35.

Preparation of 5-Butyl-5-[N-(1-methylpiperazino)]-barbituric Acid

A solution was prepared by adding 3.8g (0.038 mole) of 1-methylpiperazine to 5.0g (0.019 mole) of 5-bromo-5-butylbarbituric acid in 20 ml of methanol. Allowing this solution to stir at room temperature for 24 hours and then cooling in a refrigerator produced 1.2g (25% yield) of the desired aminobarbituric acid, m.p. 263.5-265.5°C.

Upon recrystallization from an acetone-water solution, a melting point of 268-269°C was observed. Significant bands were noted in the IR spectrum at 1710 cm^{-1} (C=O stretch), 1410 cm^{-1} (C-H bend), and 1300 cm^{-1} (C-N stretch). Bands occurring in the NMR spectrum in d_5-pyridine were at 12.60δ (broad singlet, 2H), 3.07δ (multiplet, 4H), 2.49δ (multiplet,

6H), 2.19δ (singlet, 3H), 1.36δ (multiplet, 4H), and 0.81δ (triplet, 3H). The mass spectrum gave a molecular ion at 282 (calc. 282).

Calculated, $C_{13}H_{22}N_4O_3$: C, 55.30; H, 7.85; N, 19.80.

Found: C, 55.38; H, 7.85; N, 19.80.

Preparation of 5-Butyl-5-(N-p-phenetidino)-barbituric Acid

To 10 ml of methanol containing 2.0g (0.0076 mole) of 5-bromo-5-butylbarbituric acid was added 2.0g (0.015 mole) of p-phenetidine, and the resulting solution was stirred at room temperature. After stirring for 1.5 hours, a thick solid had formed so a little methanol was added to increase the fluidity of the mixture. Stirring was continued for another half hour after which the solid was removed by filtration. By washing this with a small amount of methanol and water and drying under vacuum, one gram (42% yield) of product was obtained (m.p. 249-251°C).

Recrystallization was effected from an acetone-water solution to yield a product melting at 253.5-254.5°C. Bands in the IR spectrum appeared at 1760 cm^{-1} (C=O stretch), 1710 cm^{-1} (C=O stretch), 1510 cm^{-1} (C-H bend), and 1260 cm^{-1} (C-N stretch). Absorptions appeared in the NMR spectrum (d_6-DMSO) at 11.54δ (singlet, 2H), 6.56δ (multiplet, 4H), 6.02δ (singlet, 1H), 3.94δ (quartet, 2H), 1.98δ (multiplet, 2H), 1.30δ (multiplet, 7H), and 0.92δ (triplet, 3H). The mass spectrum gave a molecular ion at an m/e of 319

(calc. 319).

Calculated, $C_{16}H_{21}N_3O_4$: C, 60.18; H, 6.63; N, 13.16.

Found: C, 60.17; H, 6.64; N, 13.11.

Preparation of 5-Butyl-5-(N-piperidino)-barbituric Acid

A solution was prepared by dissolving 4.7g (0.018 mole) of 5-bromo-5-butylbarbituric acid in 20 ml of methanol. To this solution was added at one time 3.0g (0.036 mole) of piperidine, and the resulting reaction mixture was refluxed for one half hour. After refluxing, the solution was rotovaped until a resin had formed. This resin was shaken with water and gradually acetone was added in small amounts until the resin dissolved. A precipitate formed whereupon the mixture was cooled in a refrigerator and then filtered. The precipitate was washed with water and ether and then dried under vacuum. A yield of only 0.6g (13%), m.p. 227.5-229°C, resulted. Upon recrystallization from an acetone-water solution, a melting point of 229.5-230.5°C was noted. Significant bands occurred in the IR at 1750 cm^{-1} (C=O stretch), 1700 cm^{-1} (C=O stretch), 1420 cm^{-1} (C-H bend), 1270 cm^{-1} (C-N stretch). The NMR spectrum (d_5-pyridine) showed bands at 13.12δ (singlet, 2H), 2.88δ (multiplet, 4H), 2.29δ (broad multiplet, 2H), 1.41δ (multiplet, 10H), and 0.81δ (triplet, 3H). The mass spectrum gave a molecular ion at m/e of 267 (calc. 267).

Calculated, $C_{13}H_{21}N_3O_3$: C, 58.41; H, 7.92; N, 15.72.

Found: C, 58.41; H, 7.98; N, 15.67.

Preparation of 5-Butyl-5-[N-(4-benzylpiperidino)]-barbituric Acid

In a solution of 2.0g (0.0076 mole) of 5-bromo-5-butylbarbituric acid in 10 ml of methanol was introduced 2.7g (0.015 mole) of 4-benzylpiperidine, and the resulting reaction mixture was allowed to stir for 24 hours at room temperature. No precipitate appeared after the reaction mixture had stirred and been cooled in a refrigerator, so the solution was rotovaped until a resin was formed. This resin was shaken with water, and small amounts of acetone were added as the shaking was carried out to dissolve the resin. One gram (37% yield) of product with a broad melting range below 200°C was formed during the shaking.

Recrystallization from an acetone-water solution brought the melting point to 212.5-213.5°C. The IR gave significant bands at 1760 cm^{-1} (C=O stretch), 1700 cm^{-1} (C=O stretch), 1410 cm^{-1} (C-H bend), and 1280 cm^{-1} (C-N stretch). The NMR spectrum in d_6-DMSO gave a singlet at 11.52δ (2H), indicating the imide hydrogens of the barbituric acid. Another singlet occurred at 7.26δ (5H) from the amine moity in the molecule. These peaks are in the ratio expected from the aminobarbituric acid. The mass spectrum gave an m/e at 357, corresponding to the calculated m/e of 357 for the molecular ion.

Calculated, $C_{20}H_{25}N_3O_3$: C, 67.20; H, 7.61; N, 11.76.

Found: C, 67.28; H, 7.64; N, 11.66.

Preparation of 5-Butyl-5-[N-(1,2,3,4-tetrahydroisoquinolino)]-barbituric Acid

Two grams (0.015 mole) of 1,2,3,4-tetrahydroisoquinoline was introduced into a solution of 2.0g (0.0076 mole) of 5-bromo-5-butylbarbituric acid in 10 ml of methanol. The resulting mixture was stirred at room temperature for 24 hours. Upon cessation of the stirring a precipitate was visible in the reaction vessel. Cooling the mixture, filtering, washing the product with water, and vacuum drying gave 0.3g (14% yield) of the desired aminobarbituric acid, m.p. 248-250°C.

Recrystallization from an acetone-water solution improved the melting point to 251.5-252.5°C. In the IR spectrum significant bands were noted at 1760 cm^{-1} (C=O stretch), 1700 cm^{-1} (C=O stretch), 1370 cm^{-1} (C-H bend), and 1280 cm^{-1} (C-N stretch). The NMR spectrum (d_6-DMSO) gave absorptions at 11.64δ (singlet, 2H), 7.12δ (singlet, 4H), 3.90δ (singlet, 2H), 2.88δ (singlet, 4H), 2.10δ (multiplet, 2H), 1.28δ (multiplet, 4H), and 0.96δ (triplet, 3H). The mass spectrum did not give a molecular ion, but did give a peak at 314 (M-1) and 258 (M-57), corresponding to a loss of C_4H_9.

Calculated, $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71; N, 13.32.

Found: C, 64.64; H, 6.82; N, 13.26.

Preparation of 5-Butyl-5-[N-(4-methylpiperidino)]-barbituric Acid

Two grams (0.0076 mole) of 5-bromo-5-butylbarbituric acid was dissolved in 10 ml of methanol. To this solution was added at one time 1.5g (0.015 mole) of 4-methyl-piperidine and the solution was stirred for 24 hours at room temperature. After stirring for a few minutes, a white solid formed but this had dissolved at the end of the 24 hour reaction time. When cooled in a refrigerator a precipitate was observed to have formed; however, an IR of this material indicated it to be a salt. The remaining solution from which the salt had been isolated was rotovaped to form a resin and then shaken with water while adding small amounts of acetone until the resin dissolved. This solution was cooled, and 0.3g (15% yield) of the desired aminobarbituric acid was isolated, m.p. 241-244°C.

After recrystallization was effected from an acetone-water solution, the product had a m.p. of 248-250°C with decomposition. The IR showed significant absorptions at 1760 cm^{-1} (C=O stretch), 1700 cm^{-1} (C=O stretch), 1410 cm^{-1} (C-H bend), 1370 cm^{-1} (C-H bend), and 1280 cm^{-1} (C-N stretch). The NMR spectrum (d_5-pyridine) showed an absorption at 13.42δ (singlet, 2H) from the barbituric acid structure in the molecule and at 3.32δ (multiplet, 2H, α-equatorial) from the amine portion of the molecule. These two absorptions are in the ratio expected from the aminobarbituric acid compound.

The mass spectrum gave a molecular ion at 281.

Calculated, $C_{14}H_{23}N_3O_3$: C, 59.77; H, 8.24; N, 14.94.

Found: C, 59.61; H, 8.29; N, 14.83.

Preparation of 5-Ethyl-5-[N-(2,6-dimethylmorpholino)]-barbituric Acid

After dissolving 5.0g (0.021 mole) of 5-bromo-5-ethylbarbituric acid in 20 ml of methanol, 4.8g (0.042 mole) of 2,6-dimethymorpholine was added at one time, and the resulting solution stirred for 24 hours at room temperature. Upon completion of stirring, the solution was cooled and a precipitate appeared. This was removed to give 1.7g (30% yield) of product, m.p. 252-253.5°C.

Recrystallization was effected from an acetone-water solution to yield a pure product melting at 253.5-254.5°C. Significant bands in the IR were located at 1760 cm^{-1} (C=O stretch), 1700 cm^{-1} (C=O stretch), 1420 cm^{-1} (C-H bend), and 1320 cm^{-1} (C-N stretch). The NMR spectrum (d_5-pyridine) showed absorptions at 13.08δ (singlet, 2H), 3.80δ (multiplet, 2H), 2.90δ (multiplet, 4H), 2.37δ (quartet, 2H), and 1.07δ (complex multiplet, 9H). The mass spectrum showed a molecular ion at 269.

Calculated, $C_{13}H_{22}N_4O_3$: C, 55.30; H, 7.85; N, 1984.

Found: C, 55.38; H, 7.85; N, 1980.

Preparation of 5-Ethyl-5-[N-(3-methylpiperidino)]-barbituric Acid

Five grams (0.021 mole) of 5-bromo-5-ethylbarbituric acid was dissolved in 20 ml of methanol, and 4.2g (0.042 mole) of 3-methypiperidine was added at one time. The solution was stirred for 24 hours at room temperature. When no precipitate appeared during this time, the reaction mixture was rotovaped until a resin formed. The resin was shaken with water while small quantities of acetone were added until the resin just dissolved. The solution was cooled and filtered, yielding 2.3g (43% yield) of product, m.p. 178-181°C.

Recrystallization from an acetone-water solution gave a product melting at 186-187°C. The IR spectrum showed significant bands at 1760 cm^{-1} (C=O stretch), 1700 cm^{-1} (C=O stretch), 1410 cm^{-1} (C-H bend), 1370 cm^{-1} (C-H bend), 1320 cm^{-1} (C-H bend), and 1250 cm^{-1} (C-N stretch). The NMR spectrum (d_5-pyridine) showed bands at 13.04δ (broad singlet, 2H), 3.16δ (multiplet, 2H, α-equatorial), 2.34δ (multiplet, 4H), 1.58δ (broad multiplet, 4H), 1.00δ (triplet, 4H), and 0.77δ (doublet, 3H). The mass spectrum gave a molecular ion at m/e of 253 (calc. 253).

Calculated, $C_{12}H_{19}N_3O_3$: C, 56.90; H, 7.56; N, 16.59.

Found: C, 56.75; H, 7.61; N, 16.51.

Reaction of 5-Bromo-5-butylbarbituric Acid with Benzylamine

Two grams (0.0076 mole) of 5-bromo-5-butylbarbituric

acid was dissolved in 10 ml of methanol, and 1.6g (0.015 mole) of benzylamine was added at one time. This mixture was allowed to stir for 24 hours at room temperature and was then cooled. After cooling, since no product appeared, the solution was rotovaped to remove solvent and form a resin. The resin was shaken with water while small quantities of acetone were added until the resin just dissolved. On cooling one gram of solid formed. By rotovaping the mother liquor and shaking with acetone, another gram of solid was obtained. Total yield was 2.0g (80% yield of salt); m.p. 206-209°C. All the spectral data on this product indicated it was not the desired aminobarbituric acid adduct but rather a salt of the amine and butylbarbituric acid. The IR spectrum gave significant bands at 1700 cm^{-1} (C=O stretch), 1570 cm^{-1} (N-H bend from amine salt), and 1380 cm^{-1} (C-H bend). The NMR spectrum in d_6-DMSO gave bands at 8.74δ (singlet, 5H), 7.62δ (singlet, 5H), 4.22δ (singlet, 2H), 2.20δ (multiplet, 2H), 1.40δ (multiplet, 4H), and 1.06δ (triplet, 3H). The mass spectrum gave as a base peak an m/e of 128, typical of 5-butylbarbituric acid, and large peaks at 107 and 106 from benzylamine (calc. 107). On reprecipitation of the salt from an acidic solution, 5-butylbarbituric acid was recovered, m.p. 211-212°C. A mixed melting point with a known sample of 5-butylbarbituric acid gave a m.p. of 211-212°C.

Reaction of 5-Bromo-5-butylbarbituric Acid with 4-Hydroxypiperidine

To 2.0g (0.0076 mole) of 5-bromo-5-butylbarbituric acid in 10 ml of methanol was added 1.5g (0.015 mole) of 4-hydroxypiperidine, and the resulting solution was stirred at room temperature for 24 hours. Upon cooling no product crystallized; therefore, the mixture was rotovaped to form a resin. The resin was shaken with water while adding small amounts of acetone until the resin was just dissolved. When cooled one gram of solid crystallized (45% yield of salt) and had a melting point of 207-211°C. Spectral data indicated a salt had been formed. The IR spectrum gave the typical amine salt absorption at 1570 cm^{-1} (N-H bend), along with an absorption at 1660 cm^{-1} (C=O stretch) and an absorption at 1380 cm^{-1} (C-H bend). The NMR spectrum of this compound in d_6-DMSO gave a very broad band at 6.09δ (amine salt protons); however, the overlapping of proton signals from the butyl group and the piperidine ring prevented further identification of signals. The mass spectrum was typical of those obtained from the other amine salts. A base peak occurred at 128, typical of 5-butylbarbituric, and a large peak occurred at 101 (calc. for 4-hydroxypiperidine, 101). Upon reprecipitation of the salt from an acidic solution 5-butylbarbituric acid was obtained, m.p. 210.5-211.5°C. A mixed melting point of the product obtained and a known sample of 5-butylbarbituric gave no change of the melting point.

Reaction of 5-Bromo-5-butylbarbituric Acid with Allylamine

After adding 0.9g (0.015 mole) of allylamine to 2.0g (0.0076 mole) of 5-bromo-5-butylbarbituric acid in 10 ml of methanol, the resulting solution was allowed to stir for 24 hours at room temperature and was then cooled overnight. When no precipitate appeared, the mixture was rotovaped to form a resin which was shaken with acetone to give 1.3g (72% yield of salt) of solid, m.p. 195-203°C. Part of the product was recrystallized from absolute ethanol and gave a melting point of 213-217°C. The IR showed a strong band at 1580 cm^{-1} (N-H bend), indicating formation of the amine salt. The IR also gave significant absorptions at 1700 cm^{-1} (C=O stretch) and 1370 cm^{-1} (C-H bend). The NMR spectrum in d_6-DMSO gave the three expected butyl absorptions and a very broad band at 6.38δ (amine salt protons). The mass spectrum gave peaks at 128, typical of 5-butylbarbituric acid, and 56 (allylamine-1H). Reprecipitation of part of the product from an acidic solution (dil. HCl) gave 5-butylbarbituric acid, m.p. 210.5-212°C. A mixed melting point of the above sample and a known sample of 5-butylbarbituric acid gave a melting point of 210.5-211.5°C.

Reaction of 5-Bromo-5-butylbarbituric Acid with 2-Aminopyrimidine

Immediately upon adding 1.4g (0.015 mole) of 2-aminopyrimidine to 2.0g (0.0076)mole) of 5-bromo-5-butylbarbituric

acid in 10 ml of methanol a precipitate formed. The solution was allowed to stir for several hours and was then filtered and the precipitate vacuum dried to give 2.0g (74% yield of salt) of solid. Recrystallization from absolute ethanol gave a solid having a melting point of 156.5-158°C. The spectral data indicated a salt containing bromine (mass spectrum). The IR gave absorptions at 1720 cm^{-1} (C=O stretch), 1700 cm^{-1} (C=O stretch), 1640 cm^{-1} (C=N stretch), 1580 cm^{-1} (N-H bend), 1420 cm^{-1} (C-H bend), and 1380 cm^{-1} (C-H bend). The NMR spectrum in d_6-DMSO gave bands at 11.96δ (singlet, 2H), 8.40d (doublet, 2H), 6.68δ (triplet, 3H), 2.40δ (multiplet, 2H), 1.36δ (multiplet, 4H), and 1.00δ (triplet, 3H). The mass spectrum gave a pair of peaks of about equal intensity at m/e 206 and m/e 208. These peaks also occur in the mass spectrum of 5-bromo-5-butyl-barbituric acid. The base peak appeared at m/e 95, corresponding to the molecular weight of 2-aminopyrimidine. Reprecipitation of the salt from a dilute HCl solution gave a compound melting at 109.5-111°C (reported m.p. for 5-bromo-5-butylbarbituric, 109°C). The IR spectrum for the product obtained from dilute acid is identical to an IR spectrum of a known sample of 5-bromo-5-butylbarbituric acid.

CHAPTER IV

CONCLUSIONS

Thirteen new 5-(N-amino)-barbituric acid derivatives have been prepared, and infrared, nuclear magnetic resonance, and mass spectral data has been recorded and interpreted. In some instances the reaction of the 5-bromo-5-alkylbarbituric acid with an amine failed to give the 5-(N-amino) derivative but rather a salt was formed. Two types of amine salts were observed: one being a salt of the 5-bromo-5-alkyl-barbituric acid and the other being a salt of the 5-alkylbarbi-turic acid.

CHAPTER V

RECOMMENDATIONS

The technique used to prepare the fourteen 5-(N-amino)-5-alkylbarbituric acid derivatives, reported within this thesis, could be used to prepare other 5-(N-amino) derivatives which have not been prepared previously.

Further investigation into the reaction of 5-bromo-5-alkylbarbituric acids with amines to determine why in some reactions one obtains the 5-(N-amino) adduct and in others a salt would be interesting.

The new barbiturates prepared should be tested for physiological activity.

APPENDICES

APPENDIX A

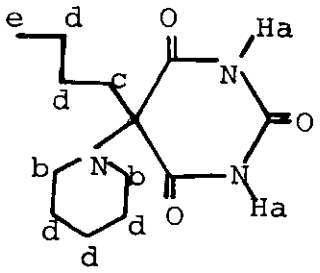
LIST OF NEW 5-(N-AMINO) DERIVATIVES

	m.p.
5-Butyl-5-(N-ethylisonipecotato)-barbituric acid	199.5-200.5°C
5-Butyl-5-(N-pyrrolidino)-barbituric Acid	243-244°C
5-Butyl-5-[N-(2,6-dimethylmorpholino)]-barbituric Acid	227-228°C
5-Butyl-5-[N-(3-methylpiperidino)]-barbituric Acid	236-237°C
5-Butyl-5-(N-ethyl-N'-piperazinocarboxylato)-barbituric Acid	196.5-197.5°C
5-Butyl-5-N-(1-methylpiperazino)-barbituric Acid	268-269°C
5-Butyl-5-(N-p-phenetidino)-barbituric Acid	253.5-254.5°C
5-Butyl-5-(N-piperidino)-barbituric Acid	229.5-230.5°C
5-Butyl-5-[N-(4-benzylpiperidino)]-barbituric Acid	212.5-213.5°C
5-Butyl-5-[N-(1,2,3,4-tetrahydroisoquinolino)]-barbituric Acid	251.5-252.5°C
5-Butyl-5-[N-(4-methypiperidino)]-barbituric Acid	248-250°C
5-Ethyl-5-[N-(2,6-dimethylmorpholino)]-barbituric Acid	253.5-254.5°C
5-Ethyl-5-[N-(3-methylpiperidino)]-barbituric Acid	186-187°C

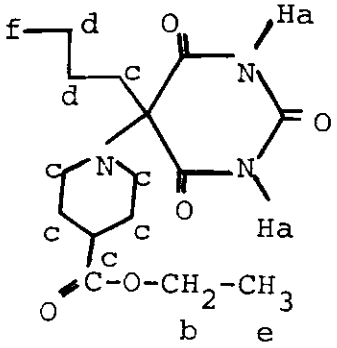
APPENDIX B

NMR SHIFT VALUES IN UNITS OF δ FOR 5-(N-AMINO)-BARBITURIC ACID DERIVATIVES

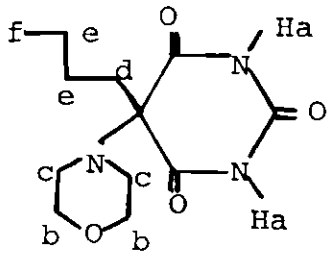
Table 1. NMR Shift Values in Units of δ for 5-(N-amino) barbituric Acid Derivatives



(a)	(b)	(c)
13.12δ (singlet,2H)	2.88δ (multiplet,4H)	2.29δ (broad multiplet,2H)
(d)	(e)	
1.41δ (multiplet,10H)	0.81δ (triplet,3H)	



(a)	(b)	(c)
12.94δ (singlet,2H)	4.13δ (quartet,2H)	1.58-3.55δ (complex group of signals,11H)
(d)	(e)	(f)
1.20δ (multiplet,4H)	1.14δ (triplet,3H)	0.78δ (triplet,3H)



(a)
13.46δ
(singlet,2H)

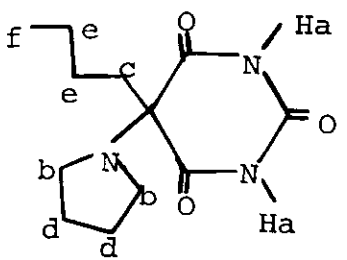
(b)
3.76δ
(triplet,4H)

(c)
2.97δ
(triplet,4H)

(d)
2.30δ
(multiplet,2H)

(e)
1.32δ
(multiplet,4H)

(f)
0.82δ
(triplet,3H)



(a)
13.14δ
(singlet,2H)

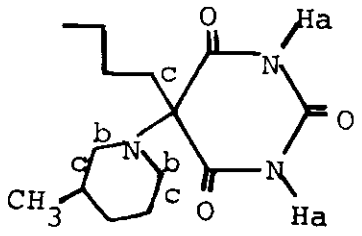
(b)
3.02δ
(triplet,4H)

(c)
2.44δ
(multiplet,2H)

(d)
1.64δ
(multiplet,4H)

(e)
1.34δ
(multiplet,4H)

(f)
0.82δ
(triplet,3H)



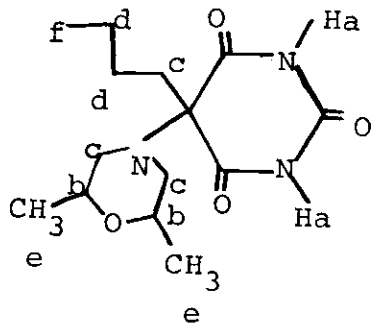
(a)
12.84δ
(singlet,2H)

(b)
3.16δ
(multiplet,2H,
α-equatorial)

(c)
2.39δ
(multiplet,4H)

(d)
1.47δ
(broad complex
multiplet,8H)

(e)
0.77δ
(multiplet,7H)



(a)
12.74δ
(singlet,2H)

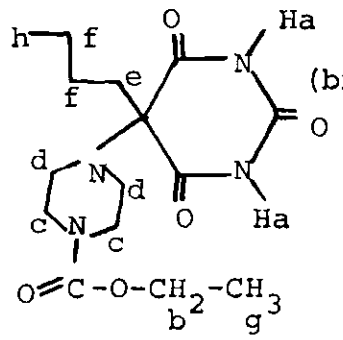
(b)
3.84δ
(multiplet,2H)

(c)
2.17-3.33δ
(complex group of signals,6H)

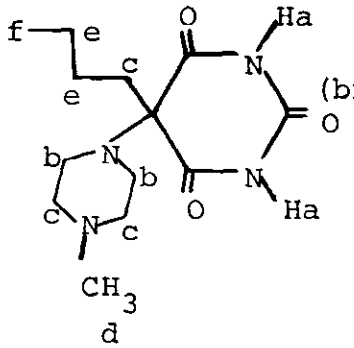
(d)
1.38δ
(multiplet,4H)

(e)
1.08δ
(doublet,6H)

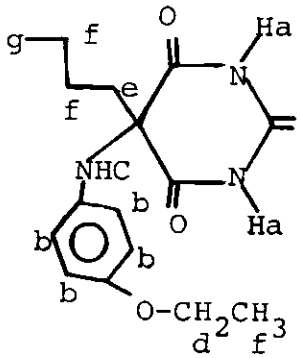
(f)
0.83δ
(triplet,3H)



(a)	(b)	(c)	(d)
13.52δ	4.20δ	3.60δ	2.95δ
(broad singlet,2H)	(quartet,2H)	(multiplet,4H)	(multiplet,4H)
(e)	(f)	(g)	(h)
2.30δ	1.25δ	1.16δ	0.81δ
(multiplet,2H)	(broad multiplet,4H)	(triplet,3H)	(triplet,3H)



(a)	(b)	(c)
12.60δ	3.07δ	2.49δ
(broad singlet,2H)	(multiplet,4H)	(multiplet,6H)
(d)	(e)	(f)
2.19δ	1.36δ	0.81δ
(singlet,3H)	(multiplet,4H)	(triplet,3H)



(a) 11.54δ (singlet,2H)

(b) 6.56δ (multiplet,4H)

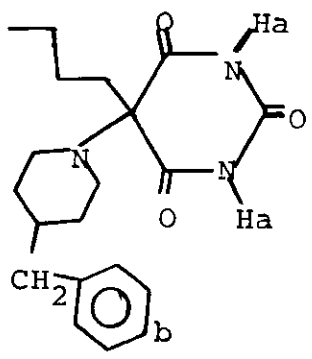
(c) 6.02δ (singlet,1H)

(d) 3.94δ (quartet,2H)

(e) 1.98δ (multiplet,2H)

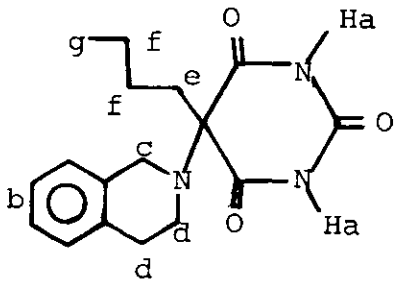
(f) 1.30δ (multiplet,7H)

(g) 0.92δ (triplet,3H)



(a) 11.52δ (singlet,2H)

(b) 7.26δ (singlet,5H)



(a)
11.64δ
(singlet,2H)

(b)
7.12δ
(singlet,4H)

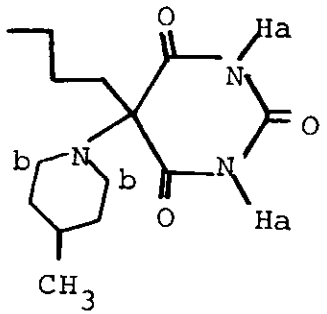
(c)
3.90δ
(singlet,2H)

(d)
2.88δ
(singlet,4H)

(e)
2.10δ
(multiplet,2H)

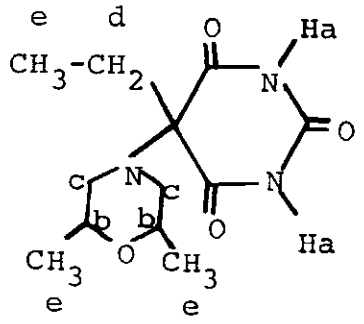
(f)
1.28δ
(multiplet,4H)

(g)
0.96δ
(triplet,3H)



(a)
13.42δ
(singlet,2H)

(b)
3.32δ
(multiplet,2H,
α-equatorial)



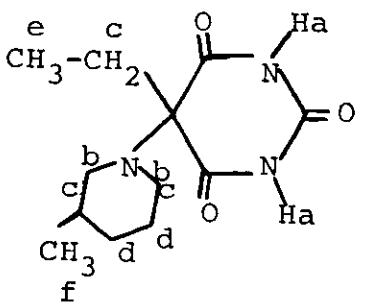
(a) 13.08δ (singlet,2H)

(b) 3.80δ (multiplet,2H)

(c) 2.90δ (multiplet,4H)

(d) 2.37δ (quartet,2H)

(e) 1.07δ (complex multiplet,9H)



(a) 13.04δ (broad singlet,2H)

(b) 3.16δ (multiplet,2H, α-equatorial)

(c) 2.34δ (multiplet,4H)

(d) 1.58δ (broad multiplet,4H)

(e) 1.00δ (triplet,4H)

(f) 0.77δ (doublet,3H)

APPENDIX C

INFRARED SPECTRA

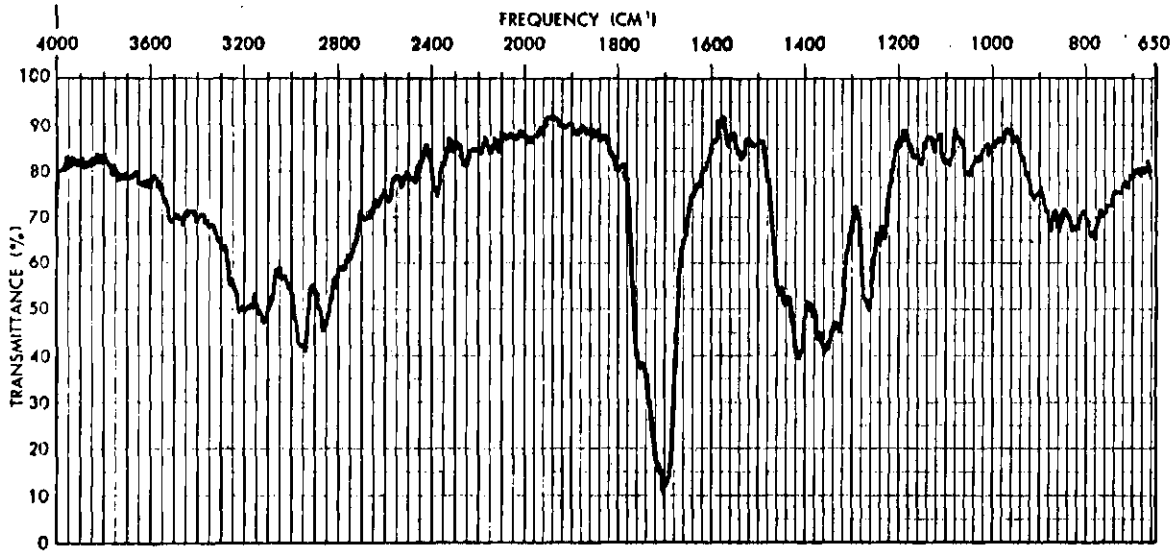


Figure 8. Infrared Spectrum of 5-Butyl-5-[N-(piperidino)]-barbituric Acid

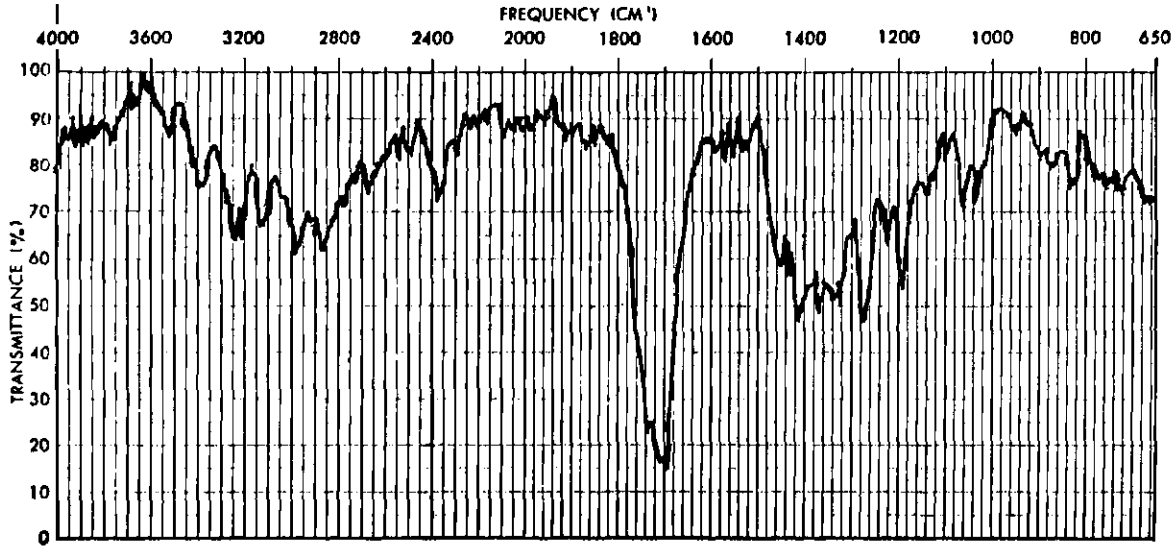


Figure 9. Infrared Spectrum of 5-Butyl-5-[N-(ethylisonipecotato)]-barbituric Acid

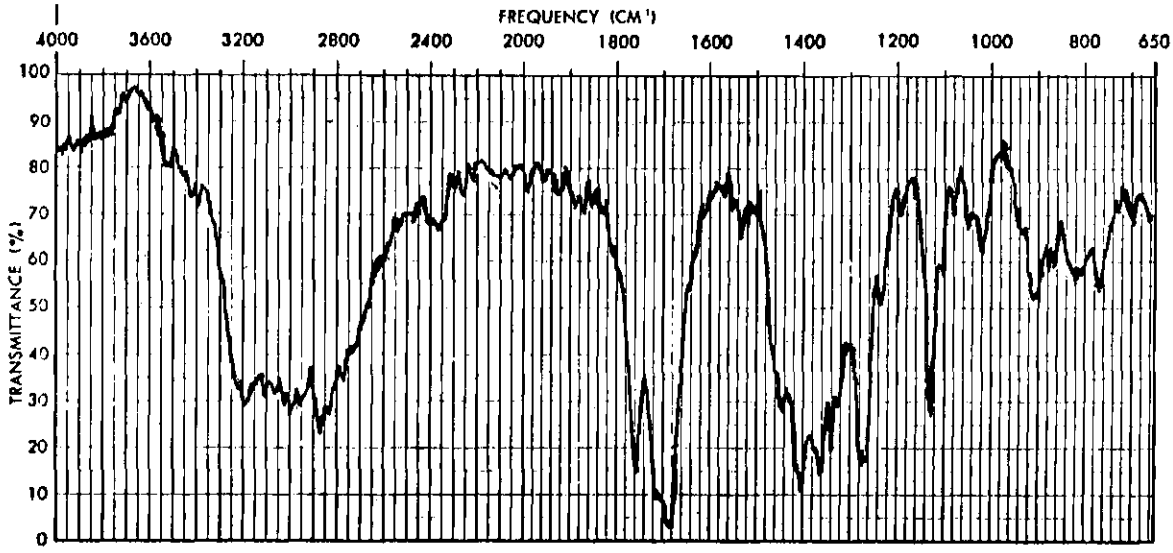


Figure 10. Infrared Spectrum of 5-Butyl-5-[N-(morpholino)]-barbituric Acid

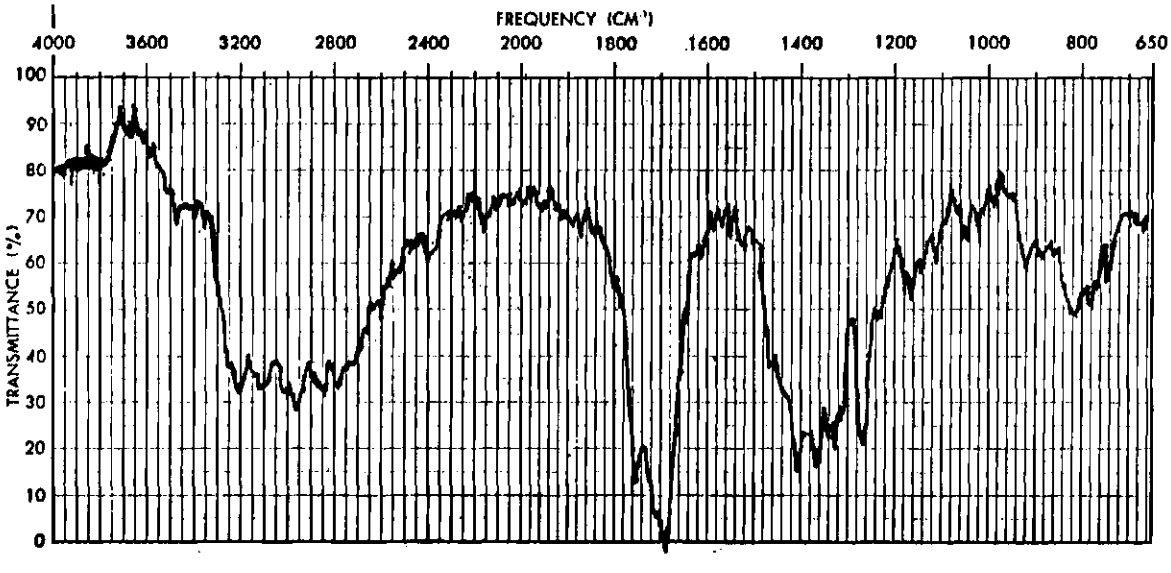


Figure 11. Infrared Spectrum of 5-Butyl-5-[N-(pyrrolidino)]-barbituric Acid

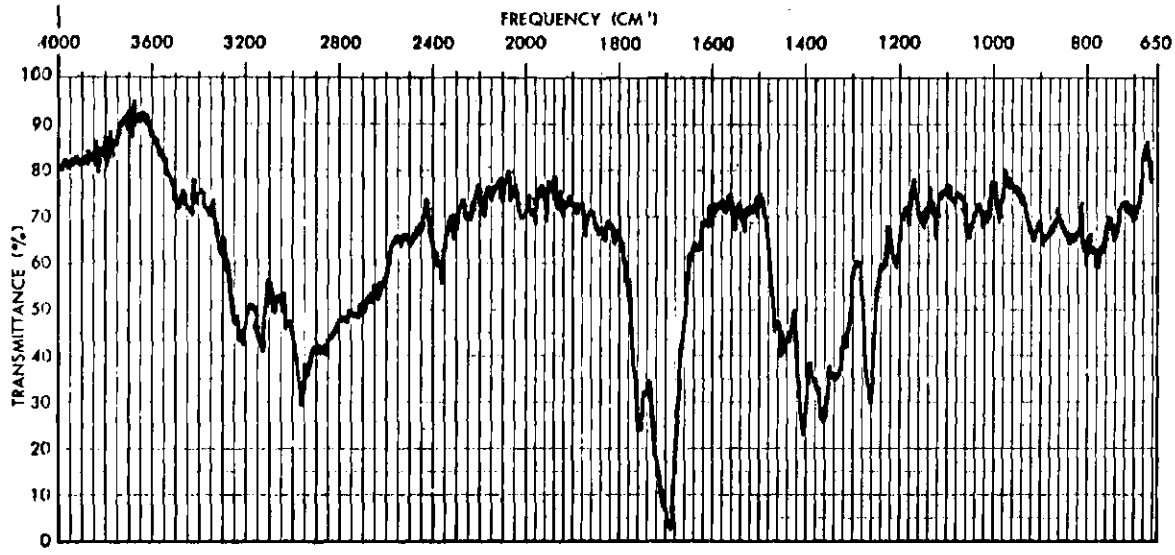


Figure 12. Infrared Spectrum of 5-Butyl-5-[N-(3-methylpiperidono)]-barbituric Acid

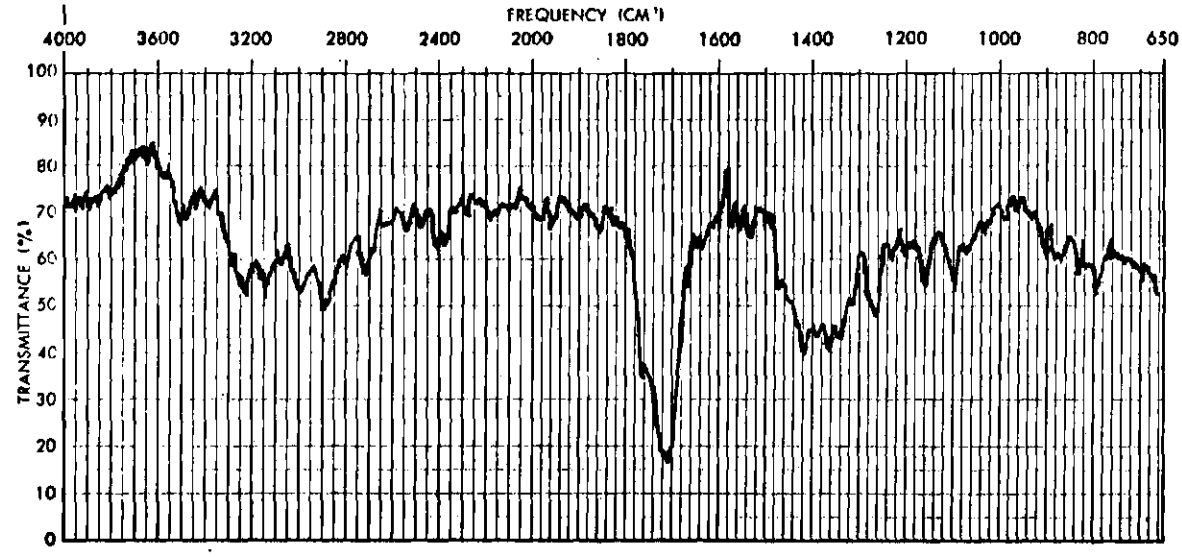


Figure 13. Infrared Spectrum of 5-Butyl-5-[N-(2,6-dimethylmorpholino)]-barbituric Acid

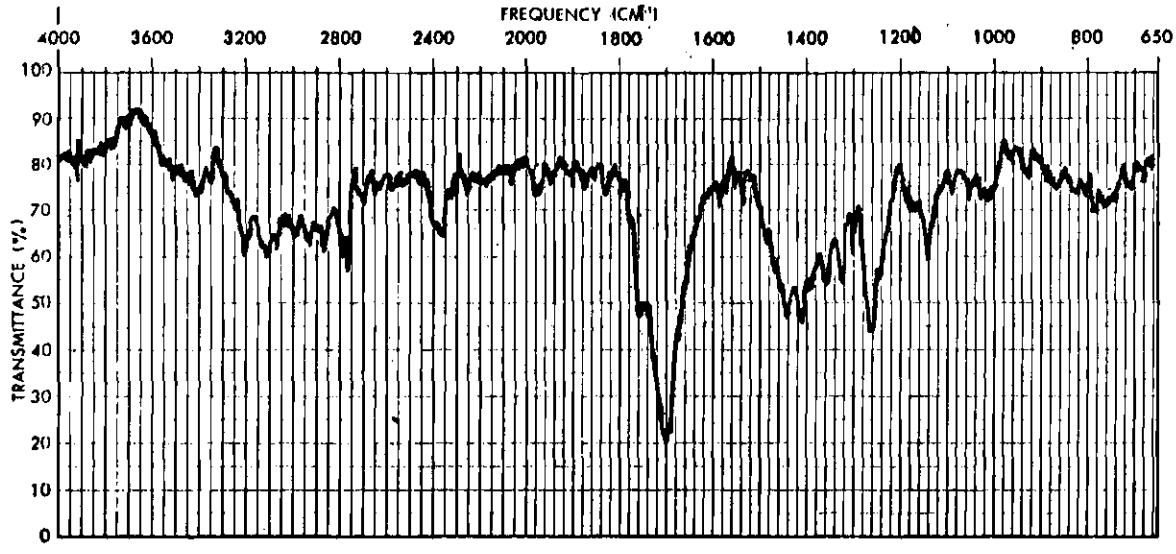


Figure 14. Infrared Spectrum of 5-Butyl-5-[N-(ethyl-N'-piperazino-carboxylato)]-barbituric Acid

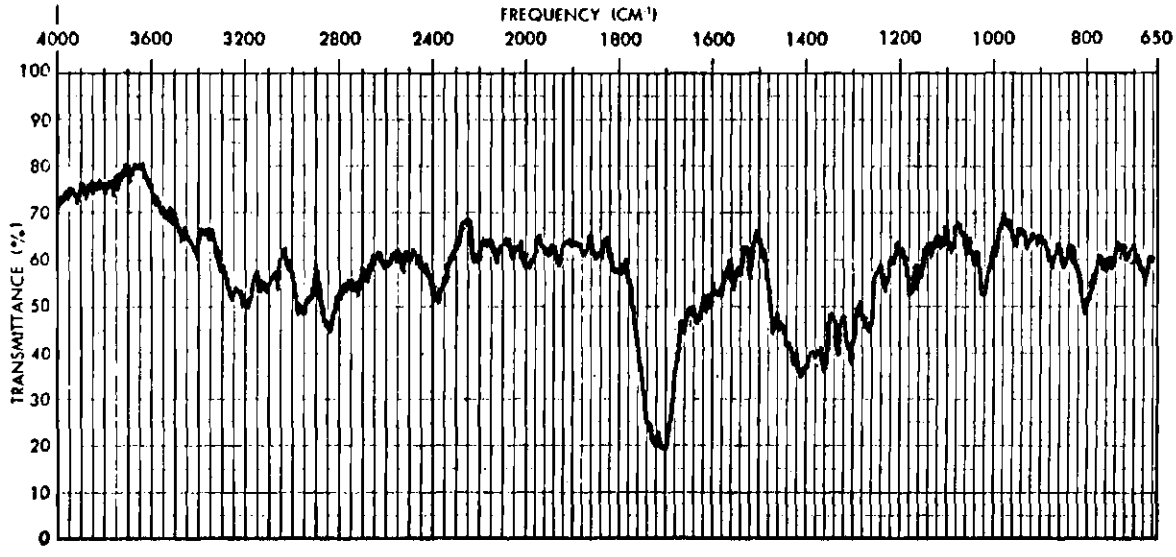


Figure 15. Infrared Spectrum of 5-Butyl-5-[N-(4-methylpiperazino)]-barbituric Acid

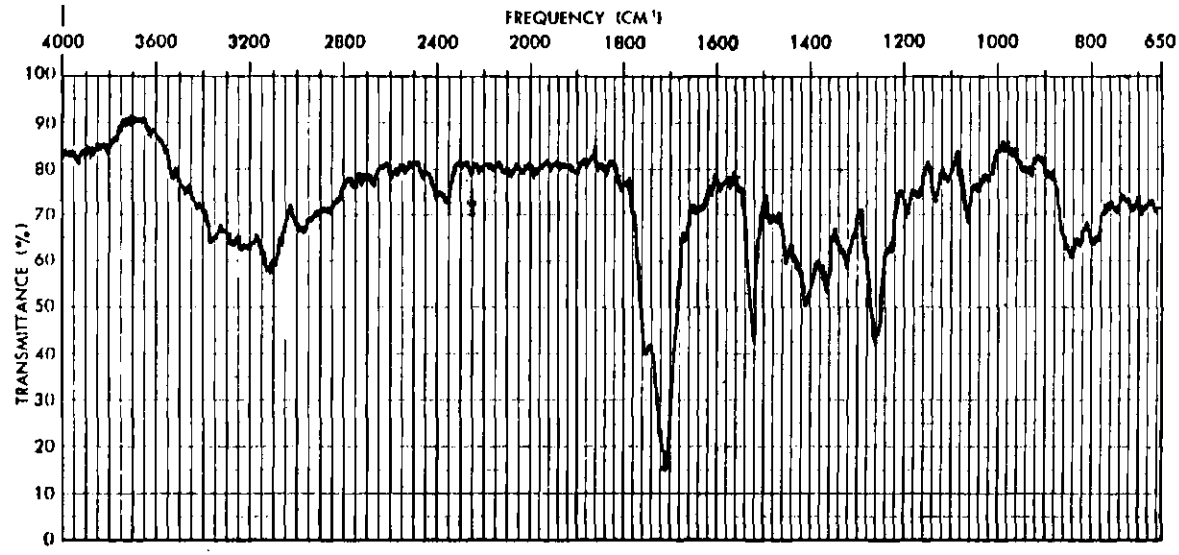


Figure 16. Infrared Spectrum of 5-Butyl-5-[N-(p-phenetidino)]-barbituric Acid

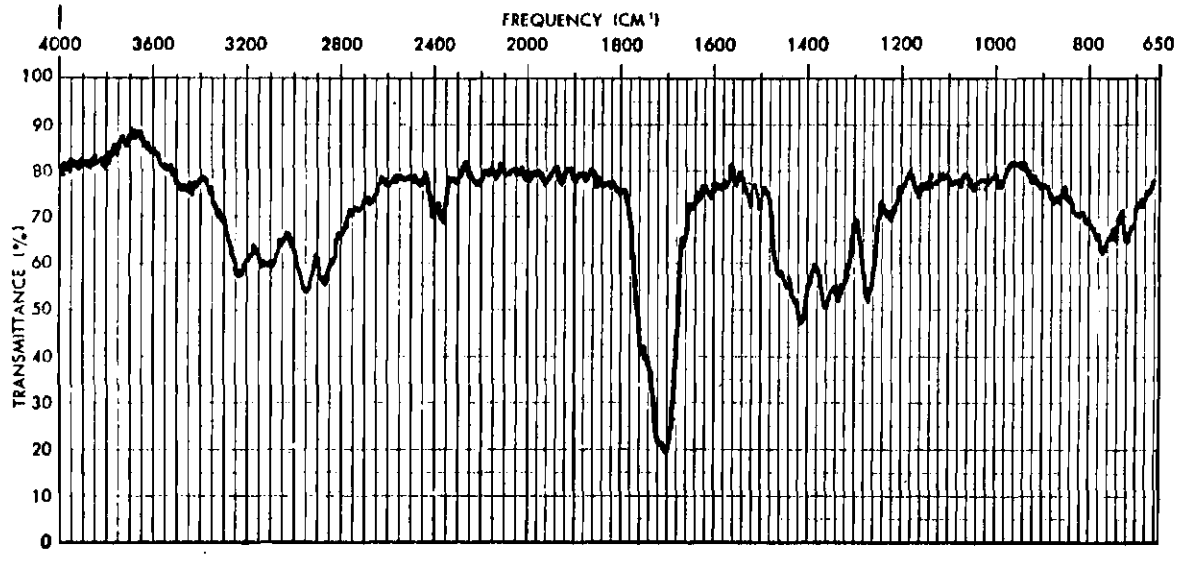


Figure 17. Infrared Spectrum of 5-Butyl-5-[N-(4-benzylpiperidino)]-barbituric Acid

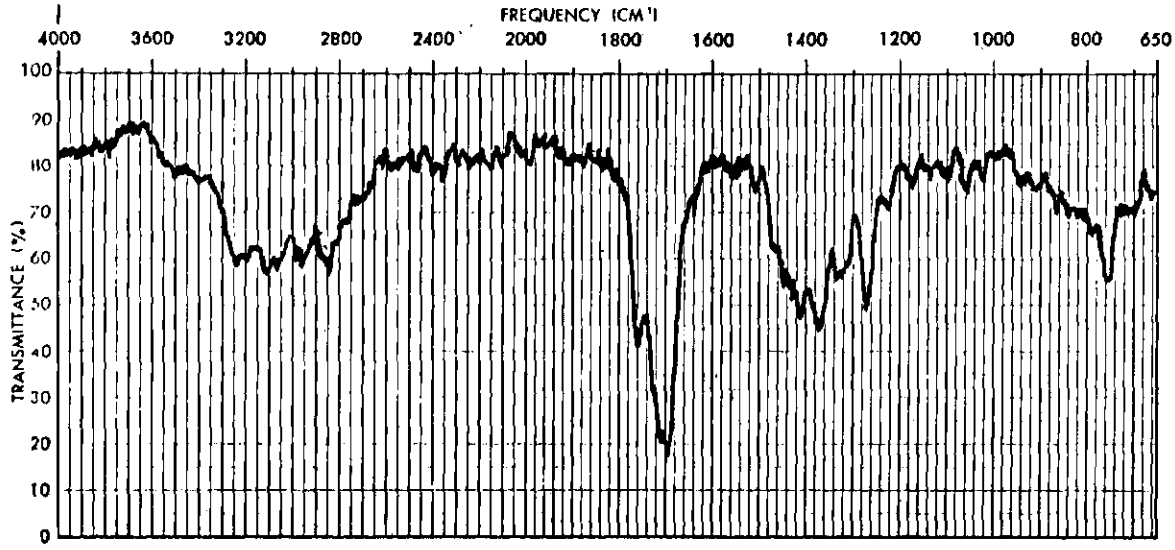


Figure 18. Infrared Spectrum of 5-Butyl-5-[N-(1,2,3,4-tetrahydroisoquinolino)]-barbituric Acid

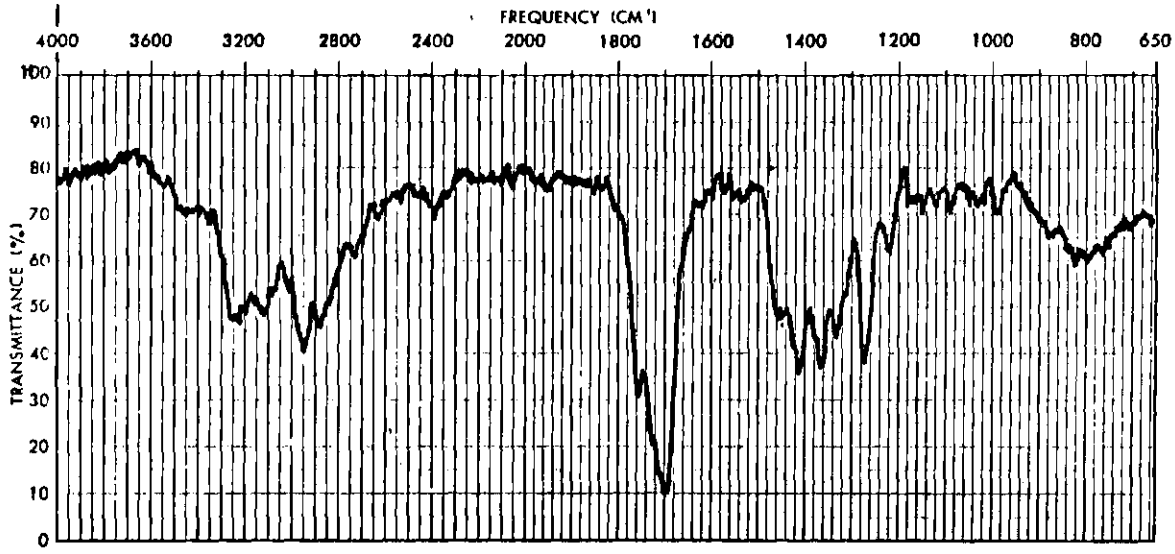


Figure 19. Infrared Spectrum of 5-Butyl-5-[N-(4-methylpiperidino)]-barbituric Acid

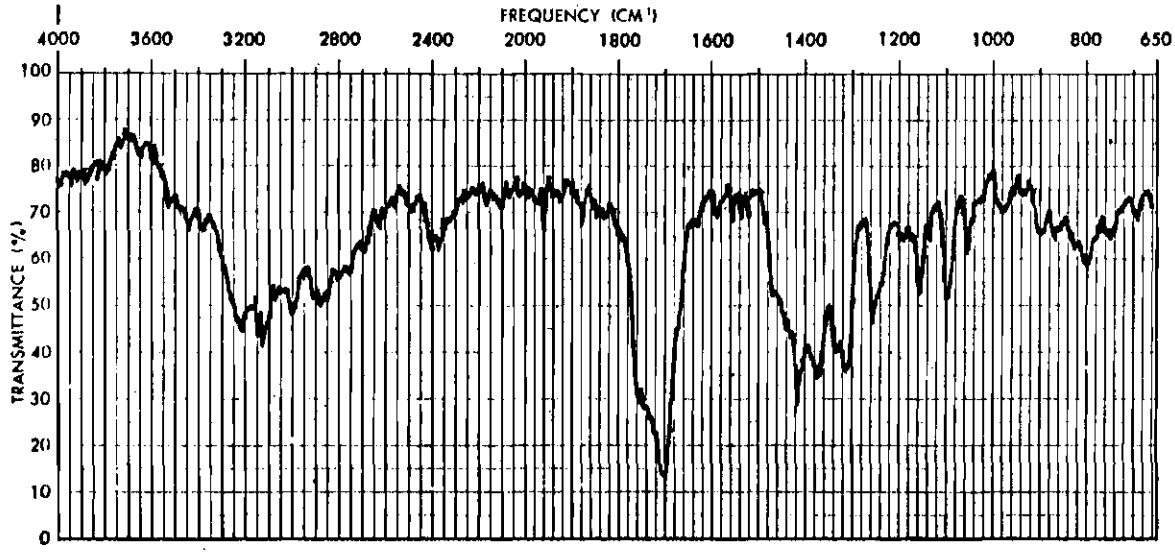


Figure 20. Infrared Spectrum of 5-Ethyl-5-[N-(2,6-dimethylmorpholino)]-barbituric Acid

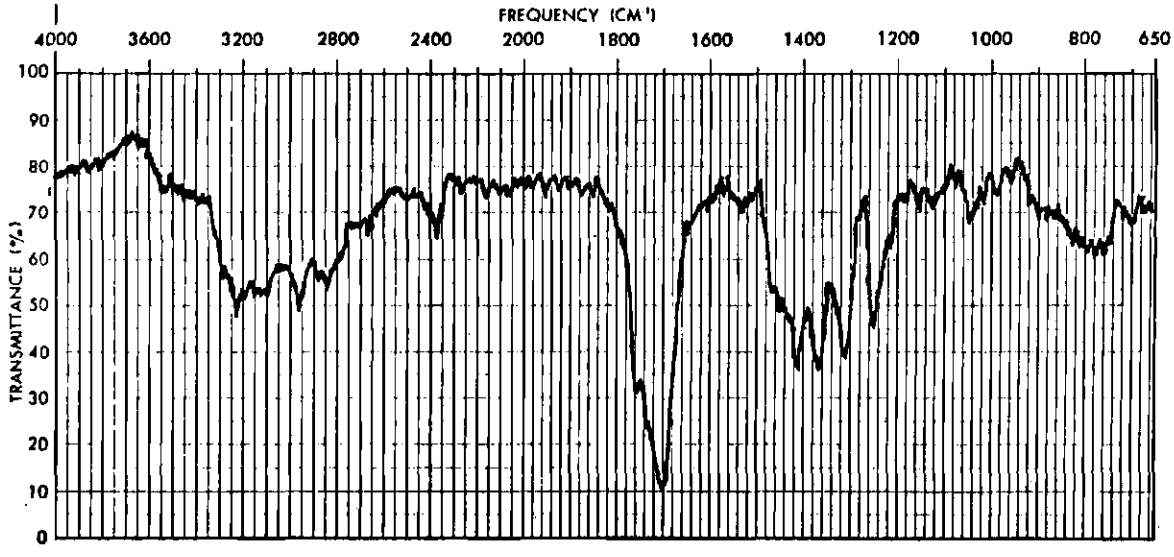


Figure 21. Infrared Spectrum of 5-Ethyl-5-[N-(3-methylpiperidino)]-barbituric Acid

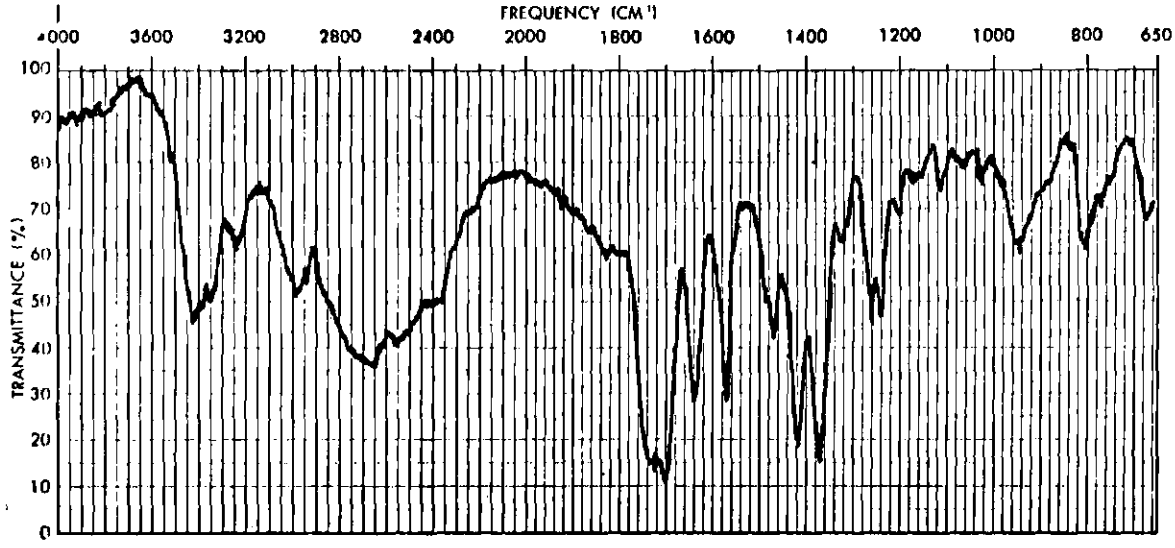


Figure 22. Infrared Spectrum of the Salt 5-Butyl-5-bromobarbituric Acid and 2-Aminopyrimidine

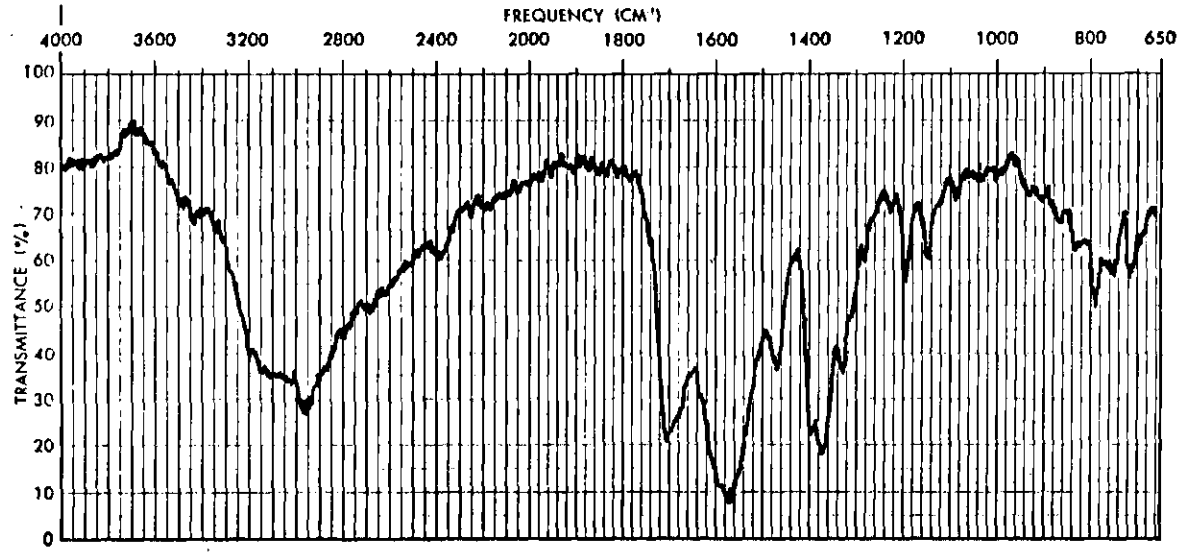


Figure 23. Infrared Spectrum of the Salt of 5-Butylbarbituric Acid and Benzylamine

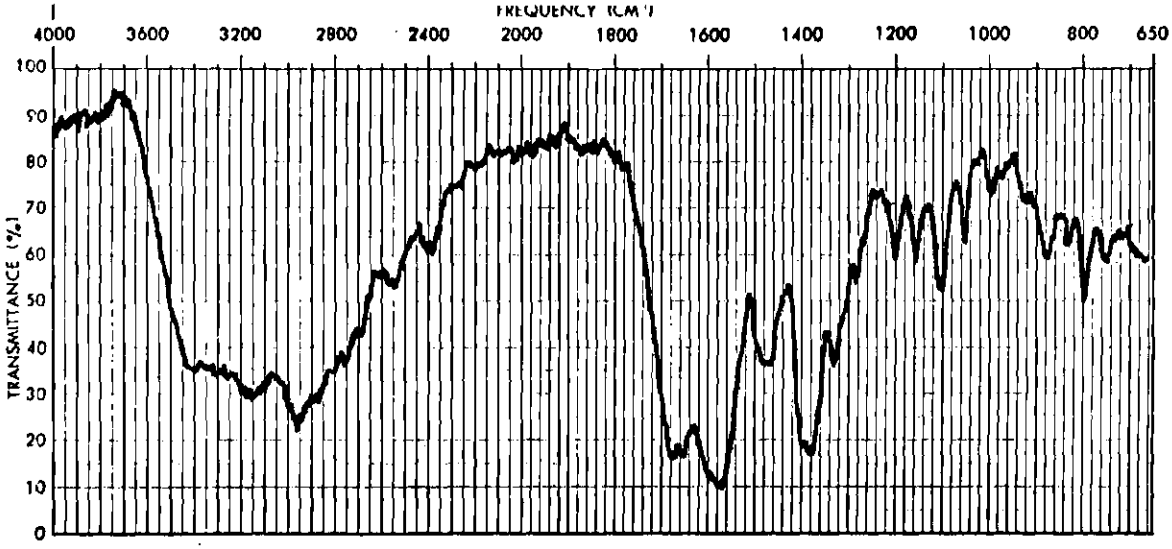


Figure 24. Infrared Spectrum of the Salt of 5-Butylbarbituric Acid and 4-Hydroxypiperidine

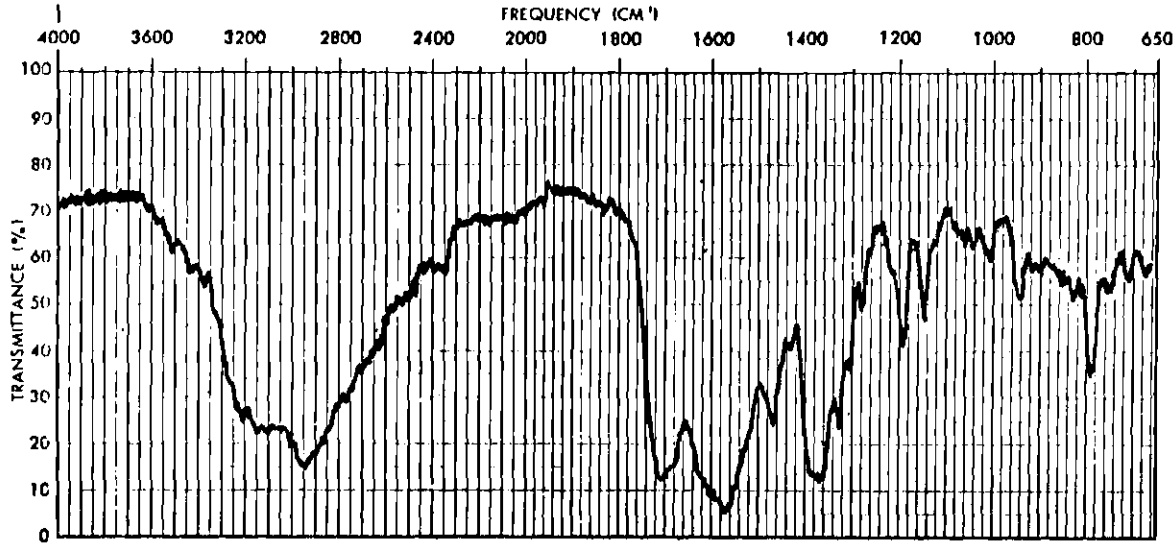


Figure 25. Infrared Spectrum of the Salt of 5-Butylbarbituric Acid and Allylamine

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