SYNTHESIS OF BARBITURIC ACID AND 1,3-DIMETHYLBARBITURIC ACID DERIVATIVES

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SYNTHESIS OF BARBITURIC ACID

AND 1,3-DIMETHYLBARBITURIC ACID DERIVATIVES

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SUMMARY

The purpose of this research was to study the reactions of 5-bromo-5-phenylbarbituric acid and 1,3-dimethyl-5-bromo-5-phenyl-barbituric acid with various amines in order to prepare compounds in which synergistic effects might be unusual. The starting bromo-barbituric acids were obtained via bromination of their respective 5-phenylbarbituric acid in 0.6 N aqueous sodium hydroxide with bromine water.

Phenothiazine, with its known pharmacological properties such as anthelmintic and antihistaminic activities, was selected as the first model amine compound. From the failure of the formation of substitution derivative, namely 5-phenyl-5-[N-(phenothiazinyl)]-barbituric acid, it was suggested that two possible factors, the facile oxidation process of phenothiazine or the steric hindrance around the nitrogen atom, might be responsible.

In order to study these possibilities, the phenothiazine derivative, 10-(3-methylaminopropyl)phenothiazine which would be free of steric hindrance at the reactive nitrogen position, was synthesized in two steps: the preparation of 10-(3-chloropropyl)phenothiazine and the reaction of this with methyl amine. The possibility of a steric hindrance around the nitrogen atom was eliminated or at least minimized but even so, the reaction with 5-bromo-5-phenylbarbituric acid yielded no substitution product. Another approach was studied by reacting the compound carbazole (which has essentially the same carbon skeleton

as phenothiazine except it lacks a sulfur atom in the ring) with 5-bromo-5-phenylbarbituric acid. Although no reaction was observed in this case, its derivative, 9-(γ-methylaminopropyl)carbazole was found to give a crystalline adduct, 5-phenyl-5-[N-(3-carbazolyl-propylmethylamino)]-barbituric acid. This strongly suggested that the irreversible oxidation of the phenothiazine ring was the principal cause for the failure of phenothiazines to react.

Indole compounds, including indole, 2-phenylindole, and 3-methylindole also failed to give substitution products with 5-bromo-5-phenylbarbituric acid. A mechanism of generating a bromonium ion and a barbiturate ion from 5-bromo-5-phenylbarbituric acid has been proposed. This bromonium ion reacted with indole compounds to form bromine containing compounds. The 5-phenylbarbiturate ion picked up a proton from the reaction mixture to give the only isolable product, 5-phenylbarbituric acid.

Cyclopropylamine compounds gave inconsistent results. Cyclopropylamine reacted with 5-bromo-5-phenylbarbituric acid to form a new adduct, 5-phenyl-5-cyclopropylaminobarbituric acid; on the other hand, trans-2-phenylcyclopropylamine gave an ammonium barbiturate salt, trans-2-phenylcyclopropylammonium 5-phenylbarbiturate. The exact reason for this different behaviour is not clear.

In the reaction of 1,3-dimethyl-5-bromo-5-phenylbarbituric acid, five primary amines and seven secondary amines successfully gave the desired adducts. The five primary amines included propylamine, cyclopropylamine, 2-methoxyethylamine, benzylamine, and p-phenetidine and the seven secondary amines included pyrrolidine, piperidine, morpholine,

N-methylpiperazine, N-β-hydroxyethylpiperazine, ethyl isonipecotate, and 1,2,3,4-tetrahydroisoquinoline. The general properties of these adducts were tabulated. The reaction with 1,3-dimethyl-5-bromo-5-phenylbarbituric acid was found to proceed rapidly and without the complications of salt formation. The possible cause for these phenomena was attributed to the elimination of the amido-imidol tautomerism of its pyrimidine structure.

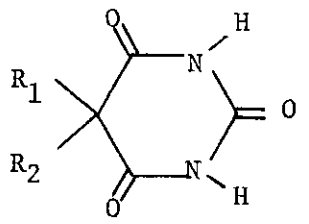
The sterically hindered amine, 2,2,6,6-tetramethylpiperidine, failed to react with 1,3-dimethyl-5-bromo-5-phenylbarbituric acid in solvents such as benzene or methanol, although in the latter solvent the solvent itself was found to react to give a product, 5-methoxy-5-phenylbarbituric acid.

CHAPTER I

INTRODUCTION

The purpose of this research was to investigate the methods of preparation of certain new derivatives of barbituric acid which may have potential pharmacological applications. Barbituric acid, which was first isolated by von Baeyer[1,2] more than a hundred years ago from his study of uric acid, was established to be a derivative of pyrimidine by its synthesis from malonyl chloride and urea by Grimaux.[3,4] Interest in this class of compounds was greatly stimulated when Fischer *et al.*[5,6] reported the convenient synthesis of 5,5-diethyl-barbituric acid and observed its hypnotic properties. Since the initial report, thousands of mono- and polysubstituted barbituric acids and salts of many of these have been reported. Among them approximately twenty have achieved appreciable therapeutic importance and usefulness.[7] The barbiturates finding widest use as pharmaceuticals are the compounds, for instance, Barbital and Phenobarbital (Figure 1). Most of the commercially used barbiturates are characterized by the presence of an ethyl group and another alkyl or aryl group at the 5 positions; practically none have substituents on the nitrogen atoms.

In the medical field, synergistic effects are not uncommon. The word "synergism" may be defined as the combined action of two or more agents that is greater then the action of either agent used alone. In fact, one of the substances may actually have little or no activity.



Barbituric Acid	$R_1 = R_2 = H$
Barbital	$R_1 = R_2 = C_2H_5$
Phenobarbital	$R_1 = C_2H_5$ $R_2 = Ph$

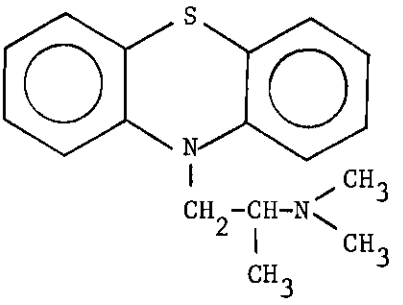
Figure 1. Barbiturates

It is not an uncommon practice to administer two or more agents in order to accomplish that which either of these agents separately could not effect or could achieve with less efficiency.[8-11] Examples of such synergism involving the combined effects of barbiturates and sulfanilamides have been reported in a number of instances.[12-16] In these cases, for example, the sulfanilamides, which have no anaesthetic properties of their own, are able effectively to reduce the dosage of barbiturates, such as Barbital, required to produce anaesthesia in test animal. Concerning these sulfanilamides individually, they have been used during the last forty years as chemotherapeutic agents for the treatment of diseases of protozoal and bacterial origin, their pharmacological properties having no relation to those of barbiturates. The combination dosage of these sulfanilamides

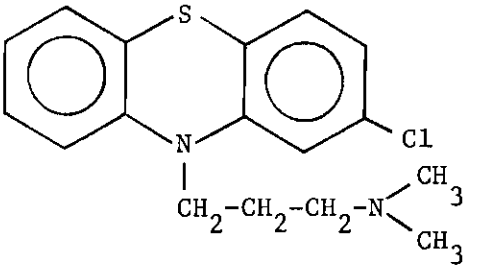
which showed a synergistic effect with barbiturates suggested the possibility of forming a single molecule containing the structural features of each of these components. This new adduct might also show enhanced barbiturate effects on the central nervous system. Such an approach was investigated by Peters.[16]

A parallel study of this approach was planned by selecting phenothiazine as the compound to be coupled with barbiturates. Phenothiazine, with its peculiar ring structure, two benzene ring are linked together by a sulfide and an imine bridge, was first synthesized by Bernthsen[17] more than ninety years ago. The studies of this compound can be roughly divided into three periods. Initially, phenothiazine was of interest owing to its quinonoid derivatives - an important chapter in sulfur dye chemistry. Then research work in the field of phenothiazine was stimulated by the discovery of anthelmintic action[18] of unsubstituted and some C-substituted phenothiazines. During the last two decades, the exceptional pharmacological properties of some N-substituted phenothiazines,[19-22] e.g., the antihistaminic activity of promethazine, 10-(2-dimethylamino-1-propyl)phenothiazine, and, particularly, the psychotherapeutic action of chloropromazine, 2-chloro-10-(3-dimethylamino-1-propyl)phenothiazine[23,24] (Figure 2), focused interest mainly on the synthesis and testing of a great number of derivatives of this basic nucleus. The phenothiazine drugs now play a very important part in chemotherapy.

Hundreds of reactions of phenothiazine compounds have been studied and reported in the literature. Of these reactions those of interest to this research were those involving substitution at the



Promethazine



Chloropromazine

Figure 2. Phenothiazine Derivatives

nitrogen atom. Works were reported such as N-alkylation with halides [25], alkenes[26], alkynes[27], and esters[28] and N-acylation with acetic anhydride [29], examples of which are shown in Figure 3.

It was considered that perhaps the chemical combination of phenothiazine and barbiturates could similarly be achieved. For the reaction, 5-phenylbarbituric acid was selected as the model barbiturate compound. The reaction sequence to be followed for the barbituric acid would incorporate the general method utilized by Fischer and Dilthey[6] for the synthesis of barbituric acid derivatives. The proposed route is shown in Figure 4.

In addition to unsubstituted phenothiazine, derivatives such as

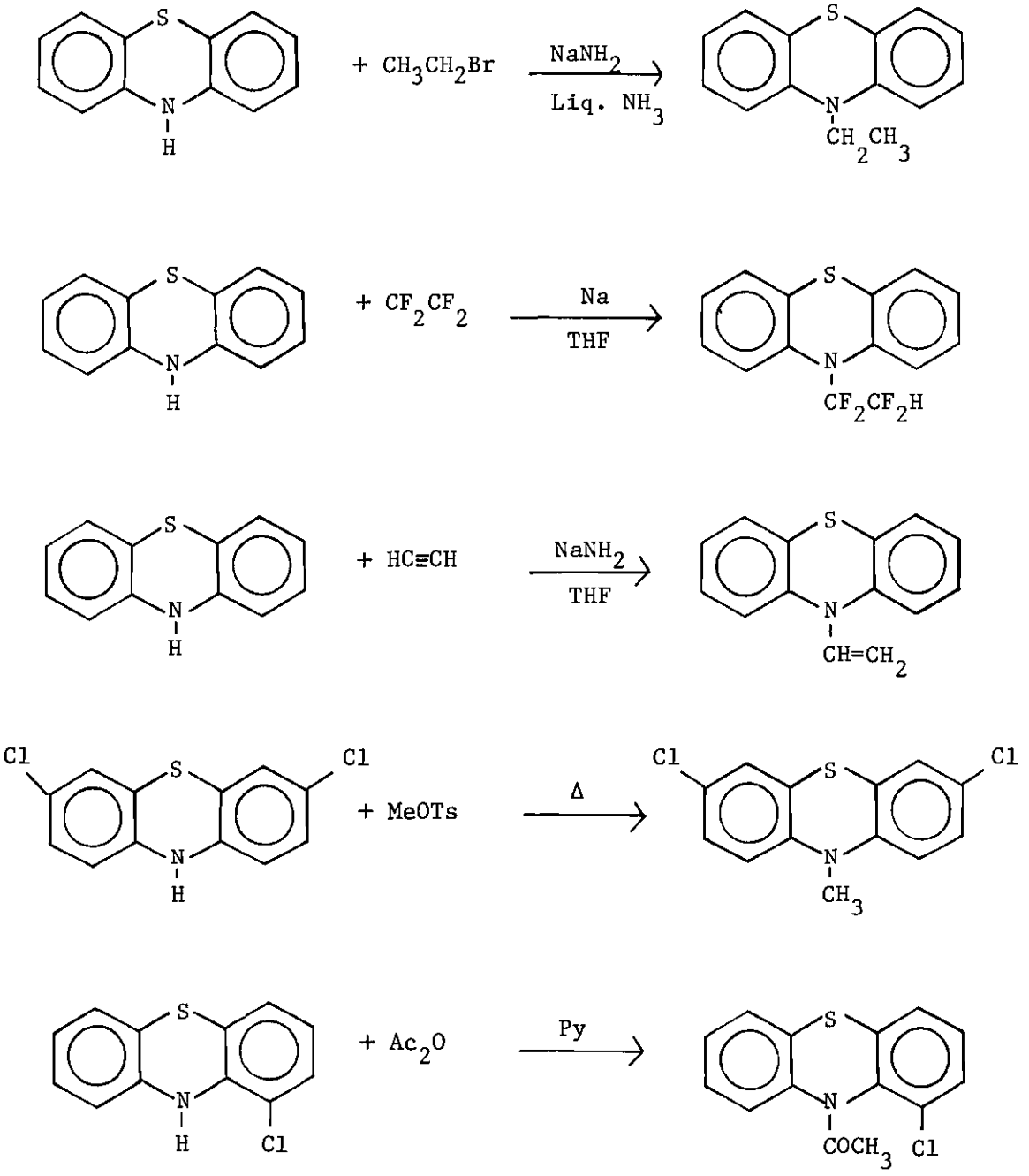


Figure 3. Typical N-substition Reactions of Phenothiazine

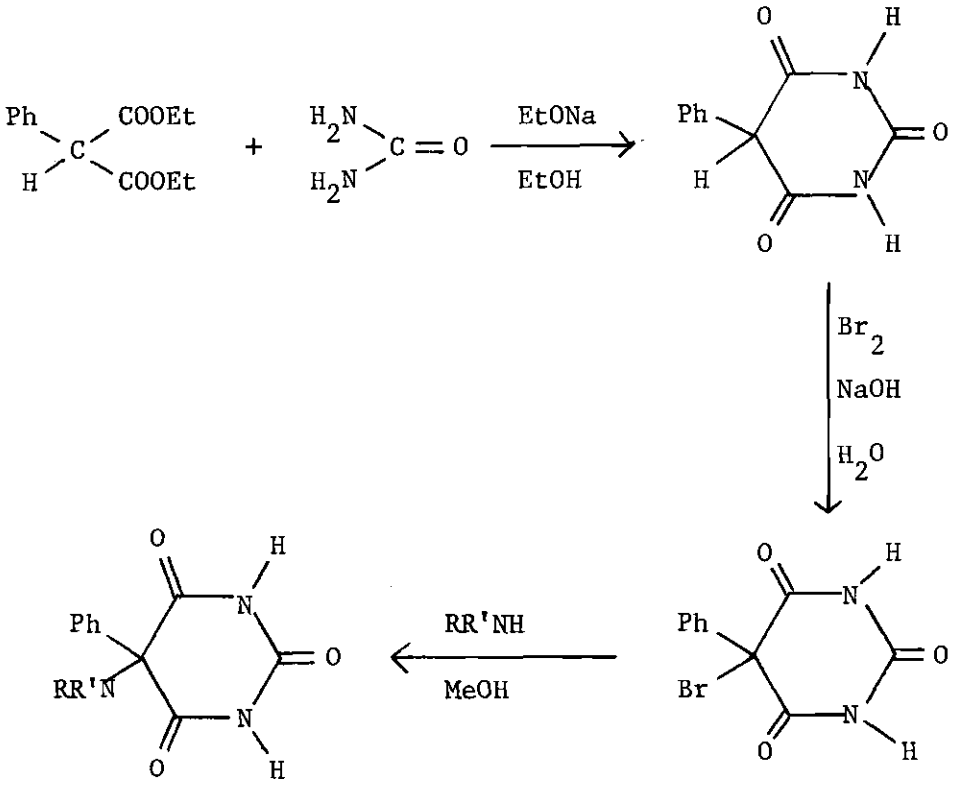


Figure 4. Proposed Reaction Sequences

N-(3-methylaminopropyl)phenothiazine, related to the physiologically active promazine or promethazine (see Figure 2) would be of particular interest, since these would be stronger bases and would be less sterically hindered at nitrogen. Carbazole which has a similar structure near nitrogen was also planned to be studied.

Further studies of substituted barbituric acids such as 1,3-

dimethyl-5-phenylbarbituric acid as parent compound, were also considered feasible. With the presence of methyl substituents on the nitrogen atom, this compound could not have the amido-imidol tautomeric structure. It might, therefore, be likely that this compound would show less tendency toward salt formation when treated with the amine, a side reaction frequently encountered in the works of Wheeler[30] and Walker.[31]

Although 5,5-dialkylbarbituric acids generally produce anesthesia at higher dosage levels, they are not ordinarily used for surgical anesthesia. Barbiturates with a shorter duration of action are much more satisfactory for this purpose. In many instances, it has been found that N-alkylated barbituric acids are of shorter acting duration than the corresponding barbituric acids. Thus, for example, hexobarbital, 5-(1-cyclohexen-1-yl)-1,5-dimethylbarbituric acid, has been used in recent years for anesthetic purpose.[32] The pharmacological activity of 1,3-dimethyl-5,5-dialkyl barbituric acids such as these has been presumed to result from their metabolic conversion, via demethylation, to the parent 5,5-disubstituted barbituric acids.[33]

However, the pharmacological activity of N-alkylbarbiturate does, in a number of instances, deviate to some extent from the parent barbiturate. N-Methylbarbiturates, such as hexobarbital, dilated the denervated pupil, while the corresponding norbarbiturates (non-N-alkylated) generally always cause contraction of the pupil. Local cocaine mydriasis was not affected by N-methyl barbiturates but was inhibited by norbarbiturates.[34]

It was thus of interest to study the ways of synthesizing these

1,3-dimethylbarbituric acid derivatives. A similar approach from Fischer and Dilthey[6] was also planned to be followed. Hence the preparation of 5-amino-N-methylated barbituric acid derivatives could possibly lead to potentially interesting physiologically active substances.

CHAPTER II

EXPERIMENTAL

Instrumentation, Equipment, and General Procedures

Infrared spectra were recorded using a Perkin-Elmer Model 700 recording spectrophotometer. Spectra of solid samples were determined employing potassium bromide pellets while those of liquids were made using films in 0.1 mm sodium chloride cells.

Nuclear magnetic resonance spectra were obtained on a Varian Associates Model A-60D or T-60A nuclear magnetic resonance spectrometer. Tetramethylsilane was used as an internal standard, and usually a 10-20 percent $CDCl_3$ solution was used.

Melting points were determined in capillary tubes of 1.5-2.0 mm (OD) on a Mel-Temp melting point apparatus. All melting points are recorded in degrees Centigrade and are uncorrected.

Elemental microanalyses were performed by Atlanta Microlab, Inc. Atlanta, Ga.

Mass spectra were obtained using either a Varian Model M-66 mass spectrometer or a Hitachi Perkin-Elmer RMU-7 mass spectrometer.

The apparatus for gas chromatographic analysis was a Model 720 F and M gas chromatograph, manufactured by the F and M Scientific Corporation, Avendale, Pennsylvania. The column used was a 6-foot, 1/4 inch o.d. stainless steel column, packed with 80-100 mesh Chromosorb and coated with 10 percent Carbowax 20-M. The flow rate of helium

was 60 ml per minute.

Solvents were removed under reduced pressure (in vacuo) using a Buchi Rotatory evaporator.

Column chromatography was carried out using Grace grade 923, 100-200 mesh silica gel or Fisher certified grade 80-200 mesh neutral alumina. Columns with 3 cm or 1.5 cm diameter were used and packed by adding silica gel or alumina into hexane.

Preparation of 5-Phenylbarbituric Acid

The general procedures of Dickey and Gray[35] and Walker[31] were followed. In a three-necked two-liter round-bottomed flask, fitted with a dropping funnel, a mechanical stirrer, a condenser, and a calcium chloride drying tube was placed one liter of absolute ethanol and 11.5 g (0.5 mole) of freshly cut sodium plates all at once. To this ethoxide solution was added 118.0 g (0.5 mole) of diethyl phenylmalonate. Urea (30.0 g) was then added in several portions and the reaction mixture was refluxed for 2.5 hours, after which about 500 ml of ethanol was removed by distillation. A 500 ml aqueous solution containing 45 ml of concentrated HCl was added slowly, following which the remaining ethanol was distilled and the solution permitted to cool overnight in the refrigerator. The solid which had precipitated was collected by filtration, washed twice with 200 ml of distilled water, and then with 500 ml of ethanol so as to remove any unreacted ester. The 5-phenylbarbituric acid thus obtained was dried under vacuum in a desiccator, and found to have a m.p. 258-260°C (lit. (36) 263°C). The yield was 77 g (75 percent). No further

purification was needed and the product was used for the following reaction of bromination.

Preparation of 5-Bromo-5-phenylbarbituric Acid

The procedure of Voorhes and Skinner[37] was followed. In 170 ml of 0.6 N aqueous NaOH solution was dissolved 20.4 g (0.10 mole) of 5-phenylbarbituric acid. Saturated bromine water was then added dropwise until the bromine color persisted for more than five minutes. The resulting solution was treated with 100 ml of 10 percent sodium bisulfite solution to remove excess bromine. After cooling overnight, the resulting white precipitate was collected, washed several times with distilled water, and dried under vacuum several days to give 23.8 g (84 percent yield) of white crystals, m.p. 210-212°C (lit. (6) 214°C).

Attempted Reaction of 5-Bromo-5-phenylbarbituric Acid with Phenothiazine

To a solution of 1.0 g (0.005 mole) of phenothiazine in 30 ml of absolute ethanol was added 0.71 g (0.0025 mole) of 5-bromo-5-phenylbarbituric acid. The reaction mixture was refluxed for two hours and then cooled. Since no precipitate was observed when *ca.* 30 ml of ether was added, the solvent was removed *in vacuo* to give a dark brown resin. The crude resin was dissolved in 2 ml of ether and then placed on a chromatographic column (diameter of 1.5 cm) packed with 30 g of neutral alumina. Elution of material was effected with 200 ml of ether. Evaporation of the solvent gave 0.45 g of yellow crystals, which was later identified as the unreacted phenothiazine

from its m.p., IR and NMR spectrum. Further elution with 200 ml of 1:1 ether-ethanol and 100 ml of ethanol afforded ca. 1 g of dark green tar like viscous liquid after then solvents were evaporated. This liquid was examined by IR and NMR, but no identifiable compound was able to be determined.

The same reaction was also carried out in benzene. A solution of 1.0 g (0.005 mole) of phenothiazine in 20 ml of benzene was mixed with 0.71 g (0.0025 mole) of 5-bromo-5-phenylbarbituric acid in 35 ml of benzene. The reaction mixture was refluxed for two hours and then cooled. The precipitate formed was collected by filtration and dried to give 0.50 g of crude crystals. Recrystallization of these crystals from ethanol gave a white product, m.p. 259-260°C. This was identified as 5-phenylbarbituric acid by comparison of its IR and NMR spectrum with a known sample. The remaining filtrate was evaporated in vacuo to give 1.12 g of residues. Recrystallization from a minimum amount of benzene afforded 0.45 g of crystals, m.p. 162-164°C. The IR and NMR spectrum of this material showed it to be phenothiazine. It thus seemed evident that no reaction occurred or at best only a very small amount of material could have reacted.

Reaction of 5-Bromo-5-ethylbarbituric Acid with Phenothiazine

One gram (0.00425 mole) of 5-bromo-5-ethylbarbituric acid and 1.70 g (0.0085 mole) of phenothiazine were mixed in about 150 ml of benzene. Actually, the 5-bromo-5-ethylbarbituric acid did not quite dissolve completely in the mixture. The reaction mixture was refluxed however, for 4 hours. During the initial portion of the reflux

period, the 5-bromo-5-ethylbarbituric acid all dissolved. Gradually thereafter a white precipitate began to form and, after the reaction period, was collected by filtration, dried, and found to weigh 0.60 g. It had a m.p. 189-191°C. Both its IR and NMR spectra showed the compound to be identical to 5-ethylbarbituric acid. Thus the amount of product obtained represented a yield of 91 percent. Isolation of any other compound from the reaction mixture was not successful.

Preparation of Ethyl Bromophenylmalonate

The general bromination procedure from Wheeler and Johnson[38] was followed. In a 50 ml three-necked round-bottomed flask equipped with a reflux condenser, a dropping funnel, and a heating mantle was placed 10.0 g (0.042 mole) of ethyl phenylmalonate and heated to ca. 140°C. Bromine 2 ml was added dropwise into the flask with stirring, and the HBr which was evolved was dissolved into water through a trap connected to top of the condenser. The reaction mixture was stirred with continued heating at 140°C for half an hour. The resulting solution was cooled to room temperature and checked by NMR and GLC analysis. It was found that the GLC analysis at 150°C gave a peak which corresponded to ethyl bromophenylmalonate at 7.7 min and a peak which corresponded to ethyl phenylmalonate at 3.3 min in a ratio of ca. 3:2. Additional bromine (1.5 ml) was then introduced in order to improve the yield of brominated product and the solution was reheated at 140°C for one hour. The ratio of ethyl bromophenylmalonate to ethyl phenylmalonate was increased to 7:3. Distillation of this crude product under vacuum, and collecting that fraction of b.p. 127-134°C/

0.65 mm yielded 7.34 g of product which was found to contain 70 percent of the bromo compound (39 percent yield) and 30 percent or 2.2 g (22 percent recovery) of the starting malonate.

Another method of bromination, that of Palmer and McWherter[39], was also followed. A one liter three-necked round-bottomed flask was fitted with a magnetic stirrer, a reflux condenser with a tube leading into a flask of water for the absorption of HBr, and a separatory funnel for addition of bromine. A solution of 118.0 g (0.50 mole) of ethyl phenylmalonate in 100 ml of carbon tetrachloride was placed in the flask. In the separatory funnel was placed 82.5 g (26.5 cc; 0.515 mole) of bromine. The stirrer was started and a few ml of bromine was added into the solution. A large electric bulb was held under the flask until the reaction started and then turned off. Then the rest of bromine was added slowly at such a rate as to keep the liquid boiling gently. The reaction mixture was refluxed overnight after which time no more HBr appeared to be evolved. The resulting solution was cooled and washed five times with 100 ml portions of 5 percent sodium carbonate solution. The organic portion was dried over anhydrous magnesium sulfate after which the CCl_4 was removed <u>in vacuo</u>. Distillation of the resulting crude oil under reduced pressure afforded 130.8 g (83 percent yield) of colorless oil, b.p. 130-134°C/0.65 mm. The NMR spectrum (neat) gave absorptions at 7.2-7.8 δ (multiplet, 5H, aromatic H), 4.20 δ (quartet, 4H, two $-CH_2-$), and 1.13 δ (triplet, 6H, two $-CH_3$).

Attempted Reaction of Ethyl Bromophenylmalonate with Phenothiazine

To a solution of 6.3 g (0.032 mole) of phenothiazine in 25 ml of absolute ethanol was added all at once 5.0 g (0.016 mole) of ethyl bromophenylmalonate. The reaction mixture was refluxed for five hours after which it was cooled. A dark green colored solution with a small quantity of precipitate was obtained. The dark green solid was collected by filtration, dried, and found to weigh 0.58 g. The solid did not melt even when heated to 360°C. The remaining filtrate was evaporated *in vacuo* to give a dark green oil, weight 10.5 g. GLC analysis at 190°C of this oil showed the existence of starting malonate with a retention time of 1.5 min while no phenothiazine (retention time 8.8 min from authentic sample) was observed. The only isolable product identified was the starting malonate which was recovered quantitatively.

Attempted Reaction of Ethyl Bromophenylmalonate with Carbazole

In a 250 ml round-bottomed flask equipped with a condenser was placed a solution of 5.0 g (0.030 mole) of carbazole in 150 ml of absolute alcohol and to this was added 4.73 g (0.015 mole) of ethyl bromophenylmalonate. The reaction mixture was refluxed for four hours. After cooling to room temperature, a white precipitate formed which was collected by filtration and dried, 4.8 g, m.p. 244-246°C. Its NMR spectrum showed it to be the unreacted carbazole. The remaining solution was evaporated *in vacuo* to give 4.5 g of brown oil which was proven by NMR to be the recovered ethyl bromophenylmalonate. Obviously, no reaction had occurred.

Synthesis of 10-(3-Chloropropyl)phenothiazine

The general procedure of Zschiedrich[40] was followed. In a 250 ml round-bottomed flask equipped with a reflux condenser and a heating mantle was placed 6.0 g (0.030 mole) of phenothiazine, 6.0 g (0.150 mole) of sodium hydroxide pellets, and 75 ml of 3-bromochloropropane. The mixture was heated at reflux for ca. ten hours with stirring. After cooling to room temperature, this solution was filtered, neutralized with 5 percent aqueous hydrochloric acid, and extracted with two 100 ml portions of ether. The ether layers were combined, and dried. Following filtration, the ether and most of the 3-bromochloropropane were removed in vacuo to give a dark brown tar-like oil. This oil was dissolved in 5 ml of ether and placed on a 3 cm diameter column containing 80 g of silica gel with ether-hexane mixture as the eluent. The fractions eluted with 300 ml of hexane and 100 ml of 5 percent ether in hexane were collected to give 3.10 g of a yellow oil which was crystallized slowly from methanol to give 2.20 g (27 percent) of white crystals. Further purification by recrystallization twice from methanol gave 1.55 g of white prisms, m.p. 66-67°C. The IR spectrum showed absorptions at 1460 cm^{-1} (aromatic), 1270, and 770 cm^{-1}. The NMR spectrum (CCl_4 solution) indicated peaks at 2.83 δ (quintet, 2H, $-C-CH_2-C-$), 3.27 δ (triplet, 2H, $-CH_2Cl$), 4.03 δ (triplet, 2H, $-N-CH_2-$), and 6.5-7.5 δ (multiplet, 8H, aromatic H). The mass spectrum showed a peak for the molecular ion at the calculated position: m/e 275.

Anal. Calculated for $C_{15}H_{14}NSCl$: C, 65.34; H, 5.12; N, 5.08; S, 11.61;

Cl, 12.86. Found; C, 65.28; H, 5.16; N,5.12; S, 11.68; Cl, 12.76.

Another method, that of Gilman and Shirley[41], was also followed. A solution of 4.0 g (0.020 mole) of phenothiazine in 100 ml of ether was added dropwise and with stirring into a 250 ml round-bottomed flask containing 12 ml (0.020 mole) of 15 percent n-butyllithium in hexane. The resulting mixture was stirred in an ice bath for one hour and then treated with a solution of 5.0 g (0.020 mole) of γ-chloropropyl p-toluene-sulfonate in 30 ml of ether. After stirring 30 min, the mixture was hydrolyzed by the slow addition of 50 ml of water. The ether layer was separated and dried. Removal of the solvent in vacuo gave a dark green oil which crystallized from minimum amount of methanol after standing several days in the refrigerator. Recrystallization twice from methanol afforded 1.80 g (34 percent yield) of colorless prisms, m.p. 67-68°C. The NMR and IR spectra of this compound were identical to the spectra of 10-(3-chloropropyl)phenothiazine prepared from the previous method.

Synthesis of 10-(3-Methylaminopropyl)-phenothiazine

The general procedure of Thiel and Stach[42] was followed. A solution of methylamine in methanol was prepared first by mixing 13.4 g (0.20 mole) of methylamine hydrochloride and 8.0 g (0.20 mole) of NaOH in 100 ml of methanol, stirring at room temperature for two hours, and then removing the NaCl salt by filtration. To this solution was added 1.60 g (0.005 mole) of 10-(3-chloropropyl)phenothiazine. The resulting mixture was refluxed overnight. Removal of the solvent in vacuo gave 5.03 g of a residual mixture containing both white solid and brown oil. This residue was then neutralized with 10 percent NaOH

solution and extracted with two 100 ml portions of ether. The ether extracts were combined, dried, and the ether removed in vacuo to give 1.38 g of a brown oil. Distillation of this brown oil under reduced pressure (0.2 mm) at bath temperature 170-180°C, afforded 0.73 g (47 percent yield) of a pale yellow oil which was found to be the desired amine. NMR (CCl_4): 6.2-7.3 δ (multiplet, 8H, aromatic H), 3.80 δ (triplet, 2H, $N-CH_2-$), 2.53 δ (triplet, 2H, $-NH-CH_2-$), 2.20 δ (singlet, 3H, $-N-CH_3$), and 1.90 δ (quintet, 3H, $-C-CH_2-C-$).

The hydrogen chloride salt of 10-(3-methylaminopropyl)phenothiazine was prepared by adding excess alcoholic HCl into an ethereal solution of 0.5 g of 10-(3-methylaminopropyl)phenothiazine. The salt was formed immediately as white precipitate and collected quantitatively on a Hirsch funnel. Recrystallization twice from methanol-ether mixture afforded a colorless prism, m.p. 162-163°C. The mass spectrum gave a peak at 199 corresponding to the side chain cleavage. The IR spectrum gave absorptions at 1580 and 1450 cm^{-1} (aromatic), and 770 cm^{-1}. Anal. Calculated for $C_{16}H_{19}N_2SCl$: N, 9.15; Cl, 11.56. Found: N, 9.19; Cl, 11.71.

Attempted Preparation of 5-Phenyl-5-[N-(3-phenothiazinylpropylmethylamino)]-barbituric Acid

To a solution of 0.382 g (1.35 mmole) of 5-phenyl-5-bromobarbituric acid in 15 ml of methanol was added 0.726 g (2.70 mmole) of 10-(3-methylaminopropyl)phenothiazine. The solution turned to a dark blue color on mixing with no evidence of heat evolution. The reaction mixture was then heated at reflux for half an hour and cooled. A

greenish blue solid, 0.16 g, was removed by filtration and washed with water, m.p. 168-170°C. Efforts were made to identify both this solid and the rest of the solution. Their IR and NMR spectra were found not analizable and no desired product could be detected.

Synthesis of γ-Chloropropylcarbazole

The procedure of Mihami, Morimoto, and Murakami[43] was followed with modification. To a solution of 8.4 g (0.05 mole) of carbazole in 200 ml of acetone was added 20.0 g (0.08 mole) of 3-chloropropyl p-toluenesulfonate and 8.4 g of sodium hydroxide in 8 ml of water. The reaction mixture was heated at reflux for 2.5 hours and then was treated with an additional 4.0 g of 3-chloropropyl p-toluenesulfonate and 1.7 g of sodium hydroxide in 2 ml of water. The resulting mixture was refluxed for 2.5 hours. After cooling to room temperature, the reaction mixture was neutralized by adding carefully 10 percent hydrochloric acid solution and then extracted with two 250 ml portions of ether. The ether layers were combined, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 19.5 g of dark brown oil which was found to be a mixture of at least two components by GLC. At 200°C, it showed a peak at 3.2 min corresponding to the tosylate ester and a second peak at 7.4 min corresponding to the desired γ-chloropropylcarbazole. Vacuum distillation was attempted to remove the excess tosylate but was found not to be efficient. The crude mixture was then chromatographed on 100 g of neutral alumina packed in a 3 cm diameter column. Fractions first with 500 ml of hexane and followed by 200 ml of 2 percent ether in hexane as eluents

gave 7.2 g (58 percent yield) of pale yellow oil as γ-chloropropyl-carbazole. Later fractions with 300 ml of 10 percent ether in hexane and 300 ml of ether gave 11.6 g of recovered tosylate and carbazole. Part of the pale yellow oil (3.3 g) was further purified by distillation under reduced pressure to give 2.7 g of a colorless oil: b.p. 158-160°C/0.1 mm; NMR (CCl_4): 6.8-8.0 δ (multiplet, 8H, aromatic H), 4.03 δ (triplet, 2H, N-CH_2-), 3.07 δ (triplet, 2H, -CH_2-Cl), and 1.87 δ (quintet, 2H, C-CH_2-C).

Anal. Calculated for $C_{15}H_{14}NCl$: C, 73.92; H, 5.79; N, 5.75. Found: C, 73.89; H, 5.83; N, 5.71.

Another procedure of Gilman and Shirley[41] was also tried. In a 250 ml round-bottomed flask was placed 12 ml (0.020 mole) of 15 percent n-BuLi in hexane and to this solution was added slowly at 0°C with stirring 3.34 g (0.020 mole) of carbazole in 100 ml of ether. To this resulting mixture was added, over a one hour period, a solution of 5.0 g (0.02 mole) of γ-chloropropyl p-toluenesulfonate in 30 ml of ether. An orange slurry gradually formed. The reaction was then quenched by the slow addition of 100 ml of water. After separation, the ether layer was dried and concentrated in vacuo to give a mixture containing both solid and liquid as the residue. The liquid part was redissolved in a small amount of ether and the 1.38 g of solid present which was not soluble in ether was collected by filtration. The solid was found by NMR to be unreacted carbazole. The concentrated filtrate, 5.03 g, was found to have at least two components by GLC which gave the same pattern as that mentioned above, and was chromatographed on

25.0 g of neutral alumina as before. Distillation of the fractions eluted from hexane and 2 percent ether in hexane under reduced pressure (bath temperature 160-170°C/0.2 mm) gave 1.53 g (31 percent yield) of pale yellow oil which was found by NMR and GLC to be γ-chloropropylcarbazole.

Synthesis of 9-γ-Methylaminopropylcarbazole

The general procedure of Thiel and Stach[42] was followed. A solution of methylamine in methanol was prepared by first mixing 13.4 g (0.20 mole) of methylamine hydrochloride and 8.0 g (0.20 mole) of NaOH in 100 ml of methanol. After stirring for one hour at room temperature, the mixture was filtered to remove the sodium chloride salt. To this filtrate, in a 250 ml round-bottomed flask, was added 2.43 g (0.01 mole) of 9-γ-chloropropylcarbazole. The reaction mixture was heated at reflux overnight with stirring. The resulting solution was cooled to room temperature and filtered. Its solvent was removed in vacuo to give a residue containing both a yellow oil and a white solid. The residue was then partitioned with 200 ml of water and 150 ml of ether. The aqueous layer was further extracted with an additional 150 ml of ether. The ether layers were combined and dried. The solvent was removed in vacuo to yield 2.64 g of a yellow liquid which was found to be a mixture of starting material, 9-γ-chloropropyl-carbazole, and the desired amine by NMR. In order to isolate the amine, the yellow liquid was dissolved in 30 ml of ether and excess ethanolic hydrogen chloride was added to this ethereal solution of the crude product. A pale yellow solid was formed and, after collection

by filtration, was recrystallized from a methanol-ether mixture to give 1.41 g (51 percent yield) of 9-γ-methylaminopropylcarbazole hydrochloride as pale yellow prisms, m.p. 163-164°C.

Anal. Calculated for $C_{16}H_{19}N_2Cl$: Cl, 12.90; N, 10.20. Found: Cl, 12.80; N, 10.07.

The 9-γ-methylaminopropylcarbazole hydrochloride salt thus obtained was dissolved in 30 ml of water and treated with excess 10 percent NaOH until the solution was basic. The resulting solution was then extracted with two 50 ml portions of ether. The ether layers were combined, dried, and concentrated in vacuo to give 1.21 g (51 percent yield) of a pale yellow oil as the desired amine. The NMR spectrum (CCl_4) was observed as follows, 6.9-8.2 δ (multiplet, 8H, aromatic H), 4.10 δ (triplet, 2H, N-CH_2-), 2.23 δ (triplet, 2H, -NH-CH_2-), 2.10 δ (singlet, 3H, -N-CH_3), and 1.67 δ (quintet, 2H, -C-CH_2-C-).

Synthesis of 5-Phenyl-5-[N-(3-carbazolylpropylmethylamino)]-barbituric Acid

In a 50 ml round-bottomed flask containing 10 ml of methanol equipped with a condenser was added 1.19 g (0.05 mole) of 9-γ-methylaminopropylcarbazole and 0.71 g (0.0025 mole) of 5-bromo-5-phenylbarbituric acid. The reaction mixture was heated at reflux with stirring and a white precipitate began to be formed after ten minutes of heating. After heating for two hours, approximately one-half of the solvent was removed in vacuo, and the white solid present collected by filtration, washed with water, and dried to give 1.14 g of crude

product. Recrystallization twice from methanol and dried under vacuum at 80°C for 48 hours afforded 0.73 g (66 percent yield) of white crystals, m.p. 246-247°C; IR, 3225 cm^{-1} (strong, NH stretching), and 1700 cm^{-1} (strong, carbonyl); NMR (dmso-d_6), 6.6-10.0 δ (multiplet, 15 H, aromatic H and two -NH), 4.40 δ (triplet, 2H, N-CH_2-), 2.54 δ (triplet, 2H, -CH_2-Cl), 2.34 δ (singlet, 3H, N-CH_3) and 1.94 δ (quintet, 2H, C-CH_2-C). The mass spectrum gave fragment ions only, 207 (15), 199 (63), 167 (100).

Anal. Calculated for $C_{26}H_{24}N_4O_3$: C, 70.89; H, 5.49; N, 12.72. Found: C, 71.09; H, 5.54; N, 12.63.

Synthesis of 2-Trifluoromethylcarbazole

A similar procedure of Forbes, Stacey, Tatlow, and Wragg[44] was employed for the preparation of 2-trifluoromethylcarbazole.

m-Trifluoromethylphenylhydrazine. A suspension of 58.8 g (0.365 mole) of m-aminotrifluoromethylbenzene in a mixture of 160 ml of conc. HCl and 110 ml of water was put in a one liter three-necked flask equipped with a magnetic stirrer. The solution was cooled to 5°C in an ice bath. A solution of 32.8 g of sodium nitrite in 65 ml of water was then added slowly with vigorous stirring through a separatory funnel. The reaction mixture turned to a clear yellow solution after ∿20 minutes of stirring. This diazonium salt solution was poured slowly into a two liter Erlenmeyer flask which contained a cold (∿5°C) solution of 212 g of stannous chloride dihydrate in 212 ml of conc. HCl. The temperature was kept at 5°C-10°C by external cooling. After being stirred for an additional ten minutes, the

solution was diluted with 800 ml of water and filtered. The filtrate was rendered alkaline with sodium hydroxide pellets to give a white milky suspension. The mixture was steam distilled until two liters of distillate was collected. After separating the yellow oil as the lower layer, the aqueous portion was saturated with sodium chloride and extracted with two 500 ml portions of ether. Both ether layers and the yellow oil were combined and dried over anhydrous magnesium sulfate. The solvent was then removed in vacuo to give 51.4 g of a brownish yellow oil. Distillation of this crude oil under reduced pressure afforded 40.3 g (63 percent yield) of a pale yellow oil, b.p. 90-93°C/2.5 mm; IR ($CHCl_3$): 3350 cm^{-1} (NH stretching), 1610 cm^{-1} (NH bending), and 1330 cm^{-1} (aromatic C-N vibration); NMR (neat): 6.4-7.6 δ (multiplet, 4H, aromatic H), and 4.18 δ (br. 3H, $-NHNH_2$).

7-Trifluoromethyl-1,2,3,4-tetrahydrocarbazole. To a solution of 15.0 g (0.085 mole) of m-trifluoromethylphenylhydrazine in 30 ml of methanol and 10 ml of conc. HCl was added at once 15.0 g (0.153 mole) of cyclohexanone. An exothermic reaction ensued and a yellow precipitate was formed. The reaction mixture was filtered and the yellow solid obtained was dissolved in 30 ml of methanol, decolorized with charcoal and was recrystallized from methanol. Further recrystallization from methanol afforded 19.4 g (89 percent yield) of colorless needles as the pure hydrazone, m.p. 138-139°C. (lit. (44) 139°C) These were found to be unstable in light and air and were not analyzed.

A mixture of freshly made sample of 25.6 g (0.010 mole) of the hydrazone, 320 ml of glacial acetic acid and 80 ml of conc. H_2SO_4 was

heated on a steam bath for two hours. Upon pouring the cooling solution into two liters of ice-water, a white precipitate resulted. This crude product was collected on a Buchner funnel, washed with water, and recrystallized from hexane to give 10.6 g (44 percent yield) of white solid, m.p. 129-131°C (lit. (44) 124-127°C). It decomposed rapidly in light and air and was not analyzed further.

2-Trifluoromethylcarbazole. A solution of 5.5 g (0.023 mole) of 2-trifluoromethyl-1,2,3,4-tetrahydrocarbazole and 10.0 g of chloranil in 150 ml of xylene was heated at reflux until the liquid no longer gave a red color when a small sample was added to a solution of warm 2N NaOH, ca. eight hours was needed. After cooling, the mixture was filtered and the filtrate diluted with 100 ml of ether. It was washed first with four 200 ml portions of 2N NaOH and then with two 250 ml portions of water. The xylene layer was separated and dried over anhydrous magnesium sulfate. The solvent was then removed in vacuo to give 3.55 g of brown residue. This crude product was crystallized from ether-hexane mixture. A further recrystallization from the same solvent system gave 2.80 g (52 percent yield) of white leaflets, m.p. 209-210°C (lit. (44) m.p. 209-210°C). The IR spectrum gave absorption at 3420 cm^{-1} (NH stretching). The NMR spectrum (acetone-d_6) showed aromatic hydrogen at 7.0-8.6 δ as expected.

Synthesis of 9-γ-Chloropropyl-2-trifluoromethylcarbazole

To a solution of 1.38 g (0.0058 mole) of 2-trifluoromethylcarbazole in 25 ml of acetone was added 1.10 g of NaOH in 2 ml of water and 2.34 g (0.0094 mole) of γ-chloropropyl p-toluenesulfonate.

The reaction mixture was heated at reflux for two hours and then treated with 0.4 g of γ-chloropropyl p-toluenesulfonate and 0.2 g of NaOH. The mixture was refluxed for an additional four hours. After cooling to room temperature, the reaction mixture was neutralized by adding 10 percent HCl solution and extracted with two 50 ml portions of ether. The ether layers were combined, dried, and the ether removed in vacuo to give 3.40 g of a brown oil. The crude oil in a small amount of ether was placed on a 3 cm diameter column packed with 50 g of neutral alumina. Elution with 350 ml of hexane and removal of hexane in vacuo afforded 1.70 g of crude product which solidified upon standing. Recrystallization from hexane gave 1.25 g (69 percent yield) of a white silky solid. An analytical sample was prepared by recrystallizing two more times from hexane and drying under vacuum at room temperature for 24 hours, m.p. 65-66°C. The IR spectrum gave absorptions at 1460 (aromatic), 1340, 1120, 1090, and 750 cm^{-1}. The NMR spectrum (CCl_4) showed absorptions at 7.0-8.2 δ (multiplet, 7H, aromatic H), 4.47 δ (triplet, 2H, N-CH_2-), 3.43 δ (triplet, 2H, -CH_2-Cl), and 2.27 δ (quintet, 2H, C-CH_2-C). The mass spectrum gave the expected molecular ion at 311.

Anal. Calculated for $C_{16}H_{13}NF_3Cl$: C, 61.64; H, 4.20; N, 4.49. Found: C, 61.61; H, 4.26; N, 4.57.

Synthesis of 9-γ-Methylaminopropyl-2-trifluoromethylcarbazole

A solution of methylamine was first prepared by mixing 2.68 g (0.04 mole) of methylamine hydrochloride and 1.60 g (0.04 mole) of sodium hydroxide in 30 ml of methanol, followed by stirring at room

temperature for one hour and then removing NaCl salt by filtration. To this solution in a 50 ml round-bottomed flask was added 0.50 g (1.60 mmole) of 9-γ-chloropropyl-2-trifluoromethylcarbazole with stirring. The resulting solution was heated at reflux for 18 hours. Removal of the solvent in vacuo gave an oily solid residue. This resulting residue was then partitioned between 50 ml of a 1:1 ether-5 percent NaOH solution. The aqueous layer was extracted with an extra 20 ml portion of ether. The ether layers were combined, dried, and evaporated completely to give 0.39 g of a pale yellow oil. The NMR (CCl_4) spectrum gave absorptions at 6.9-8.1 δ (multiplet, 7H, aromatic H), 4.30 δ (triplet, 2H, $\geq N-CH_2-$), 2.37 δ (triplet, 2H, $C-CH_2-N$), 2.30 δ (singlet, 3H, $N-CH_3$), and 1.90 δ (quintet, 2H, $C-CH_2-C$).

Synthesis of 5-Phenyl-5-[N-(2'-trifluoromethyl-3-carbazolylpropyl-methylamino)]-barbituric Acid

A mixture of 0.45 g (1.58 mmole) of 5-bromo-5-phenylbarbituric acid and 0.97 g (3.17 mmole) of 9-γ-methylaminopropyl-2-trifluoromethylcarbazole in 10 ml of methanol was stirred in a 100 ml round-bottomed flask fitted with a reflux condenser. Although a white precipitate formed almost immediately upon mixing, the mixture was refluxed for an additional 15 minutes and then cooled to room temperature. The white precipitate was removed by filtration and washed with water. After removal of the methanol from the filtrate, the resulting solid was recrystallized from a minimum amount of methanol. From their m.p.'s and infrared spectra, the "white

precipitate" and the "resulting solid" were found to be identical. These were combined to give a total of 0.42 g crude product (26 percent yield). Recrystallization was effected from an ethanol-water mixture and the crystals, dried under vacuum at 80°C for 72 hours, gave a m.p. 274-275°C. The IR spectrum showed absorption at 1700 cm^{-1} (strong, carbonyl).

Anal. Calculated for $C_{27}H_{25}N_4O_3F$: C, 63.52; H, 4.94; N, 10.98. Found: C, 63.49; H, 4.72; N, 10.86.

Reaction of 5-Bromo-5-phenylbarbituric Acid with Indole

To a solution of 5.0 g (0.018 mole) of 5-bromo-5-phenyl-barbituric acid in 20 ml of methanol was added 4.2 g (0.036 mole) of indole. Heat was evolved, the solution turned to dark green immediately and a solid formed. Following stirring of the reaction mixture at room temperature for one hour, the solid was collected by filtration and washed first with cold methanol and then with ether. Recrystallization from ethanol-water mixture gave 3.2 g of white crystals, m.p. 261-262°C. Both IR and NMR showed it to be 5-phenylbarbituric acid (87 percent). The filtrate was evaporated in vacuo to give a dark brown tar like residue which was unable to be identified.

Attempted Reaction of 5-Bromo-5-phenylbarbituric Acid with 2-Phenylindole

In a 100 ml round-bottomed flask equipped with a reflux condenser was mixed 5.0 g (0.026 mole) of 2-phenylindole with 3.68 g (0.013 mole) of 5-bromo5-phenylbarbituric acid in 40 ml of methanol. The reaction mixture was refluxed for 1.5 hours and then cooled. The gray colored solid formed was filtered and recrystallized twice from an ethanol-

water mixture to give 2.3 g of white crystals, m.p. 259-261°C. IR and NMR spectra showed it to be 5-phenylbarbituric acid (87 percent yield). The filtrate was concentrated in vacuo and yielded a dark brown residue. A mixture of 30 ml of 1:1 ether-hexane was added to this residue and 0.31 g of pale yellow precipitate was obtained which was found to be the unreacted 2-phenylindole. The remaining solution was concentrated in vacuo to give ca. 4 g of dark brown tar like liquid which was unable to be identified.

Reaction of 5-Bromo-5-phenylbarbituric Acid with 3-Methylindole

Five grams (0.038 mole) of 3-methylindole was dissolved in 30 ml of methanol in a 100 ml round-bottomed flask equipped with a reflux condenser. To this solution was added 5.32 g (0.019 mole) of 5-bromo-5-phenylbarbituric acid. Heat was evolved and a white precipitate formed almost immediately. The reaction mixture was stirred at room temperature for half an hour. The solid was then collected by filtration and washed with methanol and ether. Recrystallization from ethanol-water mixture afforded 2.93 g of white crystals, m.p. 259-261°C. Both IR and NMR spectra showed it to be 5-phenylbarbituric acid. The amount obtained was 76 percent. No further investigation was made of this reaction.

Reaction of 5-Bromo-5-phenylbarbituric Acid with Indoline

To a solution of 3.68 g (0.013 mole) of 5-bromo-5-phenyl-barbituric acid in about 40 ml of methanol was added 3.13 g (0.026 mole) of indoline. A light green precipitate was formed almost immediately. The reaction mixture was stirred at room temperature for one hour. The solid was collected by filtration, washed with

methanol and dried. A light green solid weighing 3.42 g was obtained. The solid was decolorized with charcoal and recrystallized from ethanol-water mixture to give 2.91 g of white crystals. Repeated recrystallizations from the same solvent system followed by drying under vacuum at 80°C for 72 hours gave an analytical sample, m.p. 208-209°C. Elemental analysis indicated a salt, indolinyl barbiturate, was formed. The percent yield was 69 (2.91 g).

Anal. Calculated for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 12.99. Found: C, 66.49; H, 5.26; N, 12.77.

Treatment of an aqueous solution of this salt with dilute HCl yielded a precipitate, m.p. 260-261°C. A mixed melting point of this solid with a known sample of 5-phenylbarbituric acid showed no depression of the melting point. Its IR and NMR spectra were also found to be 5-phenylbarbituric acid.

Synthesis of 1-(γ-Chloropropyl)indole

In a 250 ml of boiling flask containing a solution of 5.0 g (0.043 mole) of indole in 80 ml of acetone was added 16.0 g (0.065 mole) of γ-chloropropyl p-toluenesulfonate and 7.0 g (0.175 mole) of sodium hydroxide in 8 ml of water. The reaction mixture was heated at reflux. It turned to light blue color in five minutes and then gradually became light yellow with the formation of some white solid. Reflux was continued for about 20 hours after which the mixture was cooled then filtered in order to remove the precipitated sodium salt. Concentration of the filtrate in vacuo to remove most of the acetone followed by adding 10 percent HCl solution to neutralize the excess sodium hydroxide. The solution was then extracted with two 100 ml

portions of ether. Ether layers were combined, dried, and concentrated in vacuo to give 15.3 g of crude yellow oil. By NMR the oil was found to contain both the desired product and the starting tosylate. The crude mixture was chromatographed on 100 g of neutral alumina packed in a 3 cm diameter column. Fractions with 750 ml of hexane as eluent gave 6.6 g (78 percent yield) of rather pure 1-(γ-chloropropyl)indole. This pale yellow oil was purified by distillation under reduced pressure to give a colorless oil, b.p. 127-129°C/ 0.9 mm. The IR (CCl_4) spectrum showed absorptions at 2970 (C-H stretching) and 1470 cm^{-1} (aromatic). The NMR spectrum (CCl_4) showed bands at 6.9-7.9 δ (multiplet, 4H, aromatic H), 6.83 δ (doublet, 1H, vinyl H), 6.33 δ (doublet, 1H, N-CH=C), 4.0 δ (triplet, 2H, N-CH_2), 3,12 δ (triplet, 2H, -CH_2-Cl), and 1.93 δ (quintet, 2H, C-CH_2-C). Anal. Calculated for $C_{11}H_{12}NCl$: C, 68.22; H, 6.25; N, 7.23. Found: C, 68.34; H, 6.28; N, 7.18.

Synthesis of 1-(γ-methylaminopropyl)indole

Methylamine in methanol solution was prepared by mixing 13.4 g (0.20 mole) of methylamine hydrochloride and 8.0 g (0.20 mole) of sodium hydroxide in 100 ml of methanol and removing the sodium chloride by filtration. This solution was placed in a 250 ml round-bottomed flask and 2.0 g (0.010 mole) of 1-(γ-chloropropyl)indole was added. The reaction mixture was then refluxed for 20 hours following which the solvent and the excess methylamine were removed using a rotovap. Both a yellow oil and a white solid remained as residues. To these, 50 ml of acetone was added and the white solid which did not dissolve in acetone was then removed by filtration and found to be methylamine

hydrochloride. The filtrate was concentrated in vacuo to give a brown oil and the NMR spectrum of this oil showed it to be a mixture of ca. 50 percent 1-(γ-chloropropyl)indole along with the desired product. This mixture was dissolved in 5 ml of ether and placed on a 3 cm diameter chromatographic column packed with 50 g of neutral alumina. The fractions eluted with 300 ml of hexane gave 1.14 g of 1-(γ-chloropropyl)indole and the later fractions eluted with 200 ml of methanol gave 1.14 g of rather pure 1-(γ-methylaminopropyl)indole. The NMR spectrum (acetone-d_6) showed bands at 7.1-7.7 δ (multiplet, 4H, aromatic H), 7.0 δ (doublet, 1H, vinyl H), 6.43 δ (doublet, 1H, N-CH=C), 4.20 δ (triplet, 2H,N-CH_2-), 2.50 δ (triplet, 2H, -C-CH_2-N-), 2.30 δ (singlet, 3H, -CH_3), 2.0 δ (triplet, 1H, -NH), and 1.93 δ (quintet, 2H, C-CH_2-C). No further purification was made and this product was used for the reaction with 5-bromo-5-phenylbarbituric acid.

Reaction of 5-Bromo-5-phenylbarbituric Acid with 1-(γ-Methylamino-propyl)indole

One gram (0.0053 mole) of 1-(γ-methylaminopropyl)indole and 0.76 g (0.0026 mole) of 5-bromo-5-phenylbarbituric acid were mixed in 20 ml of methanol. The reaction mixture was refluxed for 15 min and then cooled. A white precipitate which had formed in the solution was collected by filtration and dried to give 0.31 g of white crystals, m.p. 258-260°C. Both IR and NMR spectra showed it to be 5-phenyl-barbituric acid. No desired condensation product was isolated from the reaction mixture.

Synthesis of 1-Methylindole-3-acetonitrile

In a one liter round-bottomed flask was placed 10 g (0.064 mole) of 3-indoleacetonitrile in 300 ml of acetone. To this solution was added 11.9 g (0.298 mole) of sodium hydroxide in 10 ml of water. The solution turned blue in color gradually. After stirring for 30 min, the reaction mixture was treated with 18.9 g (0.102 mole) of methyl p-toluenesulfonate and heated at reflux for two hours. The blue color of the solution faded slowly and became yellow in color; a white solid also was formed. This solid was removed by filtration and the filtrate was rotovaped to give a brown oil as the residue. This brown oil was dissolved in 200 ml of ether and the resulting solution washed with two 100 ml portions of 1 N hydrochloric acid. The ether layer was dried and concentrated in vacuo until there was about 50 ml left. Hexane was added to this concentrated solution until it became cloudy. After standing in an acetone-dry ice bath for a while, it solidified to give 7.6 g (70 percent yield) of 1-methylindole-3-acetonitrile as pale yellow crystals. Recrystallization twice from ether-hexane mixture gave white crystals, m.p. 56-57°C (lit. (45) m.p. 58-59°C). The NMR spectrum (CCl_4) showed bands at 6.9-7.7 δ (multiplet, 4H, aromatic H), 6.77 δ (singlet, 1H, vinyl H), 3.43 δ (singlet, 3H, N-CH_3), and 3.40 δ (singlet, 2H, allylic H).

Synthesis of 1-Methyltryptamine

The procedure of Snyder and Eliel[45] was followed. To a hot solution of 3.4 g (0.021 mole) of 1-methylindole-3-acetonitrile in 60 ml of absolute ethanol was added, over a period of 10 minutes, 4.0 g (0.174 mole) of finely cut sodium. The reaction mixture was

refluxed until all the metal had dissolved, after which it was diluted with 60 ml of water and concentrated in vacuo to remove most of the alcohol. The residual solution was diluted with 40 ml of water and extracted with two 100 ml portions of ether. The ether solution was then extracted with ca. 75 ml of 2 N hydrochloric acid. Neutralization of the acid portion with an 10 percent aqueous sodium hydroxide, followed by extraction with three 100 ml portions of ether, drying of the ether solutions, and removing of the solvent gave 2.95 g of brown oil. Distillation of this crude oil gave 1.85 g (53 percent yield) of 1-methyltryptamine as a nearly colorless oil, b.p. 108-112°C/0.1 mm. The IR spectrum (CCl_4) showed a strong, broad absorption at 3400 cm^{-1} (NH stretching). The NMR spectrum (acetone-d_6) showed bands at 6.8-7.7 δ (multiplet, 5H, aromatic H and vinyl H), 3.63 δ (singlet, 3H, $N-CH_3$).

Reaction of 5-Bromo-5-ethylbarbituric Acid with 1-Methyltryptamine

To a solution of 0.54 g (0.0023 mole) of 5-bromo-5-ethyl-barbituric acid in 10 ml of methanol was added 0.80 g (0.0046 mole) of 1-methyltryptamine. Some evolution of heat was observed and a precipitate formed almost immediately. When the reaction mixture had been refluxed for 15 minutes, the solid was collected by filtration and washed with cold methanol and then ether. A nearly white solid was obtained, 0.54 g. Recrystallization twice from ethanol-water mixture and dried under vacuum at 80°C for 48 hours gave colorless needles, m.p. 252-253°C. This was identified as a salt of the amine and ethyl-barbituric acid, and the quantity obtained represented a 71 percent yield. The IR spectrum gave absorptions at 1700 cm^{-1} (strong, carbonyl)

and 1570 cm^{-1} (strong, NH bending from amine salt). The NMR spectrum (dmso-d_6) showed bands at 7.0-9.2 δ (multiplet, 8H, aromatic, vinyl and amine H), 3.80 δ (singlet, 3H, N-CH_3), 3.06 δ (singlet, 4H, -CH_2-CH_2-), 2.06 δ (quartet, 2H, CH_3-CH_2-), and 0.80 δ (triplet, 3H, C-CH_3).

Anal. Calculated for $C_{17}H_{22}N_4O_3$: C, 61.80; H, 6.71; N, 16.96.
Found: C, 61.69; H, 6.69; N, 16.93.

Reaction of 5-Bromo-5-phenylbarbituric Acid with 1-Methyltryptamine

In a 50 ml round-bottomed flask equipped with a reflux condenser and a calcium chloride drying tube was placed 0.65 g (0.0023 mole) of 5-bromo-5-phenylbarbituric acid in 10 ml of methanol. To this solution was added 0.80 g (0.0046 mole) of 1-methyltryptamine. Heat evolution was observed and a dense white precipitate was formed almost immediately. The reaction mixture was refluxed with stirring for 15 minutes and then cooled to room temperature. The solid was collected by filtration, washed with cold methanol, and dried. From this there was obtained 0.85 g of white crystals. Recrystallization twice from ethanol-water mixture and drying under vacuum at 80°C for 48 hours, gave white crystals, m.p. 266-266.5°C (dec.). This was identified as a salt of the amine and phenylbarbituric acid, hence the weight obtained represented 98 percent yield. The IR spectrum gave absorptions at 1700 cm^{-1} (strong, carbonyl), and 1580 cm^{-1} (strong, NH bending from amine salt). The NMR spectrum (dmso-d_6) showed bands at 9.8 δ (broad, 2H, -NH), 6.8-8.6 δ (multiplet, 11H, aromatic H and vinyl H), 3.80 δ (singlet, 3H, N-CH_3), and 3.66 δ (singlet, 4H, -CH_2-CH_2-).

Anal. Calculated for $C_{21}H_{22}N_4O_3$: C, 66.65; H, 5.86; N, 14.81.
Found: C, 65.78; H, 6.13; N, 14.68.

Reaction of 5-Bromo-5-ethylbarbituric Acid with 1-Methyltryptamine

To a solution of 0.54 g (0.0023 mole) of 5-bromo-5-ethylbarbituric acid in 10 ml of methanol was added 0.80 g (0.0046 mole) of 1-methyltryptamine. Some evolution of heat was observed and a precipitate formed almost immediately. The reaction mixture was refluxed for 15 minutes. When the solid was collected by filtration and washed with cold methanol and then ether, a nearly white solid (0.54 g) was obtained. Recrystallization twice from ethanol-water mixture and dried under vacuum at 80°C for 48 hours gave colorless needles, m.p. 252-253°C. This was identified as a salt of the amine and ethylbarbituric acid, thus a 71 percent yield had been obtained. The IR spectrum gave absorptions at 1700 cm^{-1} (strong, carbonyl) and 1570 cm^{-1} (strong, NH bending from amine salt). The NMR spectrum (dmso-d_6) showed bands at 7.0-9.2 δ (multiplet, 8H, aromatic, vinyl and amine H), 3.80 δ (singlet, 3H, N-CH_3), 3.06 δ (singlet, 4H, -CH_2-CH_2-), 2.06 δ (quartet, 2H, CH_3-CH_2-), and 0.80 δ (triplet, 3H, C-CH_3).

Anal. Calculated for $C_{17}H_{22}N_4O_3$: C, 61.80; H, 6.71; N, 16.96. Found: C, 61.69; H, 6.69; N, 16.93.

Reaction of 5-Bromo-5-phenylbarbituric Acid with trans-2-Phenylcyclopropylamine

A solution of 2.12 g (0.0075 mole) of 5-bromo-5-phenylbarbituric acid in 15 ml of methanol was introduced into a 100 ml round-bottomed flask fitted with a condenser and 2.00 g (0.015 mole) of trans-2-phenylcyclopropylamine was added. Heat evolution was observed on mixing. The dense white precipitate which formed almost immediately, necessitated addition of another 15 ml of methanol to facilitate

stirring. The reaction mixture was stirred at room temperature for 30 minutes. The white solid collected by filtration was recrystallized from ethanol-water mixture to yield 2.20 g of white crystals, m.p. 243-244°C. Further purification with repeated recrystallization gave analytical sample which dried under vacuum at 80°C for 72 hours, m.p. 245-246°C (dec.). Instead of the desired aminobarbituric acid adduct, this compound was identified as a salt of the amine and phenylbarbituric acid according to its physical properties. The IR spectrum gave significant bands at 1690 cm^{-1} (strong, carbonyl) and 1570 cm^{-1} (NH bending from amine salt). The NMR spectrum (dmso-d_6) gave bands at 6.0-9.6 δ (broad multiplet, 15 H, aromatic H and five NH), 2.66 δ (multiplet, 1H, Ph-CH<), 2.55 δ (multiplet, 1H, N-CH<), and 1.20 δ (multiplet, 2H, cyclopropyl $-CH_2-$).

Anal. Calculated for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46. Found: C, 67.54; H, 5.71; N, 12.41.

Reprecipitation of the salt from a dilute HCl solution gave 5-phenylbarbituric acid, m.p. 260-261°C. A mixed melting point of the sample and a known sample of 5-phenylbarbituric acid gave no change of the melting point.

Reaction of 5-Bromo-5-ethylbarbituric Acid with trans-2-Phenylcyclopropylamine

To a solution of 0.89 g (0.0038 mole) of 5-bromo-5-ethylbarbituric acid in 10 ml of methanol was added 1.00 g (0.0075 mole) of trans-2-phenylcyclopropylamine. No evolution of heat was observed on mixing. The reaction mixture was refluxed for 30 minutes and then cooled. The pale yellow solid collected by filtration was recrystallized

twice from ethanol-water mixture to afford 0.45 g (54 percent yield) of white crystals, m.p. 196-197°C (dec.). Elemental analysis of these crystals indicated the formation of an amine salt.

Anal. Calculated for $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.62; N, 14.52. Found: C, 62.02; H, 6.77; N, 14.44.

Upon dissolving the above salt in water, addition of dilute HCl gave a precipitate which melted at 188-189°C. A mixed melting point with a known sample of 5-ethylbarbituric acid gave an identical melting point of 188-189°C.

Synthesis of 5-Phenyl-5-[N-(cyclopropylamino)]-barbituric Acid

To a solution of 3.00 g (0.0106 mole) of 5-bromo-5-phenyl-barbituric acid in 15 ml of methanol was added 1.21 g (0.0212 mole) of cyclopropylamine. Evolution of heat was observed on mixing. A dense white precipitate was formed almost immediately and 10 ml of methanol needed to be added to facilitate stirring. After continued stirring of the reaction mixture at room temperature for one hour, the white solid was collected by filtration, washed with cold methanol, and dried to give 1.82 g of white crystals, m.p. 273-275°C. The NMR spectrum of this crude product did not suggest any possibility of the desired adduct and thus was not further investigated. Evaporation of the filtrate in vacuo gave a yellowish-brown residue which could be crystallized from ethanol-water mixture to give 0.64 g (23 percent yield) of beige crystals. Recrystallization from the same solvent system and dried under vacuum at 80°C overnight gave an analytical sample of the desired compound, m.p. 211.5-212.5°C. The IR spectrum gave absorptions at 1770 and 1700 cm^{-1} (strong, carbonyl). The NMR

spectrum (dmso-d_6) gave bands at 7.26 δ (singlet, 5H, aromatic H), 3.40 δ (multiplet, broad, 3H, -NH), 2.06 δ (multiplet, 1H, N-CH<), and 0.40 δ (multiplet, 4H, two C-CH_2-). The mass spectrum showed the expected molecular ion at m/e 259 of the desired compound.

Anal. Calculated for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.16; H, 5.05; N, 16.13.

Reaction of 5-Phenylbarbituric Acid with trans-2-phenylcyclopropylamine

To a solution of 0.20 g (0.0015 mole) of trans-2-phenylcyclopropylamine in 10 ml of methanol was introduced 0.31 g (0.0015 mole) of 5-phenylbarbituric acid. The reaction mixture was refluxed for three hours and then cooled. The solid formed was collected by filtration, washed with cold methanol and ether, and dried. Recrystallization from ethanol-water mixture gave 0.45 g of white crystals, m.p. 244-245°C. A mixed melting point of this sample and the amine salt from 2-phenylcyclopropylamine and 5-bromo-5-phenylbarbituric acid gave no depression of the melting point. The IR spectrum for this product was identical to the IR spectrum of the amine salt.

Synthesis of 1,3-Dimethyl-5-phenylbarbituric Acid

The general procedure of Dickey and Gray[35] was used with modification. In a three-necked, one liter round-bottomed flask equipped with a mechanical stirrer, a dropping funnel, and a reflux condenser to which was fitted a calcium chloride drying tube, 11.5 g (0.50 mole) of freshly cut sodium was reacted with one liter of anhydrous absolute ethanol. To this ethoxide solution was added, over a period of 30 minutes, 118.1 g (0.50 mole) of diethyl phenylmalonate. Through the

arm of the flask was added in portions 44.0 g (0.050 mole) of 1,3-dimethylurea. Vigorous stirring was continued through the addition and during a reflux period for 20 hours. A white solid was observed in the solution. After removal of 500 ml of ethanol by distillation, 42 ml (0.050 mole) of concentrated hydrochloric acid in 500 ml of water was added. The solution became clear at this stage and distillation was continued until a total volume of one liter of ethanol had been removed. The remaining solution was chilled in the refrigerator overnight. No precipitate was formed but a yellow oil was found in the solution. The reaction mixture was then extracted with three 200 ml portions of ether. The ethereal organic layers were combined and dried. The solvent was removed in vacuo to give a yellow oil. This crude oil was found by NMR to contain most of the starting materials and only approximately 14 percent of 1,3-dimethyl-5-phenylbarbituric acid. The crude oil was dissolved in a minimum amount of hot 95 percent ethanol and when chilled a white solid crystallized. These crystals were collected by filtration and dried in a vacuum desiccator to give 15.1 g (13 percent yield) of 1,3-dimethyl-5-phenylbarbituric acid. Recrystallization from 95 percent ethanol afforded long colorless needles, m.p. 138-139°C (lit. (46) m.p. 140-140.5°C).

Another procedure that of Cope[46], who had reported the synthesis of a series of 1,3-dimethyl-5-alkylbarbituric acids, was followed as another approach. In a three-necked one liter round-bottomed flask fitted with a mechanical stirrer, a reflux condenser, and a dropping funnel, were added 44.o g (0.50 mole) of 1,3-dimethylurea and 99.0 g (0.55 mole) of phenylmalonic acid dissolved in 120 ml of glacial acetic

acid. The reaction mixture was heated to about 65°C and 220 ml of acetic anhydride was added during 30 minutes. The temperature was raised to 90°C during three hours, and kept at 90°C for five hours. When the acetic acid and acetic anhydride had been removed by distillation under reduced pressure (ca. 20 mm), the residue was crystallized by chilling the residue in an ice-water bath. The crude product was collected by filtration, recrystallized from ethanol and dried throughly in a vacuum desiccator. The white needles obtained weighed 38.5 g (33 percent yield) and had a m.p. of 139.5-140.5°C. The IR spectrum showed absorptions at 1760 and 1680 cm^{-1} (strong, carbonyl). The NMR spectrum (dmso-d_6) showed bands at 7.32 δ (singlet, 5H, aromatic H), 3.90 δ (broad, 1H, -CH-), and 3.17 δ (singlet, 6H, two N-CH_3). The mass spectrum gave the expected molecular ion at m/e 232. The exact mass was calculated for $C_{12}H_{12}N_2O_3$ as 232.08479 and found as 232.08748.

Synthesis of 1,3-Dimethyl-5-bromo-5-phenylbarbituric Acid

The general procedure of Voorhes and Skinner[37] was followed with modification. A solution of 20.0 g (0.0862 mole) of 1,3-dimethyl-5-phenylbarbituric acid in 170 ml of 0.6 N aqueous NaOH solution was placed in a 500 ml three-necked round-bottomed flask equipped with a mechanical stirrer and a dropping funnel. A saturated solution of bromine in water was then added dropwise with stirring into the solution until the bromine color persisted. A sticky white resin was formed at this time. The reaction mixture was then extracted with three 100 ml portions of benzene. After combining, the benzene layers were dried over anhydrous magnesium sulfate. The solvent was removed

in vacuo to give 25.6 g of a thick pale yellow oil which solidified on standing. Recrystallization from 95 percent ethanol and drying under vacuum at room temperature for 48 hours afforded 24.1 g (90 percent yield) of white crystals with the following properties: the IR spectrum showed absorption at 1680 cm^{-1} (strong, carbonyl); the NMR spectrum (CCl_4) showed bands at 7.43 δ (singlet, 5H, aromatic H), and 3.33 δ (singlet, 6H, two N-CH_3); and the mass spectrum did not reveal a molecular ion, but did show a peak at m/e 232 corresponding to the loss of bromine.

Synthesis of 1,3-Dimethyl-5-phenyl-5-[N-(n-propylamino)]-barbituric Acid

In a 50 ml round-bottomed flask containing a solution of 2.00 g (0.0064 mole) of 1,3-dimethyl-5-bromo-5-phenylbarbituric acid in 10 ml of methanol was added 0.76 g (0.0128 mole) of n-propylamine. Heat evolution was observed during the addition, but no precipitate was formed. Even after stirring the mixture at reflux temperature for one hour no precipitate formed although the solution was cooled to 0°C. The solvent was then removed on a rotatory evaporator to give 2.7 g of a yellow resin. Crystallization of this resin from a ethanol-water mixture gave 1.42 g (77 percent yield) of white crystals, m.p. 86-87°C. Recrystallization from ethanol-water mixture and drying in vacuo at room temperature for a period of 48 hours gave an analytical sample, m.p. 88-89°C. The IR spectrum showed absorptions at 3350 cm^{-1} (medium, NH stretching), 1750 and 1660 cm^{-1} (strong, carbonyl). The NMR spectrum ($CDCl_3$) showed bands at 7.35 δ (singlet, 5H, aromatic H), 3.33 δ (singlet, 6H, two N-CH_3), 2.47 δ (triplet, 2H, N-CH_2-), 2.37 δ (singlet, 1H, -NH-), 1.50 δ (multiplet, 2H, C-CH_2-C), and 0.92 δ (triplet, 3H,

C-CH_3). The mass spectrum gave a molecular ion peak at m/e 289.

Anal. Calculated for $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.62; N, 14.52.
Found: C, 62.18; H, 6.84; N, 14.55.

Synthesis of 1,3-Dimethyl-5-phenyl-5-[N-(cyclopropylamino)]-barbituric Acid

In a 50 ml round-bottomed flask containing a solution of 2.00 g (0.0064 mole) of 1,3-dimethyl-5-bromo-5-phenylbarbituric acid in 10 ml of methanol was added 0.73 g (0.0128 mole) of cyclopropylamine. Heat evolution was observed during the addition of the amine and the mixture gradually turned to yellow color. After the mixture was refluxed for one hour it was cooled to room temperature. The resulting dark brown solution, containing only a small amount of precipitate, was concentrated on a rotatory evaporator to give a brown resin containing some solid in this viscous liquid. Crystallization of the resin from ethanol-water mixture gave 1.64 g (89 percent yield) of white crystals, m.p. 85-87°C. Further purification by recrystallization from an ethanol-water mixture gave an analytical sample of white needles, m.p. 89-90°C. The IR spectrum showed absorptions at 3340 cm^{-1} (medium, NH stretching), 1760 and 1650 cm^{-1} (strong, carbonyl). The NMR spectrum ($CDCl_3$) showed bands at 7.33 δ (singlet, 5H, aromatic H), 3.37 δ (singlet, 6H, two N-CH_3), 2.73 δ (singlet, 1H, -NH-), 2.07 δ (multiplet, 1H, $\geq$CH-N), and 0.56 δ (multiplet, 4H, two C-CH_2-). The mass spectrum gave the expected molecular ion peak at m/e 287.

Anal. Calculated for $C_{15}H_{17}N_3O_3$: C, 62.70; H, 5.96; N, 14.62.
Found: C, 62.71; H, 5.87; N, 14.64.

Synthesis of 1,3-Dimethyl-5-phenyl-5-[N-(2-methoxyethylamino)]-barbituric Acid

In 10 ml of methanol contained in a 50 ml round-bottomed flask equipped with a condenser and a calcium chloride drying tube was dissolved 1.38 g (0.0044 mole) of 1,3-dimethyl-5-bromo-5-phenyl-barbituric acid. The solution was stirred while 0.66 g (0.0088 mole) of 2-methoxyethylamine was added. Heat evolution was observed during the addition of the amine. The reaction mixture was refluxed for one hour and then cooled gradually to room temperature. Only trace amount of precipitate was observed. The solution was concentrated on the rotovap to give 2.0 g of yellow resin. The resinous residue was crystallized in ethanol-water mixture with overnight standing at 0°C to give 1.12 g (82 percent yield) of white crystals. Recrystallization twice in ethanol-water mixture gave, after drying in vacuo at room temperature for 48 hours, 0.95 g of analytical sample, m.p. 55-56°C. The IR spectrum showed absorptions at 3350 cm^{-1} (medium, NH stretching) and 1670 cm^{-1} (strong, carbonyl). The NMR spectrum ($CDCl_3$) showed absorptions at 7.37 δ (singlet, 5H, aromatic H), 3.50 δ (triplet, 2H, -NH-$\underline{CH_2}$-), 3.33 δ (singlet, 6H, two N-CH_3), 3.27 δ (singlet, 3H, -OCH_3), 2.87 δ (triplet, 2H, -$\underline{CH_2}$-OCH_3), and 2.77 δ (singlet, 1H, -NH-). The mass spectrum showed the expected molecular ion at m/e 305.

Anal. Calculated for $C_{15}H_{19}N_3O_4$: C, 59.00; H, 6.27; N, 13.76.
Found: C, 59.02 H, 6.27; N, 13.77.

Synthesis of 1,3-Dimethyl-5-phenyl-5-[N-(benzylamino)]-barbituric Acid

A solution of 2.0 g (0.0064 mole) of 1,3-cimethyl-5-bromo-5-phenylbarbituric acid in 20 ml of methanol was placed in a 50 ml round-

bottomed flask equipped with a reflux condenser. To this solution was added 1.37 g (0.0128 mole) of benzylamine. The reaction mixture was then heated at reflux for one hour. After it was cooled to room temperature the dense white precipitate which formed settled to the bottom of the flask. This white solid was collected by filtration, washed with methanol, and dried. Recrystallization of this crude product from methanol gave 1.86 g (86 percent yield) of white crystals, m.p. 165-166°C. The analytical sample which was prepared by recrystallizing a second time from the same solvent and drying overnight at 80°C under vacuum consisted of white plates, m.p. 165-166°C. The IR spectrum revealed absorptions at 3300 cm^{-1} (medium, NH stretching) and 1660 cm^{-1} (strong, carbonyl). The NMR spectrum ($CDCl_3$) showed bands at 7.1-7.6 δ (multiplet, 10H, aromatic H), 3.76 δ (singlet, 2H, benzylic CH_2), 3.35 δ (singlet, 6H, two N-CH_3), and 2.77 δ (broad, singlet, 1H, -NH-). The mass spectrum showed the molecular ion at m/e 337.

Anal. Calculated for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46. Found: C, 67.68; H, 5.68; N, 12.50.

Synthesis of 1,3-Dimethyl-5-phenyl-5-[N-(p-phenetidino)]-barbituric Acid

To a solution of 2.00 g (0.0064 mole) of 1,3-dimethyl-5-bromo-5-phenylbarbituric acid in 20 ml of methanol contained in a 50 ml round-bottomed flask was added 1.75 g (0.0128 mole) of p-phenetidine. Slight heat evolution on mixing was felt by the warmth of the reaction flask. The reaction mixture was refluxed for one hour and then cooled to room temperature. The large amount of precipitate which formed was collected by filtration, washed with methanol, and dried to give

2.20 g of light purple colored solid. This crude product was then recrystallized from a methanol-chloroform mixture to give, after drying under vacuum at 80°C overnight, 1.95 g (83 percent yield) of white needles, m.p. 203-204°C. The IR spectrum showed absorptions at 3400 cm^{-1} (strong, NH stretching), 1670 and 1720 cm^{-1} (strong, carbonyl). The NMR spectrum ($CDCl_3$) showed bands at 7.43 δ (singlet, 5H, aromatic H), 6.63 δ (multiplet, 4H, aromatic H), 3.95 δ (quartet, 2H, $-\underline{CH_2}-CH_3$), 3.53 δ (singlet, 1H, -NH-), 3.37 δ (singlet, 6H, two $N-CH_3$), and 1.37 δ (triplet, 3H, $-CH_2-\underline{CH_3}$). The mass spectrum showed a molecular ion peak at m/e 367.

Anal. Calculated for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44. Found: C, 65.21; H, 5.82; N, 11.40.

Synthesis of 1,3-Dimethyl-5-phenyl-5-[N-(pyrrolidino)]-barbituric Acid

To a solution of 3.00 g (0.0096 mole) of 1,3-dimethyl-5-bromo-5-phenylbarbituric acid in 10 ml of benzene contained in a 50 ml round-bottomed flask was added 1.36 g (0.0192 mole) of pyrrolidine. Heat evolution was felt from the reaction vessel. The resulting solution was refluxed for one hour and then cooled to room temperature. No precipitate was observed in this brownish-red solution. After the resulting solution was shaken with 50 ml of 10 percent hydrochloric acid the whole was extracted with three 50 ml portions of benzene. The benzene layers were combined, dried, and concentrated in vacuo to give about 0.8 g of yellow oil which was found to be 1,3-dimethyl-5-phenylbarbituric acid by NMR. The aqueous layer was then neutralized by addition of a saturated $NaHCO_3$ solution and extracted with two 100 ml

portions of benzene. The benzene layers were combined, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 2.65 g of light brown oil which was found to contain the desired product as evidenced by its NMR spectrum. Purification of this crude product by crystallization was unsuccessful due to the fact that no suitable solvent or solvent system could be found. The crude oil, 2.35 g was washed through a 3 cm diameter column packed with 60 g of silica gel. The fractions eluted with 120 ml of 1:9 ethanol-benzene were collected to give 2.10 g (73 percent yield) of pale yellow oil which was found rather pure from its NMR spectrum. By repeating the chromatography followed by drying under vacuum at room temperature for 48 hours an analytical sample was obtained which gave the following physical properties: the IR spectrum ($CDCl_3$) showed absorptions at 1740 and 1670 cm^{-1} (strong, carbonyl); the NMR spectrum ($CDCl_3$) showed bands at 7.35 δ (singlet, 5H, aromatic H), 3.28 δ (singlet, 6H, two $N-CH_3$), 2.82 δ (multiplet, 4H, two $N-CH_2-$), and 1.82 δ (multiplet, 4H, two $C-CH_2-$); the mass spectrum gave the expected molecular ion at m/e 301. The exact mass determination was calculated as 301.1426 and found as 301.1464.

Anal. Calculated for $C_{16}H_{19}N_3O_3$: C, 63.77; H, 6.36; N, 13.94. Found: C, 63.62; H, 6.39; N, 13.86.

Synthesis of 1,3-Dimethyl-5-phenyl-5-[N-(piperidino)]-barbituric Acid

A solution of 3.60 g (0.012 mole) of 1,3-dimethyl-5-bromo-5-phenylbarbituric acid in 15 ml of benzene was placed in a 100 ml

round-bottomed flask equipped with a condenser and a calcium chloride tube. To this solution was added 1.96 g (0.024 mole) of piperidine dissolved in 10 ml of benzene. Evolution of heat was observed on mixing and a dense white precipitate was formed almost immediately. The resulting mixture was stirred at room temperature for an additional hour and then filtered. The white solid which was obtained was washed first with benzene then with ether to give 1.68 g of white crystals. m.p. 204-206°C. The IR spectrum of this solid did not show a carbonyl absorption and thus was not further investigated. The filtrate was evaporated in vacuo almost to dryness to give an oily residue containing a small amount of white solid. This residue was crystallized from ethanol-ether mixture to give a rather impure yellow solid which was further purified via recrystallization from 95 percent ethanol to give 2.71 g (74 percent yield) of white crystals with physical properties as follows: m.p. 120-121°C (lit. (47) m.p. 114-116°C); the IR spectrum showed a strong carbonyl absorption at 1670 cm^{-1}; the NMR spectrum ($CDCl_3$) gave absorptions at 7.37 δ (singlet, 5H, aromatic H), 3.30 δ (singlet, 6H, two N-CH_3), 2.62 δ (multiplet, 4H, two N-CH_2-), and 1.4-1.8 δ (complex, 6H, -CH_2-CH_2-CH_2-). The mass spectrum showed a molecular ion at m/e 315.

Anal. Calculated for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71; N, 13.32. Found: C, 64.57; H, 6.74; N, 13.22.

Synthesis of 1,3-Dimethyl-5-phenyl-5-[N-(morpholino)]-barbituric Acid

To a solution of 3.00 g (0.0096 mole) of 1,3-dimethyl-5-bromo-5-phenylbarbituric acid in 25 ml of methanol was added with stirring 1.67 g (0.0192 mole) of morpholine. The solution turned slightly

yellow, but no precipitate was observed. The reaction mixture was then heated at reflux for one hour after which when cooled, a dense white precipitate formed. This mixture was filtered, and the solid obtained was washed with cold methanol and then with ether and dried to give 1.86 g of white crystals. In order to obtain additional product, the filtrate was concentrated on a rotatory evaporator until only about 5 ml was left to give, upon cooling, an additional 0.67 g of white crystals. The two portions of crude product were combined and recrystallized from methanol to give 2.15 g (71 percent yield) of white needles, m.p. 172.5-173.5°C. An analytical sample was prepared by a second recrystallization from the same solvent and drying overnight in an Abderhalden drying pistol under refluxing benzene at 1 mm pressure. The IR spectrum showed carbonyl absorptions at 1760 and 1680 cm^{-1} (strong). The NMR spectrum ($CDCl_3$) gave absorptions at 7.37 δ (singlet, 5H, aromatic H), 3.70 δ (triplet, 4H, two O-CH_2-), 3.30 δ (singlet, 6H, two N-CH_3), and 2,70 δ (triplet, 4H, two N-CH_2-). The mass spectrum showed a molecular ion at 317.

Anal. Calculated for $C_{16}H_{19}N_3O_4$: C, 60.56; H, 6.03; N, 13.24.
Found: C, 60.45; H, 6.05; N, 13.15.

Synthesis of 1,3-Dimethyl-5-phenyl-[N-(4-methylpiperazino)]-barbituric Acid

N-Methylpiperazine (1.28 g, 0.0128 mole) was added to a solution of 2.00 g (0.0064 mole) of 1,3-dimethyl-5-bromo-5-phenylbarbituric acid in 10 ml of benzene with stirring. Heat was evolved and a white precipitate was formed almost immediately after the addition of the

base. The reaction mixture was stirred for 24 hours. The white solid formed was collected by filtration and was found not to be the desired product by IR and NMR. The filtrate was then evaporated to remove all the solvent in vacuo to give 2.7 g of yellow resin. The resin was dissolved in 40 ml of benzene and the solution was washed with two 50 ml portions of water and the organic layer was then dried over anhydrous magnesium sulfate. Evaporation of the benzene in vacuo gave 2.0 g (95 percent yield) of pale yellow oil which solidified upon standing in the air for about three days. Attempts to purify the crude product by recrystallization were not successful. However, by washing with cold 95 percent ethanol the impurities were removed and the resulting yellow solid was dried under vacuum at room temperature for 48 hours to give a pale yellow solid, m.p. 97-99°C. The IR spectrum showed an absorption at 1660 cm^{-1} (strong, carbonyl). The NMR spectrum ($CDCl_3$) showed bands at 7.33 δ (singlet, 5H, aromatic H), 3.27 δ (singlet, 6H, two CON-CH_3), 2.62 δ (multiplet, 4H, two N-CH_2), 2.50 δ (multiplet, 4H, two N-CH_2-), and 2,27 δ (singlet, 3H, N-CH_3). The mass spectrum showed the calculated molecular ion at m/e 330.

Anal. Calculated for $C_{17}H_{22}N_4O_3$: C, 61.80; H, 6.71; N, 16.96. Found: C, 61.06; H, 6.64; N, 16.17.

Synthesis of 1,3-Dimethyl-5-phenyl-5-[N-(N'-β-hydroxylethylpiperazino)]-barbituric Acid

A solution of 1.00 g (0.0032 mole) of 1,3-dimethyl-5-bromo-5-phenylbarbituric acid in 10 ml of absolute ethanol was placed in a 50 ml round-bottomed flask equipped with a condenser. To this solution

was added 0.84 g (0.0064 mole) of N-β-hydroxylethylpiperazine. No evolution of heat was observed but the solution turned yellow in color immediately. The reaction mixture was refluxed for two hours and then cooled to room temperature. Since no precipitate was visible, the solvent was removed on a rotatory evaporator to give 1.8 g of a yellow resin. Crystallization of this crude product in ethanol-water mixture with overnight standing gave white crystals which were recrystallized to give 0.72 g (62 percent) of white crystals, m.p. 137-138°C. The IR spectrum showed absorptions at 1750, 1660 cm^{-1} (strong, carbonyl) and 3460 cm^{-1}(medium, broad, -OH stretching). The NMR spectrum ($CDCl_3$) showed bands at 7.40 δ (singlet, 5H, aromatic H), 3.60 δ (triplet, 2H, $-CH_2-O$), 3.30 δ (singlet, 6H, two $-N-CH_3$), 2.90 δ (singlet, 1H, -OH), and 2.3-2.8 δ (complex, 10H, five $N-CH_2-$). The mass spectrum showed the molecular ion at m/e 360.

Anal. Calculated for $C_{18}H_{24}N_4O_4$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.84; H, 6.75; N, 15.62.

Synthesis of 1,3-Dimethyl-5-phenyl-5-[N-(ethylisonipecotato)]-barbituric Acid

To a solution of 2.00 g (0.0064 mole) of 1,3-dimethyl-5-bromo-5-phenylbarbituric acid in 20 ml of methanol was added 2.03 g (0.0128 mole) of ethyl isonipecotate. The solution turned yellow immediately but no evolution of heat was observed. The reaction mixture was then refluxed for one hour. When no precipitate was visible upon cooling, the solvent was removed on a rotatory evaporator to give a brown resin. No suitable solvent or solvent mixture for crystallization was

found at this stage, so the resin was dissolved in 20 ml of benzene and washed with 20 ml of water twice and dried. Removal of the solvent in vacuo gave 2.40 g of yellow oil which was found to contain the desired compound by NMR. Again no satisfactory solvent was found for crystallization so the crude product was distilled under reduced pressure to give 1.60 g (64 percent yield) of a viscous yellow oil, b.p. 220-228°C/1.5 mm. A portion of this distilled oil was able to be crystallized from an ether-hexane mixture and yielded a pale yellow solid. An analytical sample was obtained by recrystallization from the same solvent system and drying in an Abderhalden drying pistol overnight, m.p. 104-105°C. The IR spectrum showed absorption at 1660 cm^{-1} (strong, carbonyl). The NMR spectrum ($CDCl_3$) showed bands at 7.35 δ (singlet, 5H, aromatic H), 4.13 δ (quartet, 2H, $-\underline{CH_2}-CH_3$), 3.28 δ (singlet, 6H, two $N-CH_3$), 2.68 δ (multiplet, 4H, two $N-CH_2-$), 2.27 δ (multiplet, 1H, CO-CH-), 1.88 δ (multiplet, 4H, two $C-CH_2-$), and 1.23 δ (triplet, 3H, $-CH_2-\underline{CH_3}$). The mass spectrum showed the expected molecular ion at m/e 387.

Anal. Calculated for $C_{20}H_{25}N_3O_5$: C, 62.00; H, 6.50; N, 10.85. Found: C, 61.80; H, 6.57; N, 10.83.

Synthesis of 1,3-Dimethyl-5-phenyl-5-[N-(1,2,3,4-tetrahydroisoquinolino)]-barbituric Acid

In a 100 ml round-bottomed flask containing a solution of 3.00 g (0.0096 mole) of 1,3-dimethyl-5-bromo-5-phenylbarbituric acid in 25 ml of methanol was introduced 2.56 g (0.0192 mole) of 1,2,3,4-tetrahydroisoquinoline. No precipitate was obtained on mixing. The reaction

mixture was then heated at reflux for one hour. After cooling to room temperature, a dense white precipitate formed from the mixture. After collecting the solid by filtration, it was washed first with cold methanol and then with ether and dried; 2.33 g of white solid was obtained. The remaining filtrate was concentrated to about 10 ml whereupon an additional 0.52 g of crude solid was obtained. Recrystallization of the combined solids from methanol gave 2.44 g (70 percent yield) of a white silky solid, m.p. 161-162°C. The IR spectrum showed a strong carbonyl absorption at 1670 cm^{-1}. Its NMR spectrum ($CDCl_3$) gave absorptions at 7.43 δ (singlet, 5H, aromatic H), 6.8-7.3 δ (multiplet, 4H, aromatic H), 3.88 δ (singlet, 2H, $-N-CH_2-$), 3.33 δ (singlet, 6H, two $-N-CH_3$), and 2.93 δ (broad, singlet, 4H, $-\underline{CH_2}-\underline{CH_2}-N-$). The mass spectrum showed a molecular ion at m/e 363. Anal. Calculated for $C_{21}H_{21}N_3O_3$: C, 69.40; H, 5.82; N, 11.56. Found: C, 69.35; H, 5.86; N, 11.58.

Attempted Preparation of 1,3-Dimethyl-5-phenyl-5-[N-(2,2,6,6-tetramethylpiperidino)]-barbituric Acid

To a solution of 1.00 g (0.0032 mole) of 1,3-dimethyl-5-bromo-5-phenylbarbituric acid in 10 ml of methanol contained in a 50 ml round-bottomed flask was added 0.91 g (0.0064 mole) of 2,2,6,6-tetramethylpiperidine. The reaction mixture was heated at reflux for one hour and then cooled. Since only a small amount of precipitate was formed, the solution was concentrated to two-thirds of its original volume. The precipitate was collected by filtration and dried to give 0.74 g of white crystals, m.p. 134-136°C. Recrystallization of this

crude product from methanol afforded white prisms, m.p. 135-136°C. Instead of the addition product, this white crystal was identified as 1,3-dimethyl-5-methoxy-5-phenylbarbituric acid as evidenced to its NMR, and elemental analysis data. The NMR spectrum ($CDCl_3$) showed bands at 7.37 δ (singlet, 5H, aromatic H), 3.47 δ (singlet, 3H,-OCH_3), and 3.33 δ (singlet, 6H, two N-CH_3).

Anal. Calculated for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68. Found: C, 59.60; H, 5.41; N, 10.68.

The filtrate was evaporated to dryness in vacuo to give 0.82 g of white solid which was identified as the hydrobromide salt of 2,2,6,6-tetramethylpiperidine according to its NMR spectrum and also its property of sublimation.

This reaction was then carried out in an identical manner but with benzene as the solvent. It was found that no reaction proceeded at all, since 1,3-dimethyl-5-bromo-5-phenylbarbituric acid was recovered quantitatively.

CHAPTER III

DISCUSSION OF RESULTS

The basic reaction examined in this research was the nucleophilic substitution at the C-Br of bromobarbituric acid (Figure 5). Bromine was expelled as bromide ion, being replaced by the basic amine function. For the reactions studied here, two equivalents of amines were used in order to trap any hydrogen bromide generated in the reaction thus decreasing the possibility of hydrolytic cleavage of the adduct.

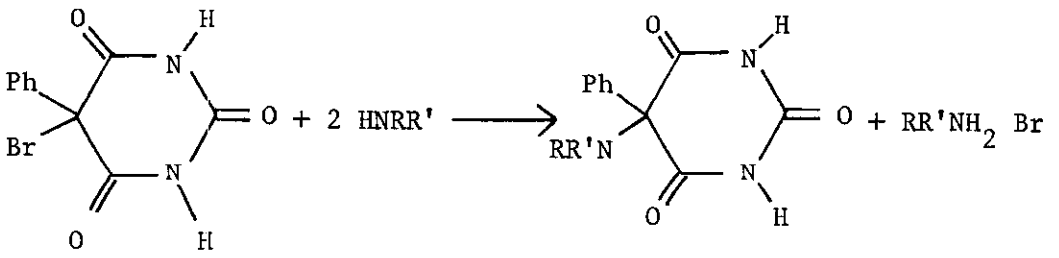


Figure 5. Nucleophilic Substitution of Bromobarbituric Acid

The starting materials, 5-bromo-5-phenylbarbituric acid and 1,3-dimethyl-5-bromo-5-phenylbarbituric acid, were synthesized in the general manner as reported by Walker.[31] Except for a few of the amines which were synthesized during the course of this study, most of

the amines were commercially available.

The reaction of phenothiazine with 5-bromo-5-phenylbarbituric acid was studied for the purposes of first investigating the nature of this reaction, and second, attempting the synthesis of the adduct which would have a potential synergistic effect on barbiturates. As expected from an arylamine, its weak nucleophilicity was detrimental to its participation in the nucleophilic attack on C-Br to yield the substitution product. In the case of phenothiazine, the presence of sulfur which could enable this compound to be oxidized more easily via formation of the sulfonium intermediates, apparently complicated the process. The reaction was run by mixing both the reagents in alcoholic solvents. The product obtained was invariably isolated as a deep colored solid which was found to be a mixture of unreacted phenothiazine and some unidentified substances. These substances are most likely an oxidized mixture of different degrees, similar to the reported reactions concerning the oxidation of phenothiazine and its derivatives. For example, the study of Shine and Mach[48] suggested the existence of phenothiazine cation radical and phenazothionium ion in acidic solutions. The existence of a radical component in the colored solutions obtained on treating phenothiazine with concentrated sulfuric acid was also detected by ESR.[49-52] When phenothiazine is dissolved in concentrated sulfuric acid, golden solutions are obtained which on standing become green. Here sulfuric acid acts as the oxidant which converts phenothiazine into S^{+}, this stage corresponding to the golden solutions; the ESR signal demonstrated that a radical is actually present. In a

slow reaction, S^+ is converted into the protonated phenazothionium cation, $[TH]^{2+}$ to which the green color is due (figure 6).

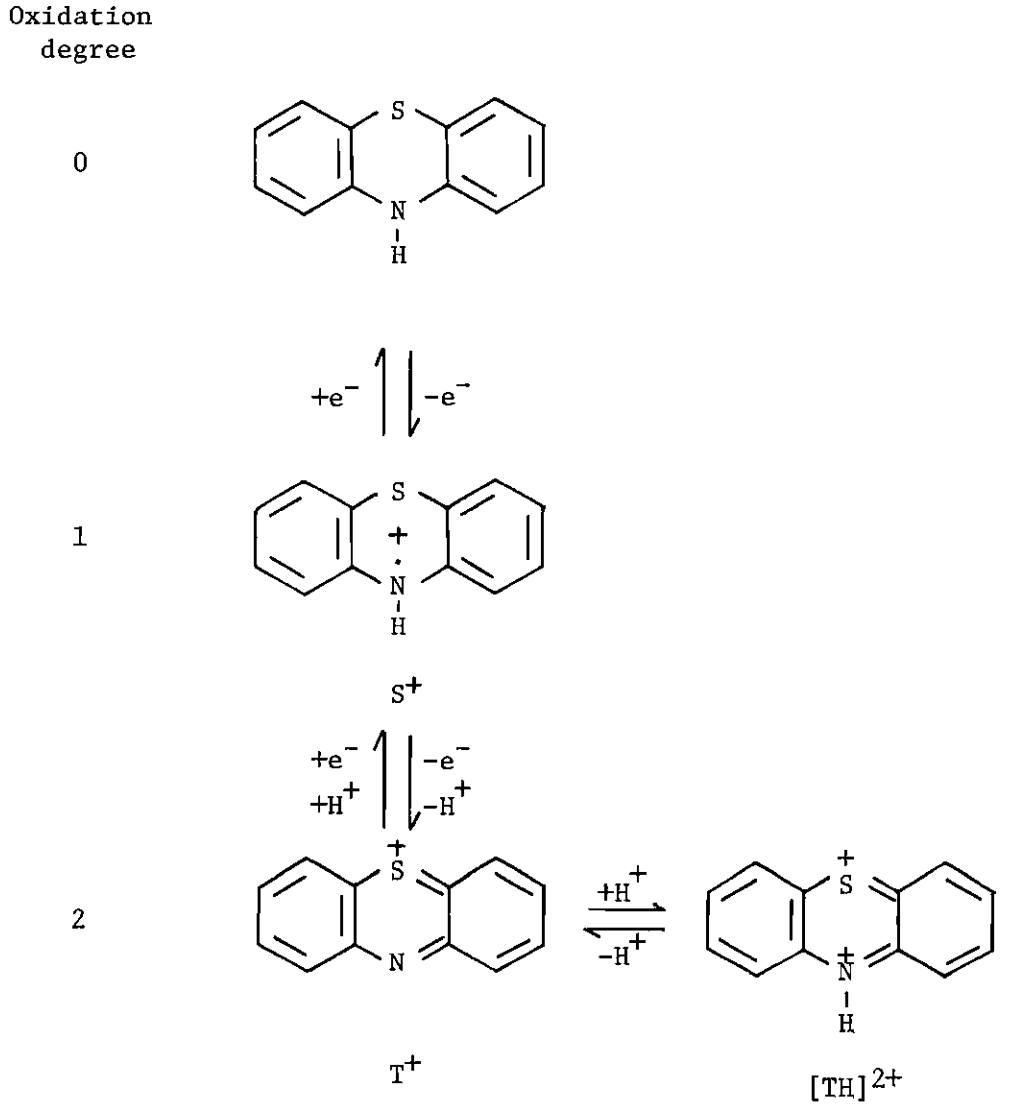
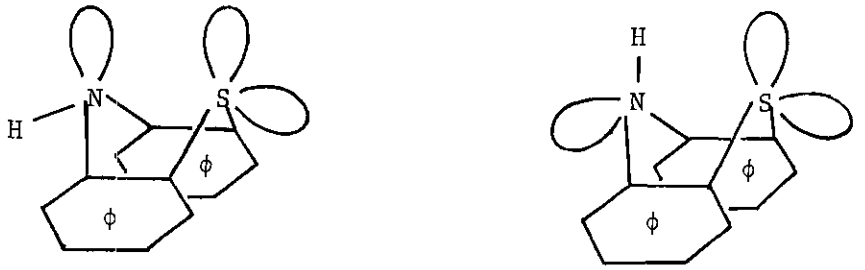


Figure 6. Oxidation Degrees of Phenothiazine

A further possibility was that reaction could have been suppressed by steric effects due to the bulkiness of the phenothiazine. The configuration of the molecule is still not clear. No agreement exists whether the phenothiazine molecule is planar or nearly so, or whether it is folded along the axis passing through the heteroatoms. It has been stated by Wood et al.,[53] on the basis of crystallographic studies, that the molecule could be planar. Subsequently, Leonard and Sutton[54] interpreted dipole moment measurements as evidence for the existence of a dihedral angle of 145 $\pm$ 5° between the planes of the benzene rings of phenothiazine.

In a theoretical approach to this question, Malrieu and Pullman[55] also pointed out that these two extreme types of configuration should be taken into account in the cases of phenothiazine, namely the planar configuration and the "tetragonal folded" one. In the latter, the nitrogen and sulfur are in the sp^3 hybridization state and the planes containing the benzene rings are folded along the axis passing through N and S. The hydrogen atom attached to nitrogen can now adopt two distinct configuration, termed "H-intra" - with the hydrogen pointing inside - and "H-extra" - when the hydrogen is directed outside with respect to the dihedral angle (Figure 7). 10-Unsubstituted phenothiazine favor the configuration with benzene π system, thus adopting the more advantageous configuration "H-intra" as suggested by Malrieu and Pullman.[55] The presence of a substituent at position 10 renders the configuration "H-intra" improbable for steric reasons, it would be too bulky on the axial position, thus decreases the reactivity toward

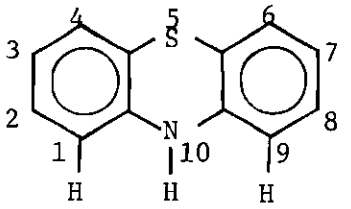
electrophilic reagents. From the favored "H-intra" configuration



H-intra H-extra

Figure 7. "Tetragonal Folded" Configurations of Phenothiazine

for phenothiazine, it would seem that possible steric hindrance may not be so important. On the other hand the other possible configuration - the planar structure - could possibly show some degree of hindrance at the 10 position due to the hydrogens at 1 and 9 positions.



The synthesis of a chain derivative was thus planned to investigate the possible steric effect. The related model compound, 10-(3-methylaminopropyl)phenothiazine, is similar to the known compound, 10-(2-dimethylamino-1-propyl)phenothiazine which has been reported to have antihistaminic activity.[56,57] In the synthesis of this

compound, an intermediate compound was also isolated and characterized. The intermediate, 10-(3-chloropropyl)phenothiazine, was obtained from phenothiazine either by reaction with 1-bromo-3-chloropropane in basic solution or by treatment with γ-chloropropyl p-toluenesulfonate and n-butyl lithium. The latter method gave better yield. Formation of the desired product, 10-(3-methylaminopropyl)phenothiazine, was achieved by treating the chloro intermediate with excess methylamine. The reactions of the amino phenothiazine with 5-bromo-5-phenylbarbituric acid and with 5-bromo-5-ethylbarbituric acid were attempted and each gave the same deep colored mixture as had phenothiazine. No alkylated product resulted. It is very likely that the similar oxidation process had occurred. No desired substitution product was found.

Another approach to react phenothiazine with diethyl bromophenylmalonate to give an adduct which could condense with urea to form the barbiturate was also found fruitless (Figure 8). The first reaction never gave the desired adduct. The similar deep colored mixture was again observed.

At this point, it appeared that the steric effect was not the main factor responsible for the failure of the reaction, but rather the presence of a sulfur atom which rendered the molecule susceptible to oxidation. In order to lend more support to this argument, a similar compound without the sulfur atom, carbazole, was studied.

The results showed that no reaction occurred between carbazole and either 5-bromo-5-phenylbarbituric acid or diethyl bromophenylmalonate. The starting materials were recovered quantitatively, and

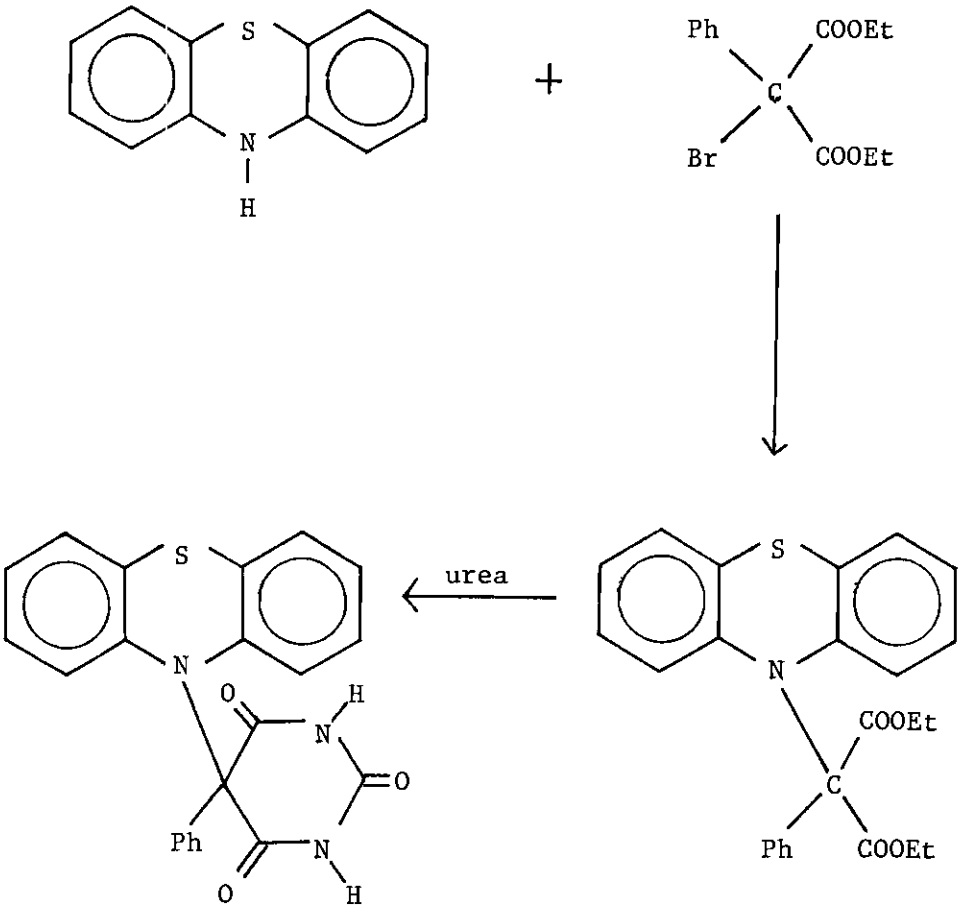


Figure 8. Proposed New Approach of Synthesizing Phenothiazine - Barbituric Acid Adduct

the complication of side reaction such as formation of deep colored mixtures was not observed. This suggested that carbazole is a typical arylamine and may be too weak a nucleophile to replace Br from the barbiturate or the malonate and permit the substitution reaction. It is also possible that the N atom is sterically hindered

in carbazole and thus unable to effect bromine displacement.

A preparation of an aminopropyl derivative of carbazole, similar to the method for the introduction of this side chain onto phenothiazine, gave the desired amine, 9-(γ-methylaminopropyl)carbazole. This amine was then successfully reacted with 5-bromo-5-phenylbarbituric acid to form the substitution product. Two factors at least may be contributing to the success of this reaction: this amine is an aliphatic secondary amine which is a stronger base than the aromatic types studied above and there is less steric hindrance than in carbazole itself. Too, the fact that this compound did react whereas the similar phenothiazine derivative did not react would support a belief that oxidation was a contributing factor in the phenothiazine case.

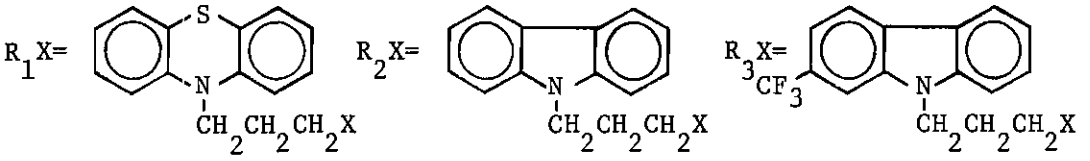
The intermediate, γ-chloropropylcarbazole and 9-γ-methylaminopropylcarbazole, both were new compounds and were also isolated in pure form. γ-Chloropropylcarbazole was obtained either by treating carbazole with n-butyl lithium and γ-chloropropyl p-toluenesulfonate or by heating carbazole with γ-chloropropyl p-toluenesulfonate and sodium hydroxide in acetone. The former procedure gave the better yield. γ-Chloropropylcarbazole was obtained as a colorless liquid upon distillation but gradually turned slightly yellow upon standing. The amine, 9-γ-methylaminopropylcarbazole, was in turn obtained by treating γ-chloropropylcarbazole with methylamine and was a very viscous liquid. Purification was achieved by converting this amine to its hydrogen chloride salt which was readily purified by crystallization techniques. Then from the pure salt, the amine was isolated by neutralization as a

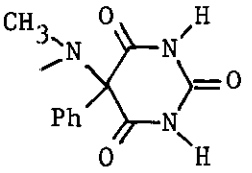
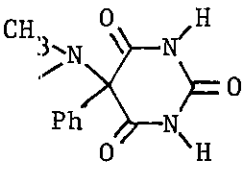
pale yellow liquid. The final product, 5-phenyl-5-[N-(3-carbazolyl-propylmethylamino)]-barbituric acid, was obtained in reasonable yield (66 percent) by treating the pure amine, 9-γ-methylaminopropylcarbazole, with 5-bromo-5-phenylbarbituric acid. The crystalline solid exhibited the expected spectroscopic properties and was characterized completely. This successful attempt strongly suggested the point that the failure of phenothiazine series is considerably due to the influences of sulfur atom in the ring. The success of carbazole series also suggested a reasonable likelihood that the same approach when applied to its derivatives might have a good chance of being successful. The trifluoromethyl derivative, 2-trifluoromethylcarbazole, was prepared from m-trifluorotoluidine via the Fisher-indole synthesis in a rather low yield (13 percent) as reported.[44] Similar reactions as in the carbazole series gave two intermediates, 9-γ-chloropropyl-2-trifluoromethyl-carbazole and 9-γ-methylaminopropyl-2-trifluoromethylcarbazole, which were formed to be new compounds and were also isolated. The final product, 5-phenyl-5-[N-(2'-trifluoromethyl-3-carbazolylpropylmethyl-amino)]-barbituric acid was obtained in 26 percent yield and was characterized.

A summary of the new compounds synthesized in phenothiazine and carbazole series appears in Table 1.

The results of indole series were not quite as expected. The reactions of indole, 2-phenylindole, and 3-methylindole with 5-bromo-5-phenylbarbituric acid were found to give only one isolable product, 5-phenylbarbituric acid, which was obtained in quantitative yield.

Table 1. New Derivatives of Phenothiazine and Carbazole



R	X	
R_1	-Cl	solid, m.p. 66-67°C
R_1	$-NHCH_3$	viscous liquid, b.p. >250°C/1.5 mm
R_2	-Cl	liquid, b.p. 158-160°C/0.1 mm
R_2	$-NHCH_3$	viscous liquid
R_2		solid, m.p.246-247°C
R_3	-Cl	solid, m.p. 65-66°C
R_3	$-NHCH_3$	viscous liquid
R_3		solid, m.p. 274-275°C

The remaining part of each reaction mixture contained the other starting material and some form of bromine-containing product which was not pursued further. The possible course of this reaction is depicted in Figure 9. The cleavage of 5-bromo-5-phenylbarbituric acid to give a bromonium ion and a 5-phenylbarbiturate ion. The barbituric acid anion could abstract a hydrogen ion from the solvent or the reaction mixture to give the barbituric acid. The addition of this bromonium ion to

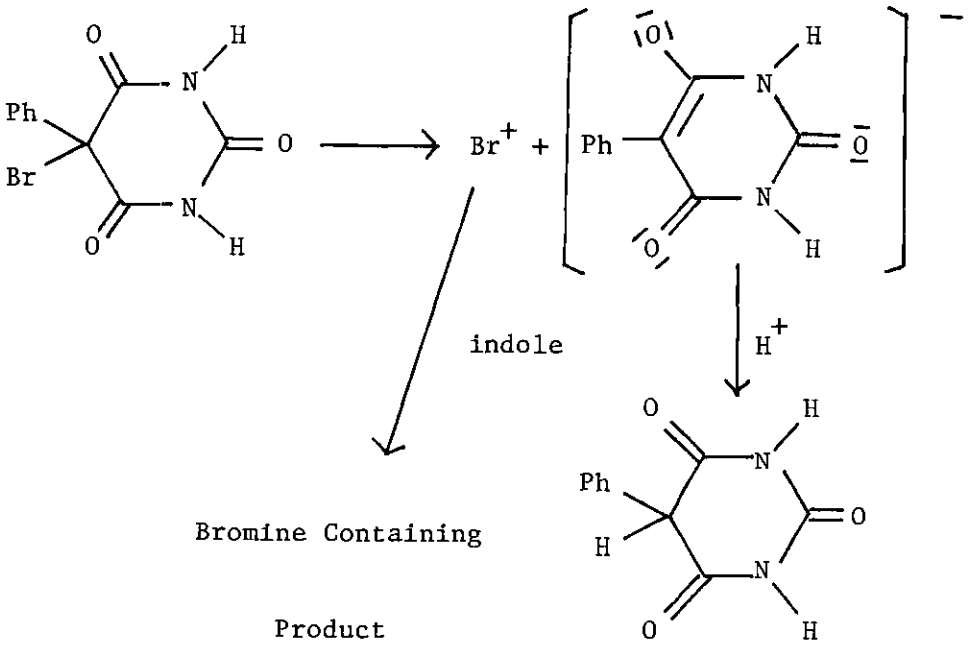


Figure 9. Possible Reaction Pathway of Indole and 5-Bromo-5-phenylbarbituric Acid

indole would give some form of bromine containing compound. The position of this bromine, most likely would be on the 3 or perhaps the N position of the indole ring. This was supported by the study of the bromination of N-acylindole in carbon disulfide which after hydrolysis gave 3-bromoindole.[58] N-Bromosuccinimide was also reported to be employed as the brominating agent in converting 1-benzoylindole into 1-benzoyl-3-bromoindole.[59] (Figure 10)

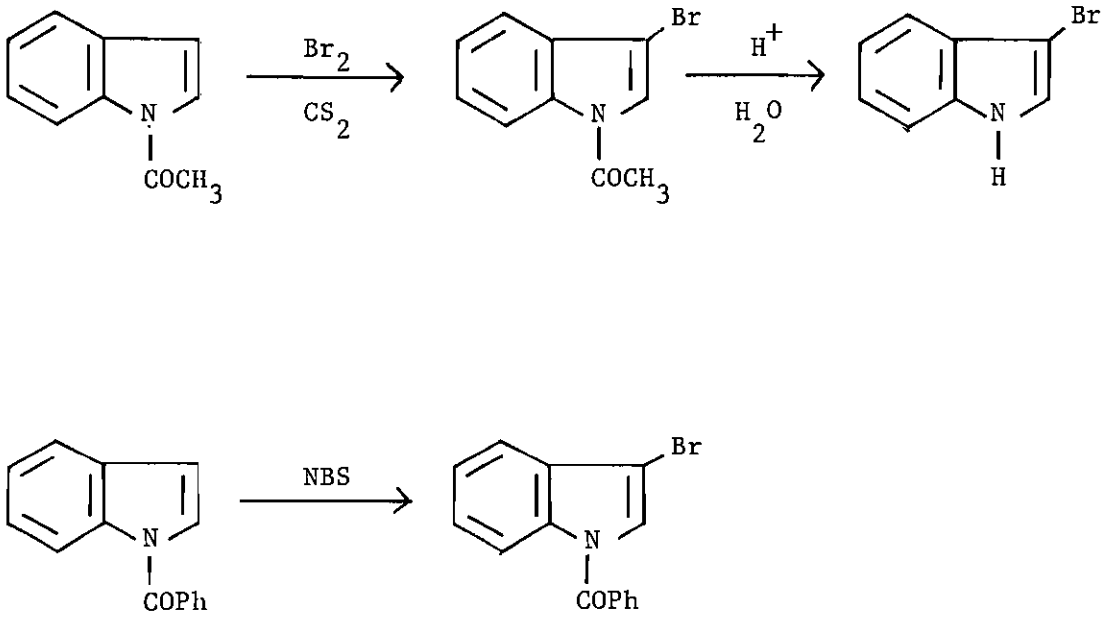


Figure 10. Typical Bromination Reactions of N-Acetylindole

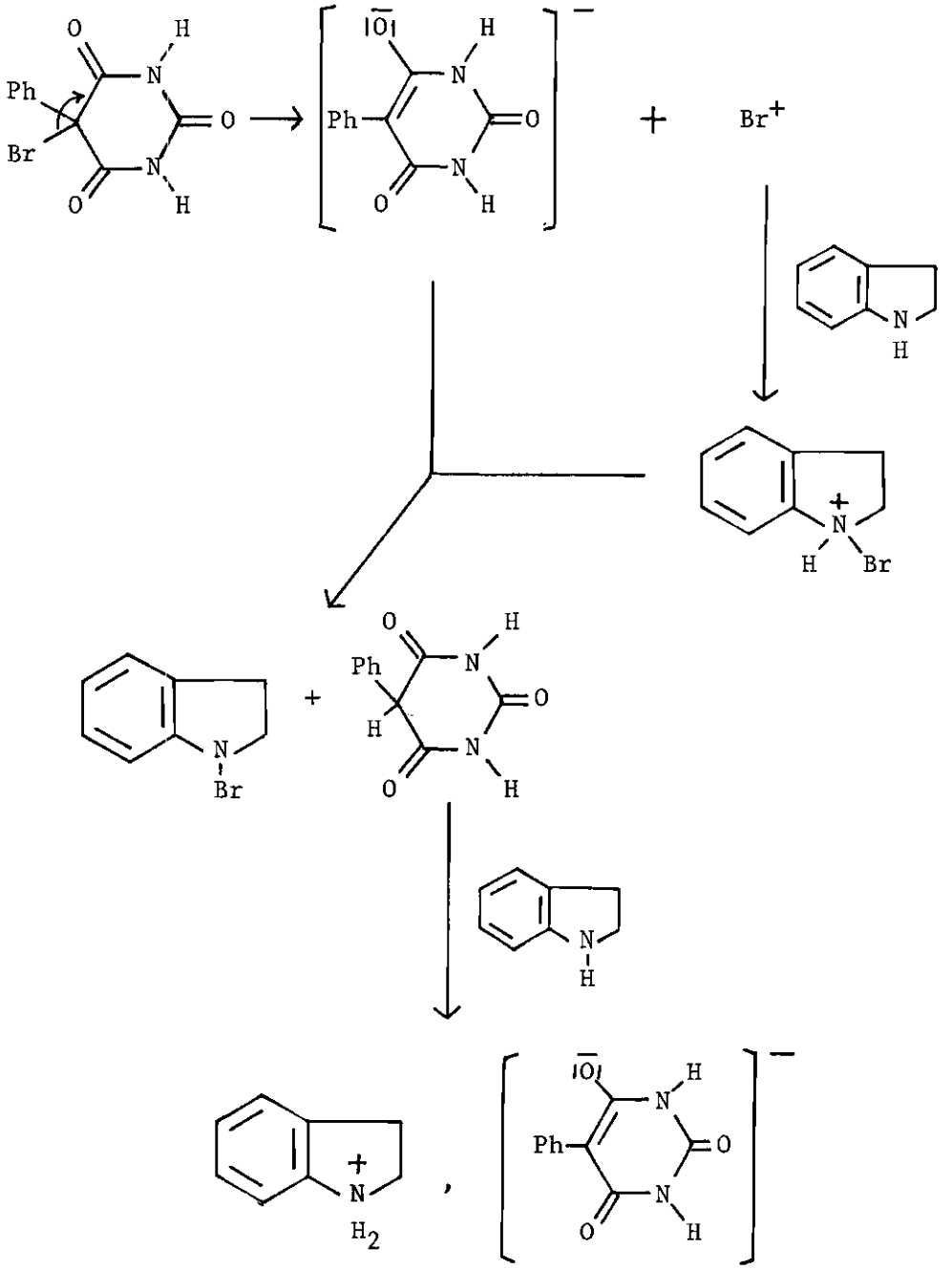
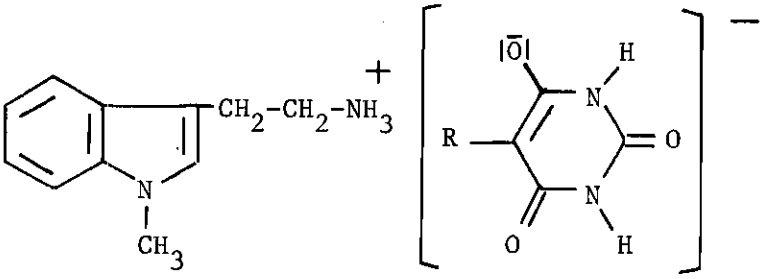


Figure 11. Possible Mechanism of Salt Formation

Further support of this possible mechanism was obtained by the reaction of indoline with 5-bromo-5-phenylbarbituric acid. A well defined crystalline solid was isolated in high yield and it was found to be the indoline salt of barbituric acid. Without the double bond, the indoline is a stronger base than indole and could associate with the bromonium ion to form a bromoammonium ion intermediate which could transfer its hydrogen ion to either the barbituric acid anion or another indoline molecule to complete the salt formation (Figure 11).

The syntheses of 1-(γ-chloropropyl)indole and 1-(γ-methylaminopropyl)indole were successfully studied. Both of these new compounds were isolated and characterized. The mixing of 1-(γ-methylaminopropyl)indole with 5-bromo-5-phenylbarbituric acid again gave quantitative yields of 5-phenylbarbituric acid.

The reaction of 1-methyltryptamine with 5-bromo-5-phenylbarbituric acid was also studied. In this particular case the primary amine formed the corresponding amine barbiturate salt.



R = Ph, Et.

A similar result was also obtained when 1-methyltryptamine was reacted with 5-bromo-5-ethylbarbituric acid.

The reactions of cyclopropylamine and trans-2-phenylcyclopropylamine with 5-bromo-5-phenylbarbituric acid gave entirely different results. Cyclopropylamine gave the crystalline substitution product, 5-phenyl-5-[N-(cyclopropylamino)]-barbituric acid, although in low yield (23 percent), whereas the trans-2-phenylcyclopropylamine gave only a salt as product (Figure 12). The salt formation of trans-2-phenylcyclopropylamine was also proved by mixing the free amine with 5-phenylbarbituric acid and obtaining the identical salt quantitatively.

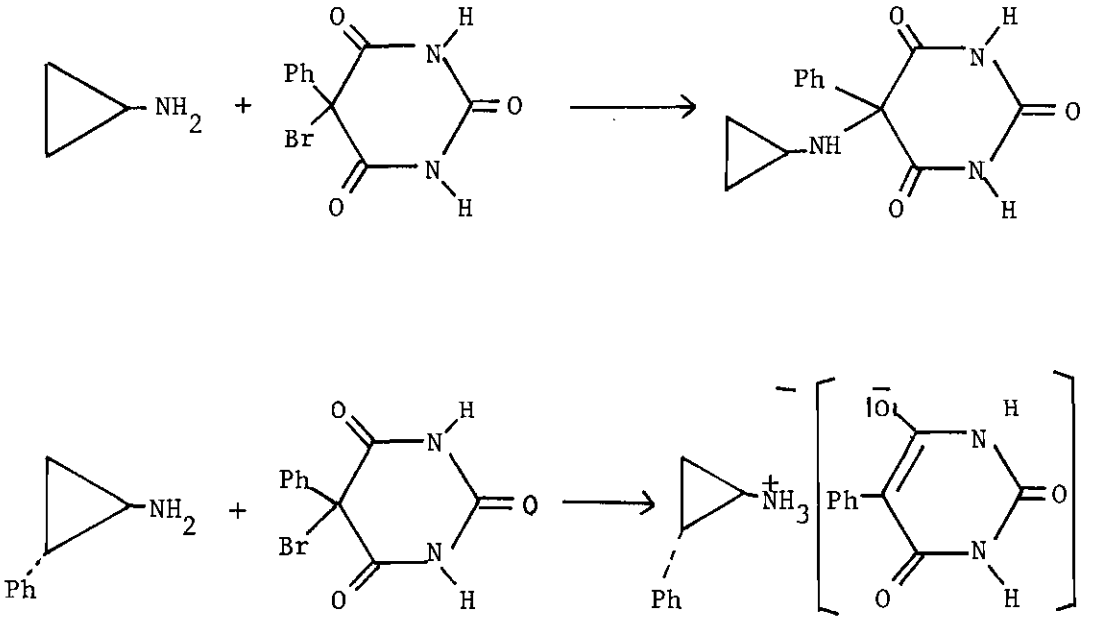


Figure 12. Reaction of Cyclopropylamines with 5-Bromo-5-phenylbarbituric Acid

The exact reason why one amine gives rise the substitution product and the other simply forms a salt is not quite clear at this moment. No structural relationship was able to be suggested in the study of 5-butylbarbituric acid derivatives by Wheeler[30] and the study of 5-phenylbarbituric acid derivatives by Walker.[31]

The final portion of this work consisted of the study of some amine reactions with 1,3-dimethyl-barbituric acid derivatives. The advantage of 1,3-dimethyl substituted barbituric acid over the non N-methylated acid is that in the former only the C-5 position has hydrogen atoms available for keto-enol isomerization; the ring system, therefore could not become aromatic. Hence, the N,N-dimethyl barbituric acid would be less acidic and the salt formation process would then be reduced or perhaps not even be observed (Figure 13).

The starting material, 1,3-dimethyl-5-bromo-5-phenylbarbituric acid, was prepared as reported by Voorhes and Skinner.[37] Five primary amines and eight secondary amines were tried and all but one were successfully reacted to form the predicted substitution products. These products are all new compounds and required complete characterization. Their physical properties are summarized in Table 2.

The only compound which did not give the desired substitution product from the reaction was 2,2,6,6-tetramethylpiperidine. Because of the steric hindrance around the amine group, the nucleophilic substitution reaction would seem unlikely. This compound was selected for the purpose of determining if a salt of the amine and the barbituric acid would even form. The reaction was run in methanol

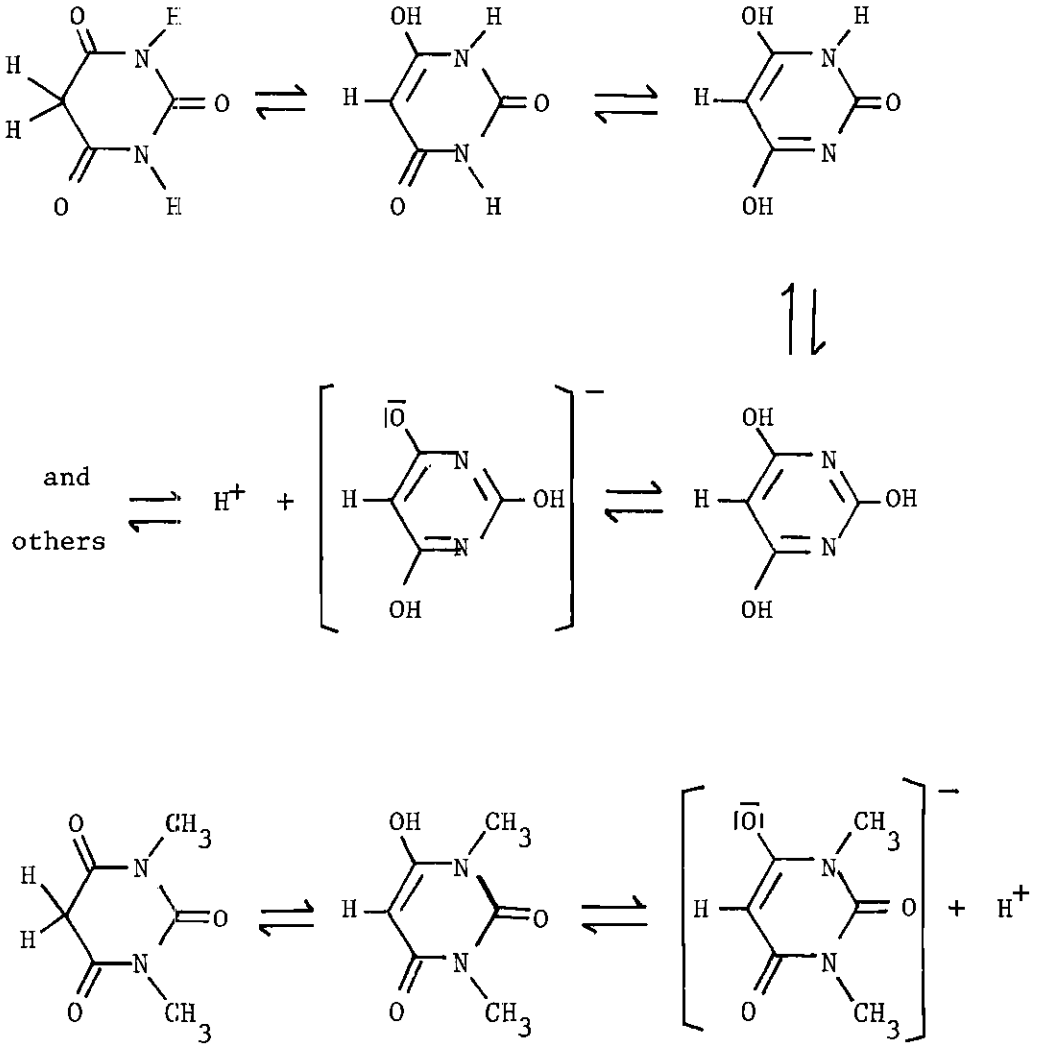
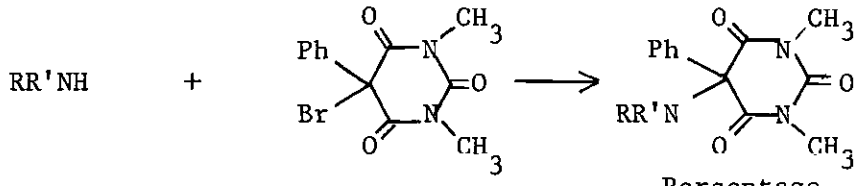


Figure 13. Tautomeric Structures of the Two Barbituric Acids

Table 2. New Derivatives of 1,3-Dimethyl-5-phenylbarbituric Acid



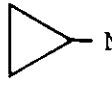
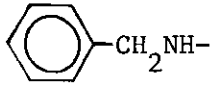
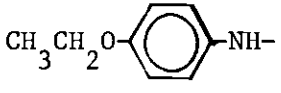
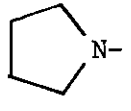
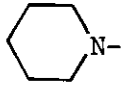
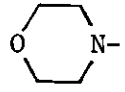
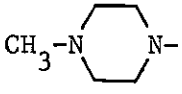
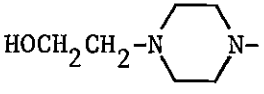
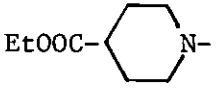
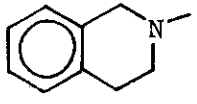
RR'N-	M.P. °C	Percentage Calculated C	H	N	Percentage Found C	H	N
$CH_3CH_2CH_2NH$-	88-89°	62.27	6.62	14.52	62.18	6.84	14.55
	89-90°	62.70	5.96	14.62	62.71	5.87	14.64
CH_3O-CH_2CH_2NH-	55-56°	59.00	6.27	13.76	59.02	6.27	13.77
	165-166°	67.64	5.68	12.46	67.68	5.68	12.50
	203-204°	65.38	5.76	11.44	65.21	5.82	11.40
	liquid, 260-280°/0.5 mm (bath temp.)	63.77	6.36	13.94	63.62	6.39	13.89

Table 2. Con't

RR'N-	M.P. °C	Percentage Calculated C	H	N	Percentage Found C	H	N
	120-121°	64.74	6.71	13.32	64.57	6.74	13.22
	172.5-173.5	60.56	6.03	13.24	60.45	6.05	13.15
	97-99°	61.80	6.71	16.96	61.06	6.64	16.17
	137-138°	59.98	6.71	15.55	59.84	6.75	15.62
	104-105°	62.00	6.50	10.85	61.80	6.57	10.83
	161-162°	69.40	5.82	11.56	69.35	5.86	11.58

first. After one hour of refluxing, a crystalline solid was precipitated and collected by filtration. Its NMR spectrum gave three sharp singlets at 3.33 δ (6H), 3.47 δ (3H), and 7.37 δ (5H) which indicated a structure of 1,3-dimethyl-5-methoxy-5-phenylbarbituric acid. The later elemental analysis proved this composition. From the filtrate, another crystalline solid was isolated which was easily found to be the hydrobromide salt of the amine. What occurred here was that the amine was so hindered it was unable to approach closely to the 5-carbon. Instead, nucleophilic attack by the methanol solvent did occur during the reaction time. Repeating this reaction in a non-polar system (benzene) there was recovered in nearly quantitative amounts of the starting materials. This could tend to lend support to the postulate that steric factors were the significant reasons for the lack of substitution of this amine for the bromine of the 5-bromo barbituric acid.

CHAPTER IV

CONCLUSIONS

Attempts to prepare 5-phenylbarbituric acid derivatives from phenothiazine and 10-(3-methylaminopropyl)phenothiazine in a plan to study the possible synergistic effect toward barbituric acid were unsuccessful, most likely due to side oxidation reactions involving the sulfur atom of the phenothiazine ring. The existence of sulfur which could enable the molecule to be oxidized more easily via formation of the sulfonium intermediates, complicated the process. While phenothiazine would exhibit steric hindrance around the 10 position (nitrogen) from its hydrogens at 1 and 9 positions, which could account for the unsuccessful reaction, its derivative, 10-(3-methylaminopropyl)-phenothiazine, which would have little or no steric hindrance around its active nitrogen of the propyl chain, showed the same lack of reaction with 5-bromo-5-phenylbarbituric acid. This strongly suggested that the steric factor was not the only determining factor in this case. The similarly sterically hindered N in carbazole also failed to react. At least in this case steric factors could have been of importance.

9-(γ-Methylaminopropyl)carbazole, which was synthesized in two steps from carbazole and provided essentially the same carbon skeleton as 10-(3-methylaminopropyl)phenothiazine but without sulfur atom present in the system, was reacted successfully with 5-bromo-5-phenyl-

barbituric acid to give the amine adduct derivative.

Indole compounds and cyclopropylamines were also reacted with 5-bromo-5-phenylbarbituric acid. Inconsistent results were observed and no structural relationships could be discerned that would explain the result. Most of the indole compounds gave 5-phenylbarbituric acid as the only isolated product while 1-methyltryptamine gave an ammonium barbiturate salt. A mechanism which involves the formation of a barbiturate ion and a bromonium ion was proposed to explain these results. The barbiturate ion could pick up one hydrogen to form barbituric acid, which would account for the only isolable product, while the bromonium ion could associate with the amines to form most of the unidentifiable mixtures.

Reactions of various amines with 1,3-dimethyl-5-bromo-5-phenyl-barbituric acid afforded excellent yields of amine adducts of 1,3-dimethylbarbiturate. The 1,3-dimethylbarbiturates were known to have similar physiological activity as their parent barbiturates. The lack of complications in this series of reactions such as salt formation in these instances was attributed to the elimination of amido-imidol tautomerism in the parent barbituric acid.

CHAPTER V

RECOMMENDATION

It is believed that additional reactions with 5-bromo-5-phenylbarbituric acid should be studied in order to attempt to find an explanation of the fact that certain amines may form salts in one instance but other similar amines form adducts in another. Amines could be selected and analyzed according to their basicities orders, such as aryl amines to alkyl amines, and their steric hindrance orders such as dimethylamines, diisopropylamine and ditertiarybutylamine. Careful analysis of these reactions should be profitable.

Reactions of 1,3-dimethyl-5-bromo-5-phenylbarbituric acid with various amines were found very successful. It might be worthwhile to extend this reaction to a number of the amines which were unsuccessfully reacted with 5-bromo-5-phenylbarbituric acid. Among these amines might be the indole compounds and trans-2-phenylcyclopropylamine.

It would be of interest to obtain data regarding the physiological activities of the new potential therapeutic agents which were prepared during the course of this investigation.

APPENDIX A

INFRARED SPECTRA

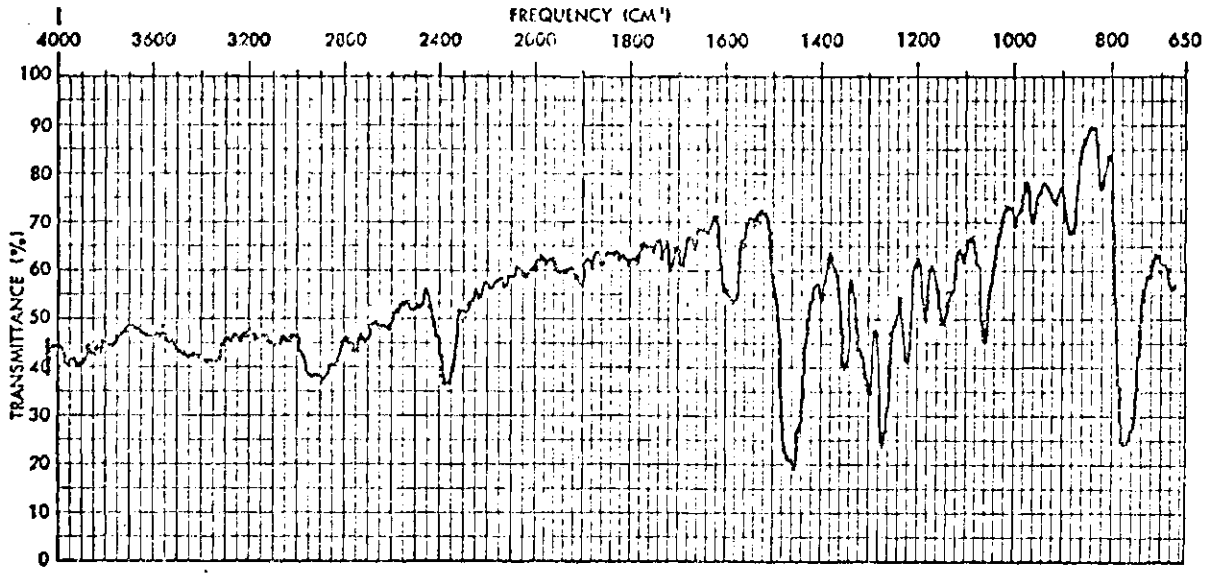


Figure 14. Infrared Spectrum of 10-(3-Chloropropyl)phenothiazine.

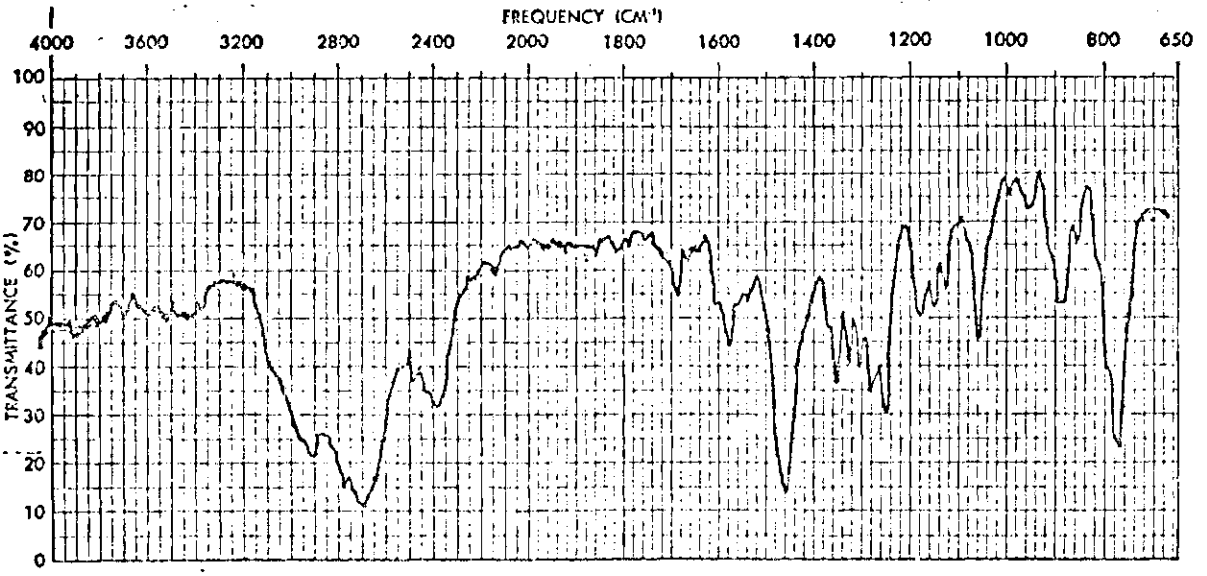


Figure 15. Infrared Spectrum of 10-(3-Methylaminopropyl)-phenothiazine.

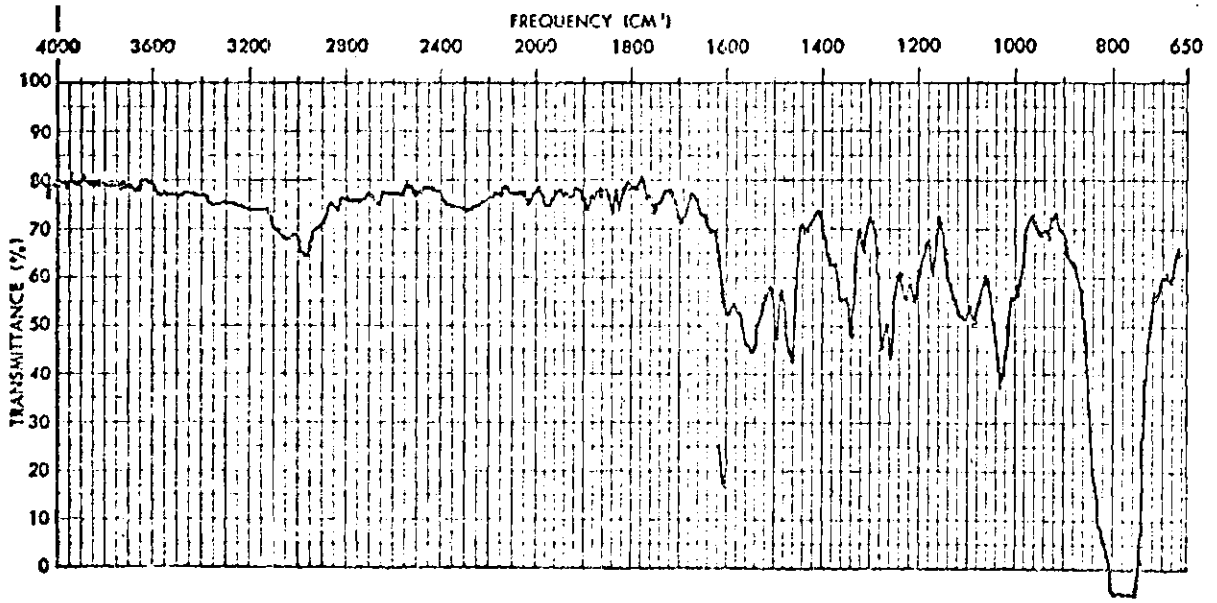


Figure 16. Infrared Spectrum of 9-(γ-Chloropropyl)carbazole.

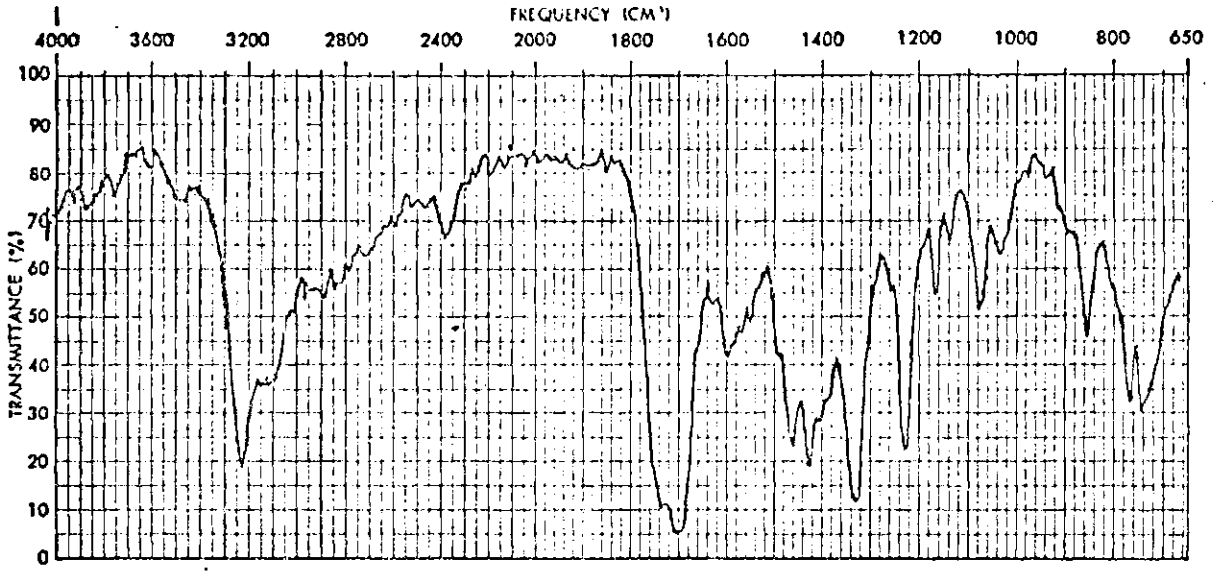


Figure 17. Infrared Spectrum of 5-Phenyl-5-[N-(3-carbazolylpropyl-methylamino)]-barbituric Acid.

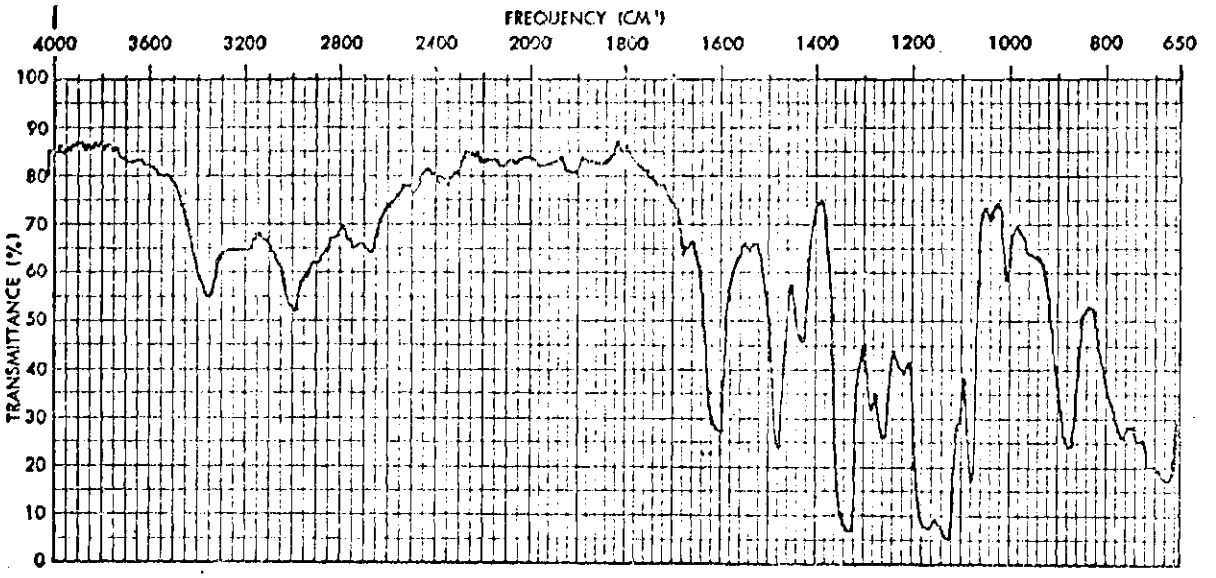


Figure 18. Infrared Spectrum of m-Trifluoromethylphenylhydrazine

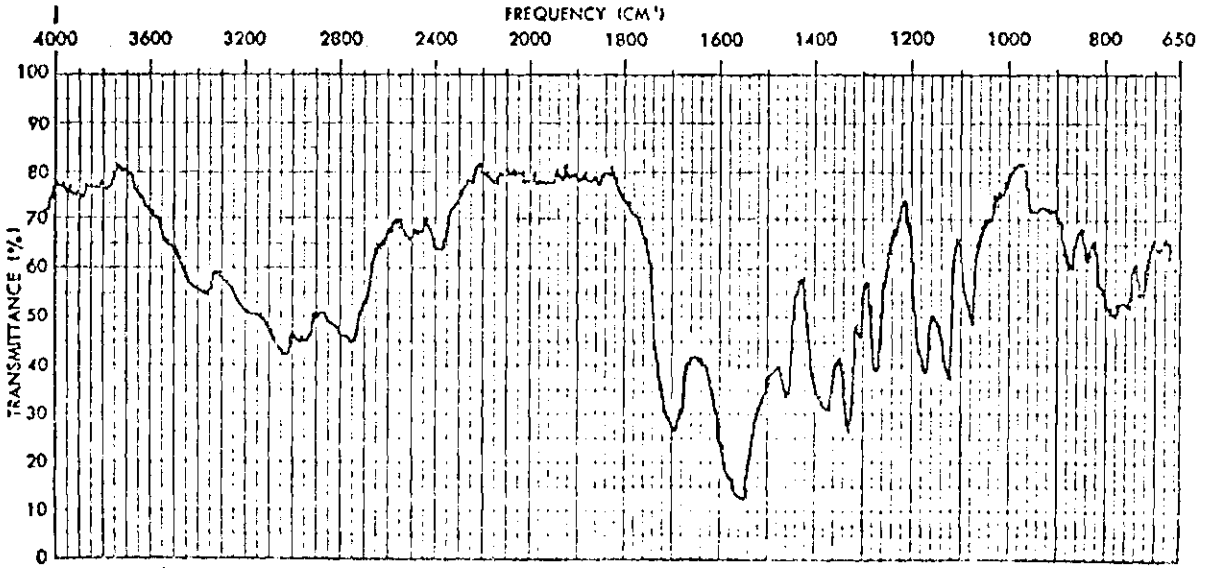


Figure 19. Infrared Spectrum of 5-Phenyl-5-[N-(2'-trifluoro-methyl-3-carbazolylpropylmethylamino)]-barbituric Acid

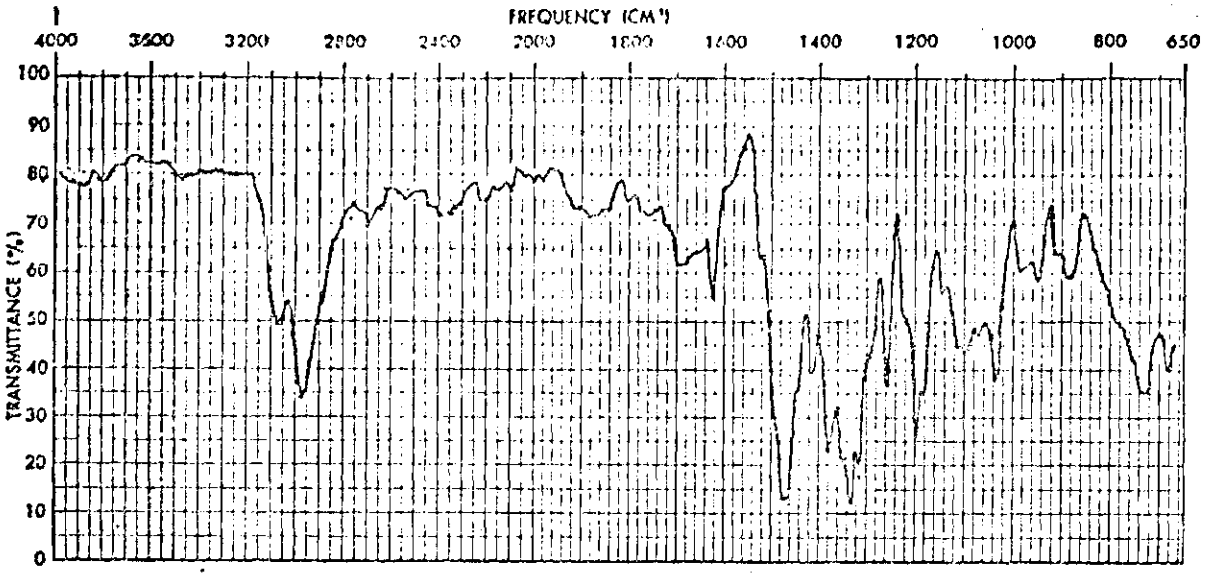


Figure 20. Infrared Spectrum of 1-(γ-Chloropropyl)indole

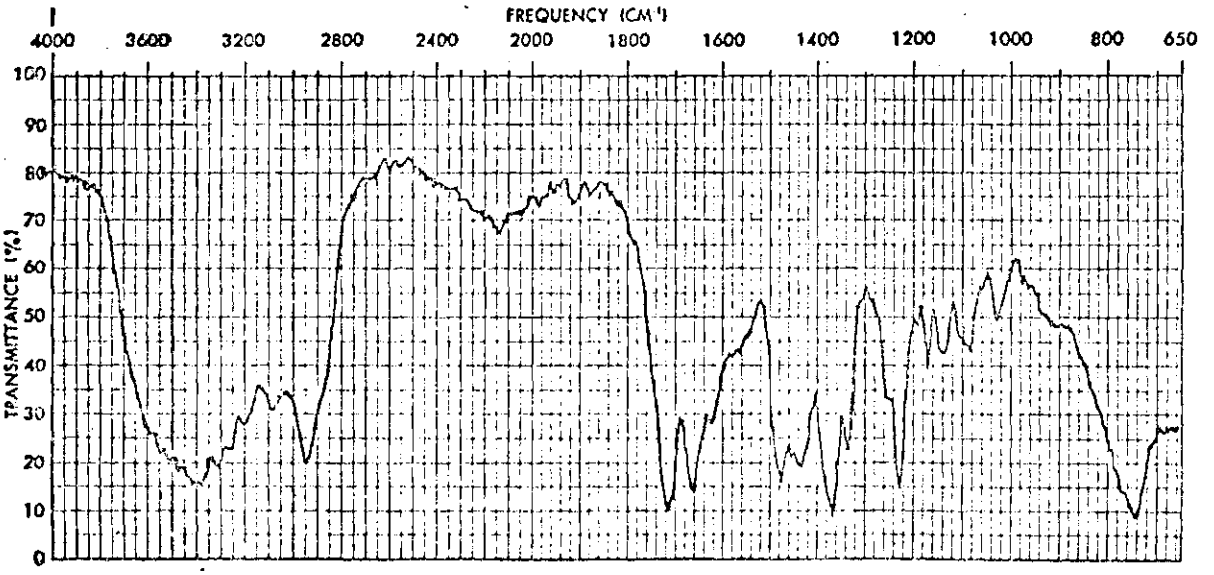


Figure 21. Infrared Spectrum of 1-Methyltryptamine

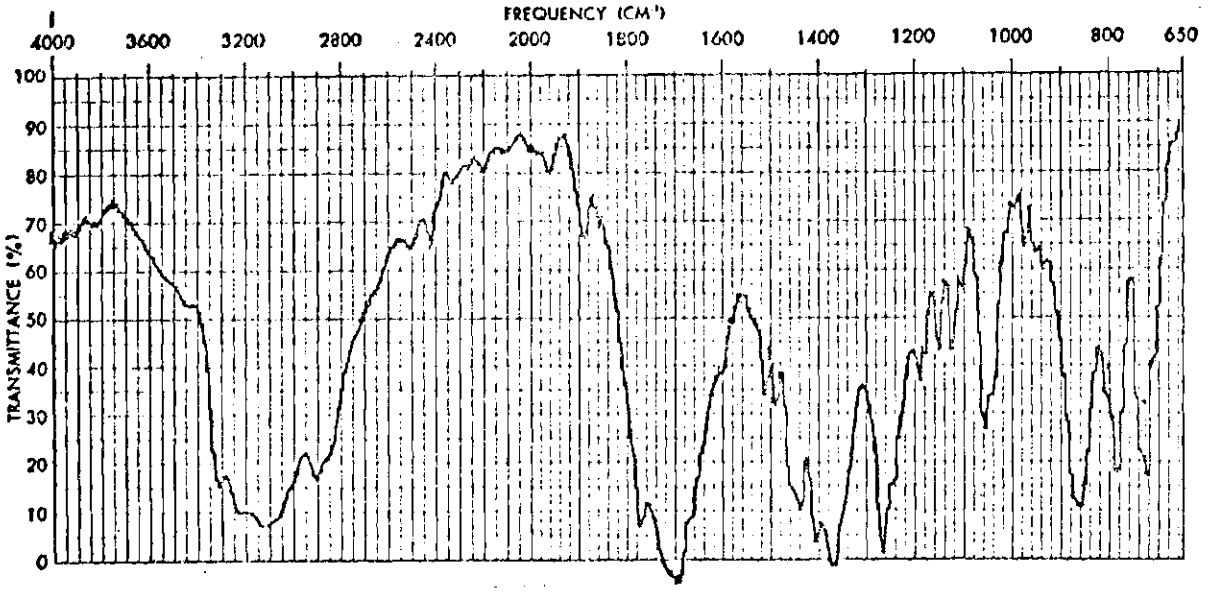


Figure 22. Infrared Spectrum of 5-Phenyl-5-[N-(cyclopropyl-amino)]-barbituric Acid

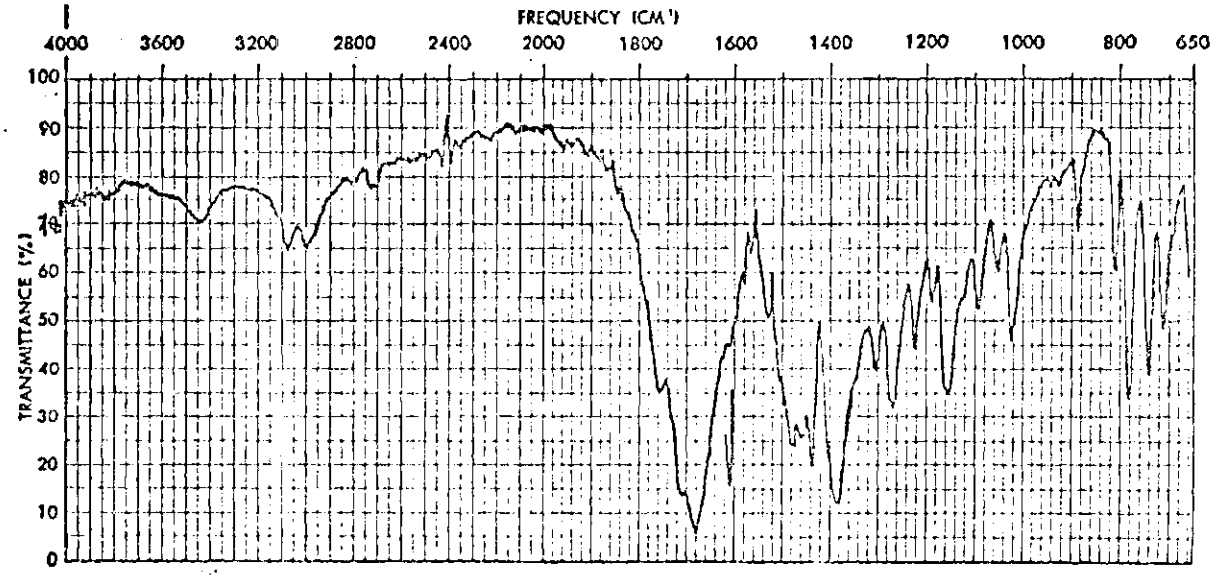


Figure 23. Infrared Spectrum of 1,3-Dimethyl-5-phenyl-barbituric Acid

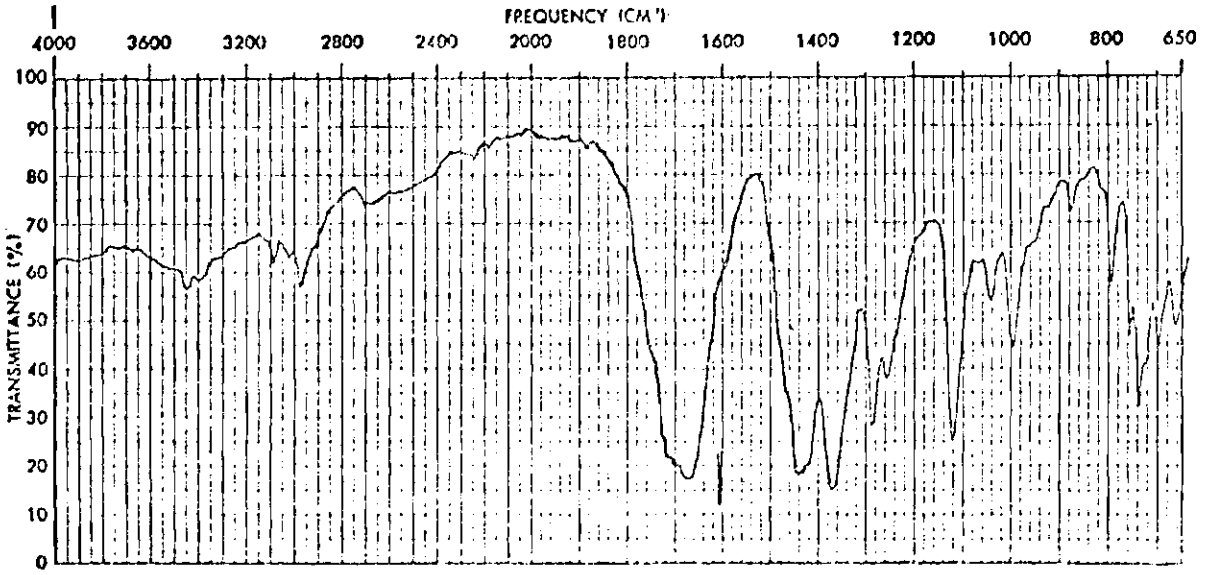


Figure 24. Infrared Spectrum of 1,3-Dimethyl-5-bromo-5-phenylbarbituric Acid

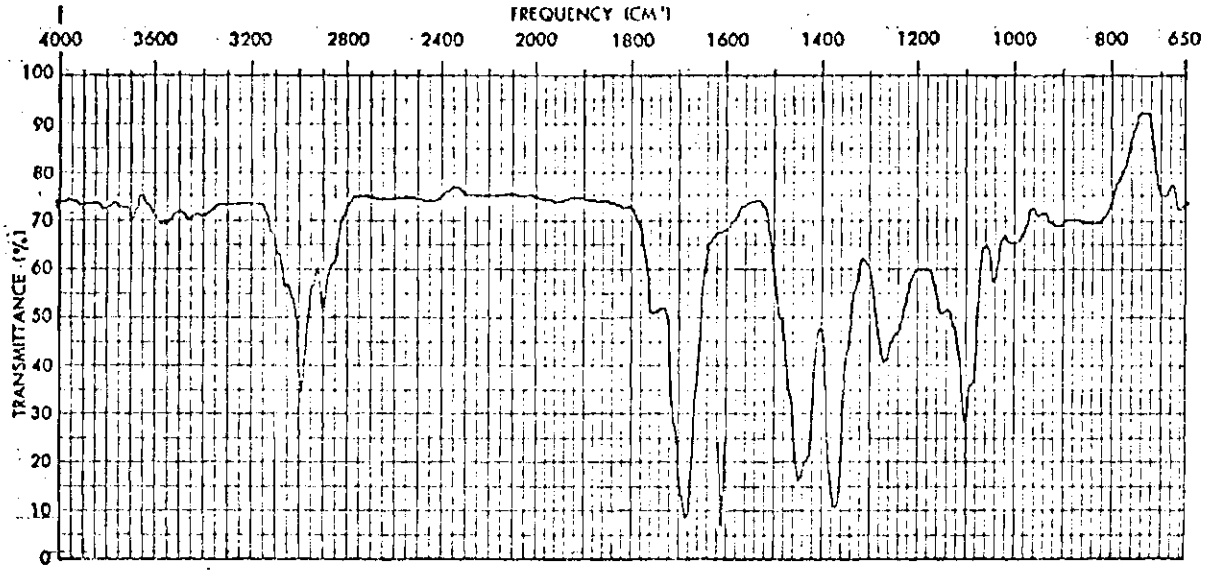


Figure 25. Infrared Spectrum of 1,3-Dimethyl-5-phenyl-5-[N-(pyrrolidino)]-barbituric Acid

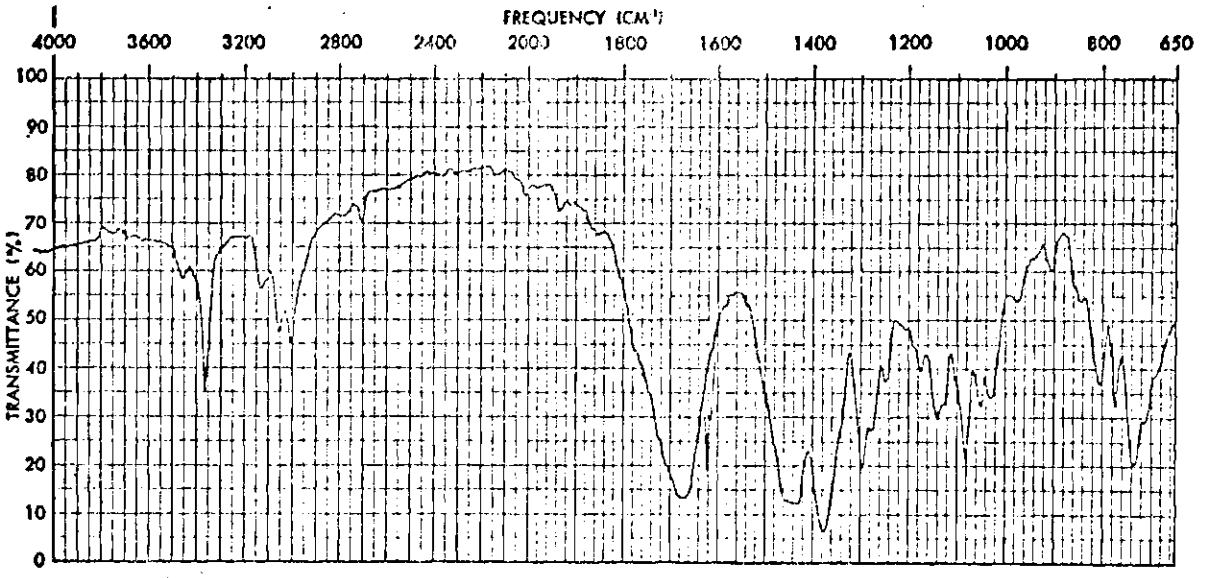


Figure 26. Infrared Spectrum of 1,3-Dimethyl-5-phenyl-5-[N-(cyclopropylamino)]-barbituric Acid

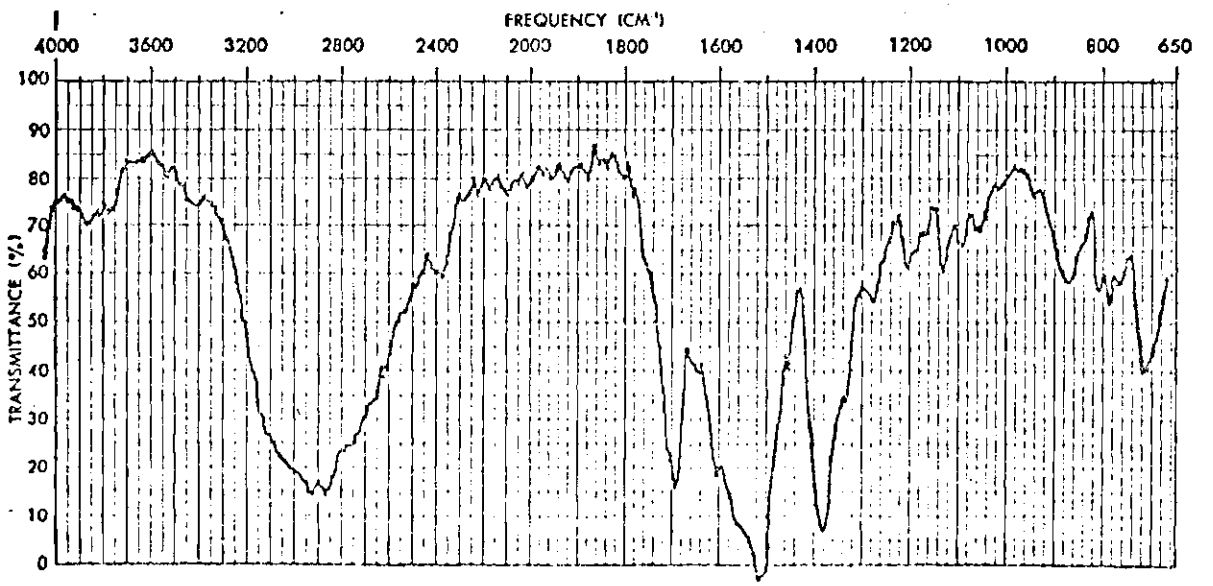


Figure 27. Infrared Spectrum of the Salt of 5-Phenylbarbituric Acid and trans-2-Phenylcyclopropylamine

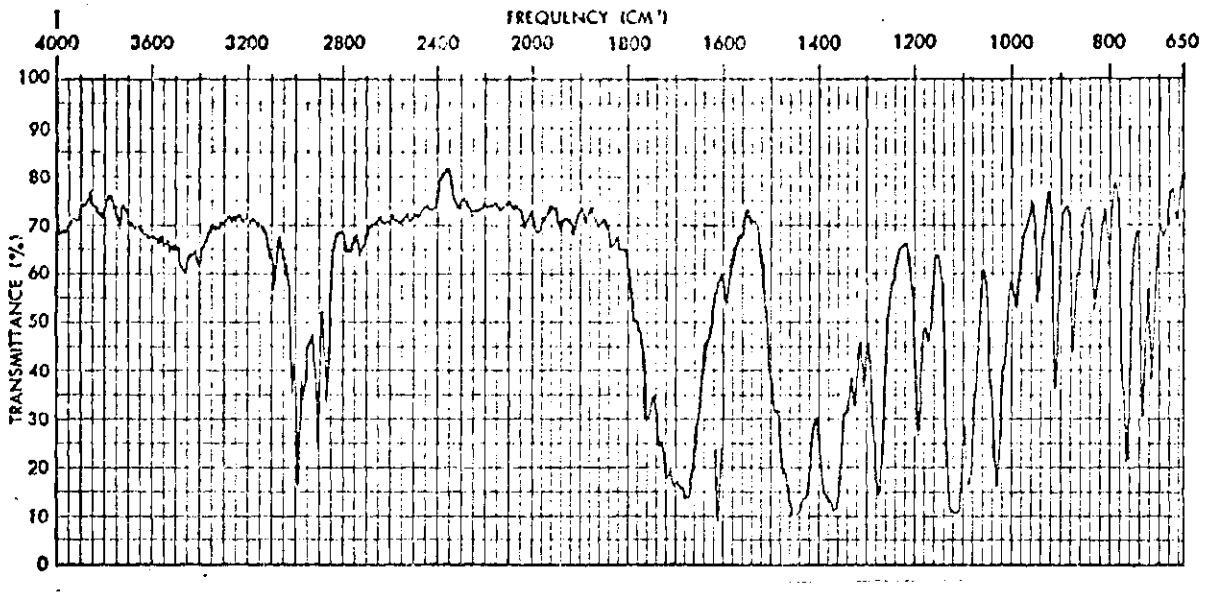


Figure 28. Infrared Spectrum of 1,3-Dimethyl-5-phenyl-5-[N-(morpholino)]-barbituric Acid

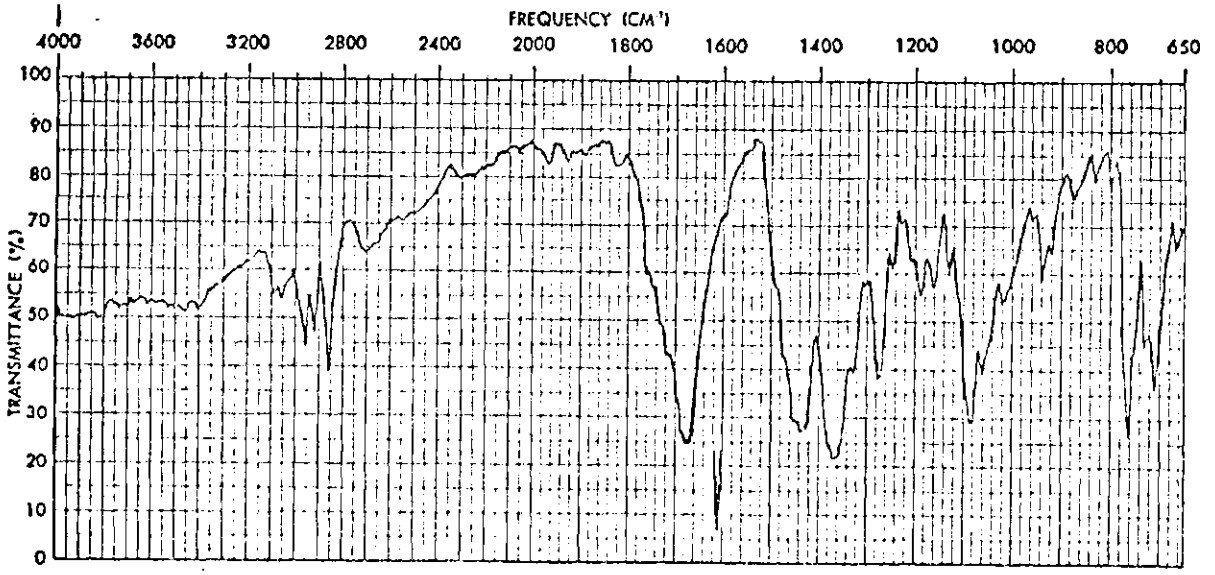


Figure 29. Infrared Spectrum of 1,3-Dimethyl-5-phenyl-5-[N-(1,2,3,4-tetrahydroisoquinolino)]-barbituric Acid

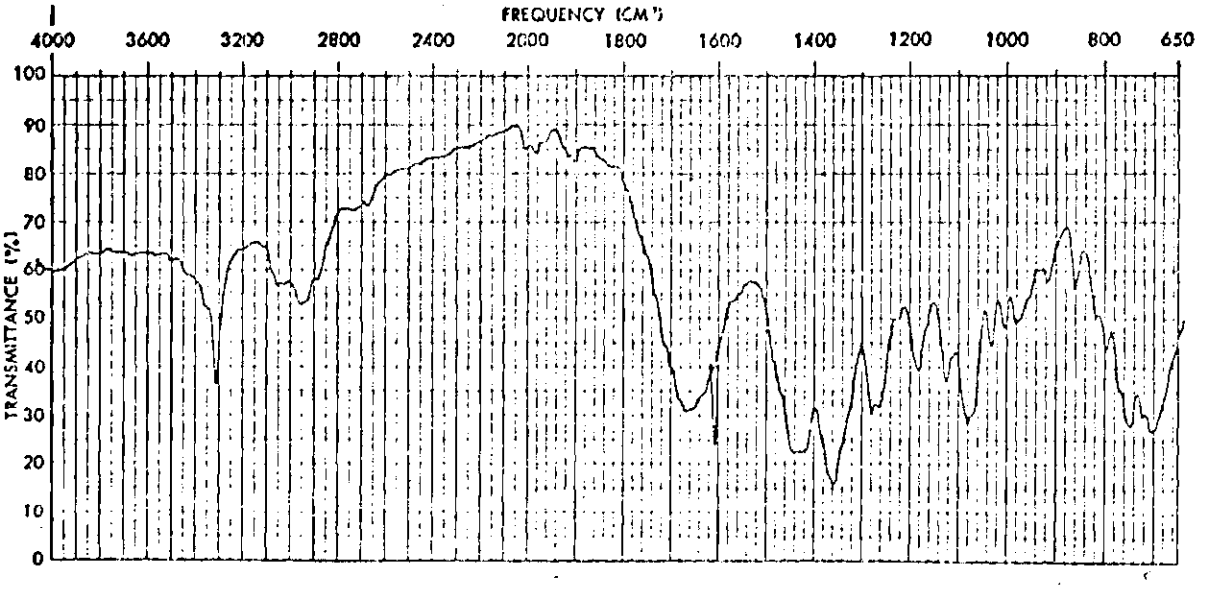


Figure 30. Infrared Spectrum of 1,3-Dimethyl-5-phenyl-5-[N-(benzylamino)]-barbituric Acid

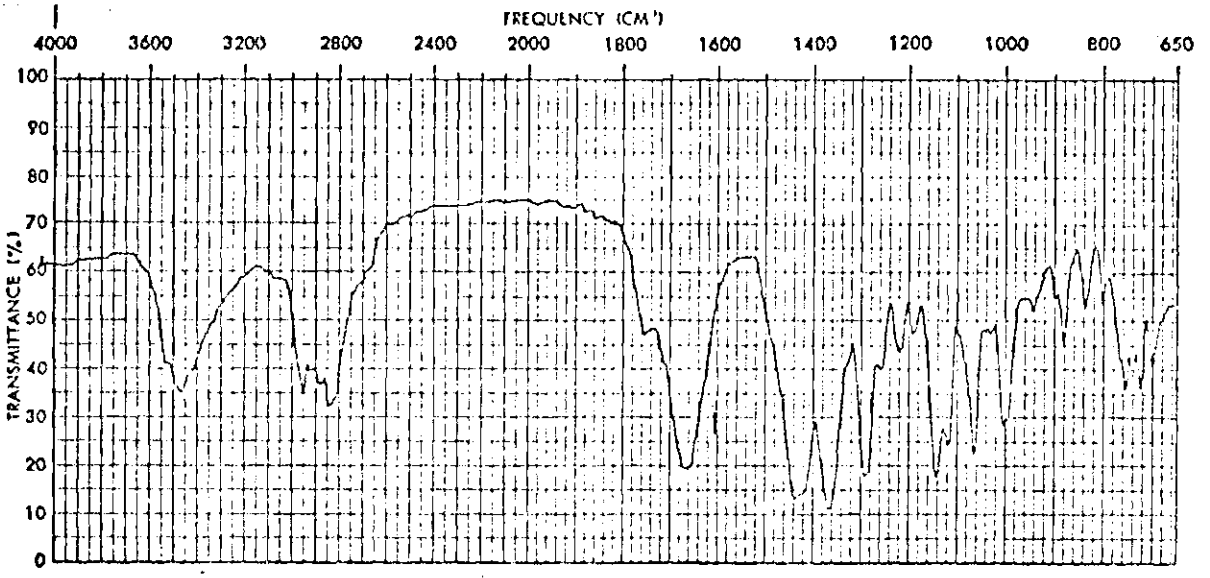


Figure 31. Infrared Spectrum of 1,3-Dimethyl-5-phenyl-5-[N-(N'-β-hydroxylethylpiperazino)]-barbituric Acid

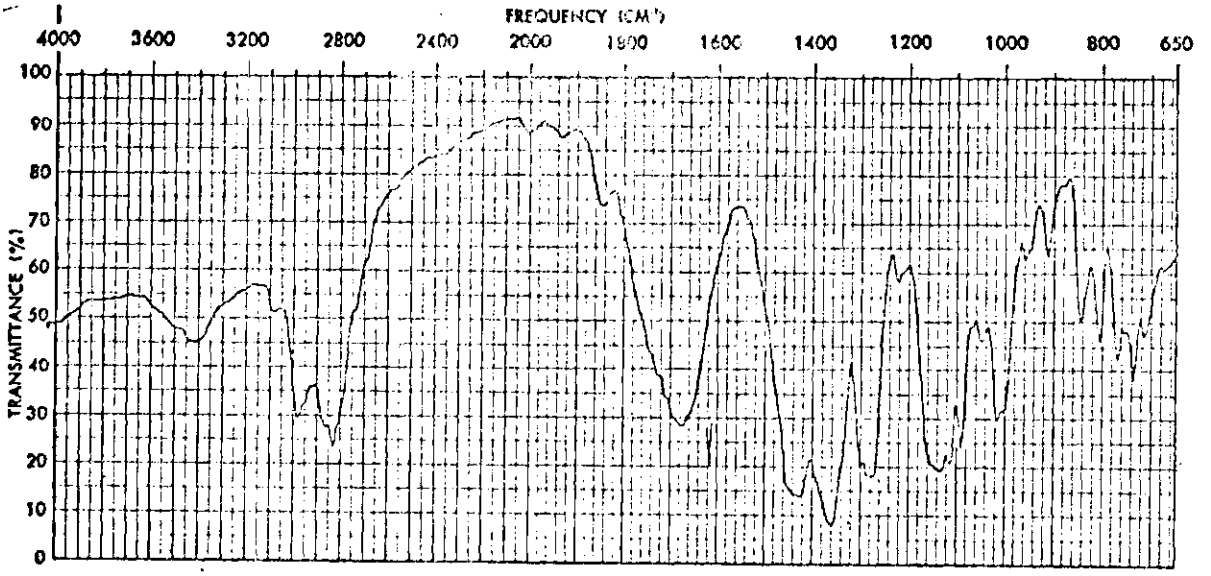


Figure 32. Infrared Spectrum of 1,3-Dimethyl-5-phenyl-5-[N-(4-methylpiperazino)]-barbituric Acid

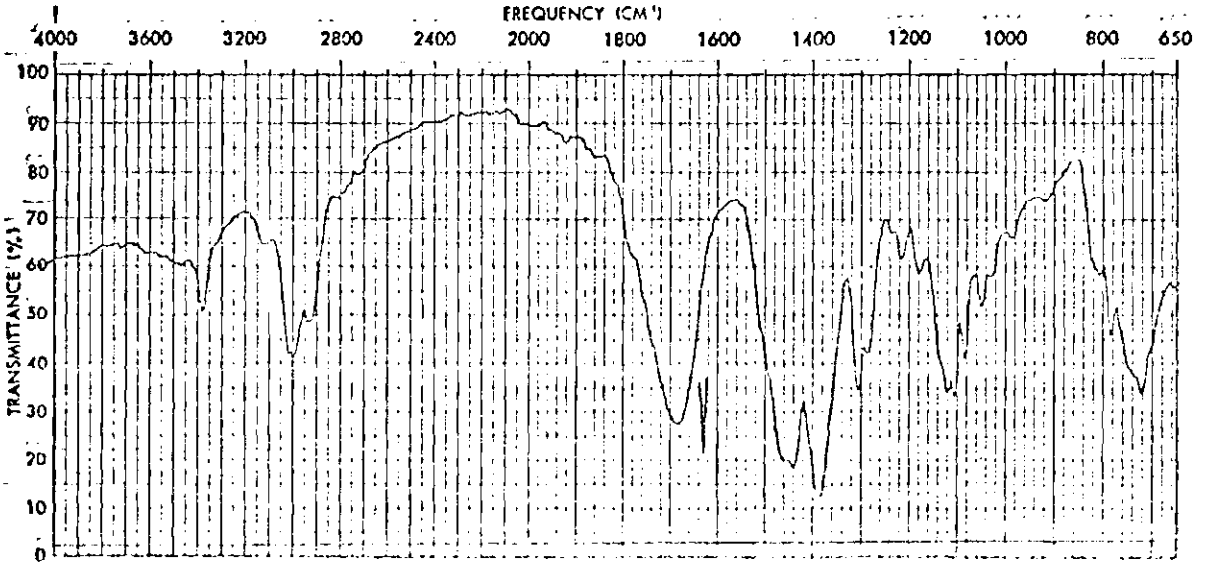


Figure 33. Infrared Spectrum of 1,3-Dimethyl-5-phenyl-5-[N-(n-propylamino)]-barbituric Acid

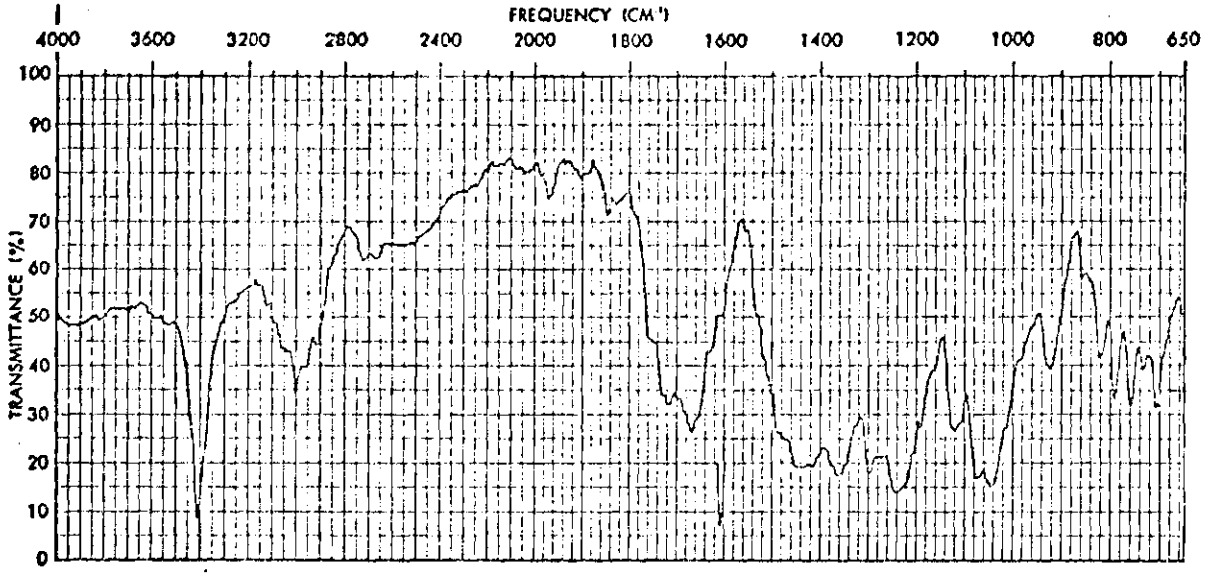


Figure 34. Infrared Spectrum of 1,3-Dimethyl-5-phenyl-5-[N-(p-phenetidino)]-barbituric Acid

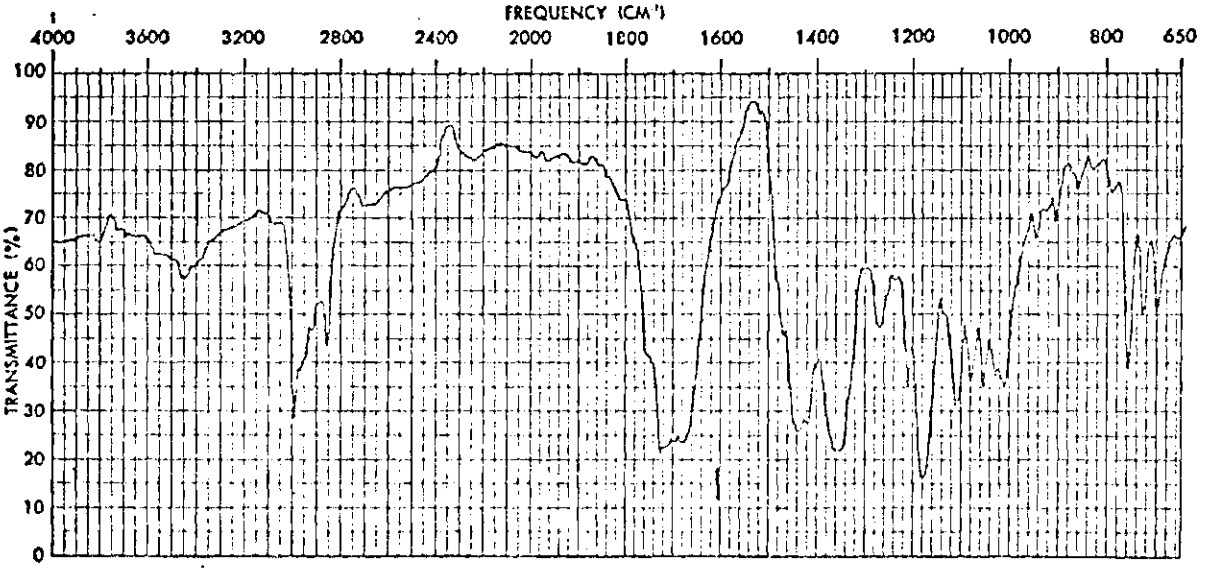


Figure 35. Infrared Spectrum of 1,3-Dimethyl-5-phenyl-5-[N-(ethylisonipecotato)]-barbituric Acid

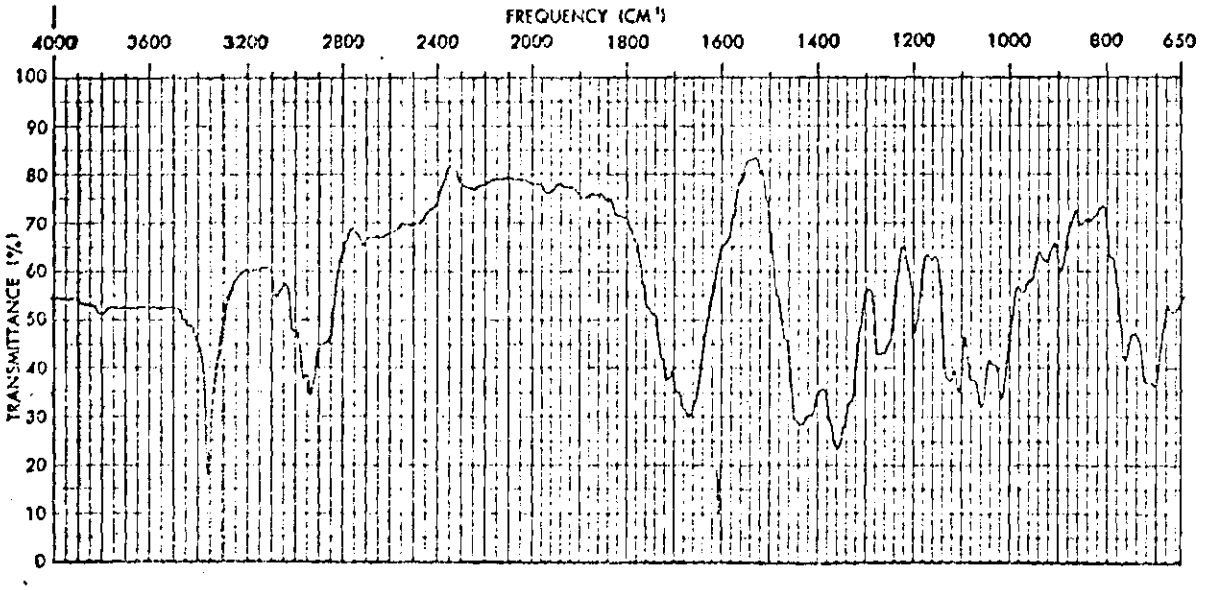


Figure 36. Infrared Spectrum of 1,3-Dimethyl-5-phenyl-5-[N-(2-methoxyethylamino)]-barbituric Acid

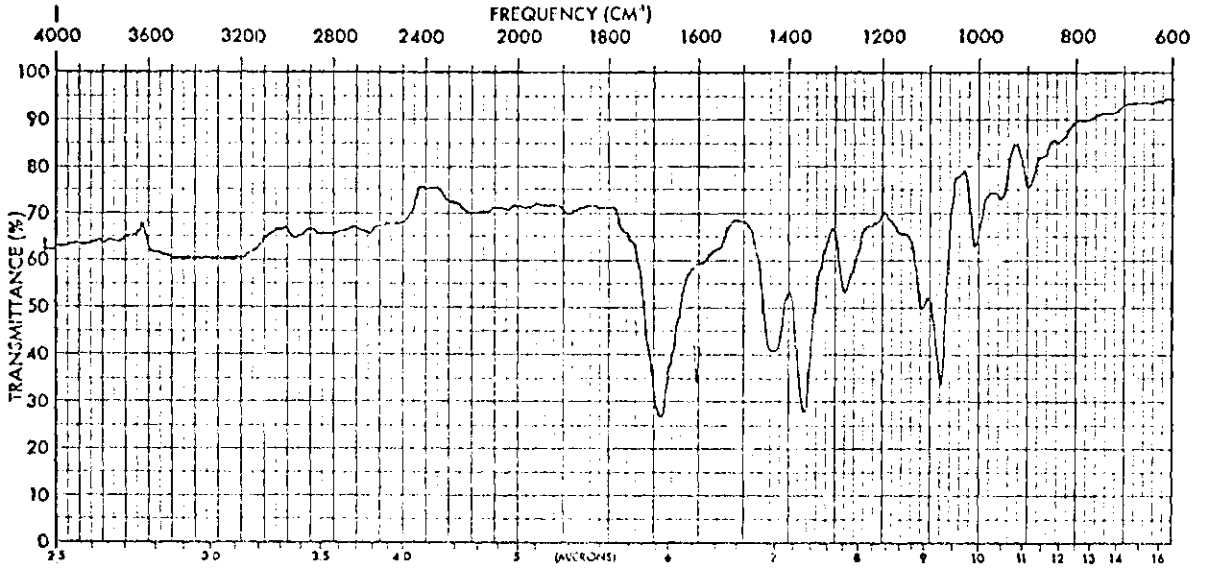
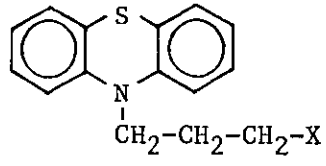
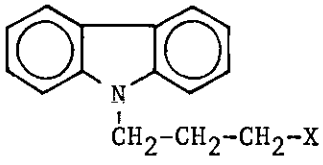
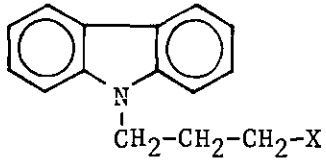


Figure 37. Infrared Spectrum of 1,3-Dimethyl-5-phenyl-5-methoxybarbituric Acid

APPENDIX B

NMR SPECTRA

Table 3. NMR Shift Values in Units of δ for Derivatives of Phenothiazine and Carbazole

R_1X=  R_2X=  R_3X= 

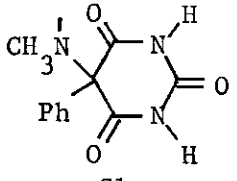
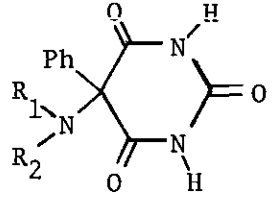
Compound		Chemical Shift					
R	X	aromatic	a	b	c	d	e
R_1	Cl	6.5-7.5 (m)	4.03 (t)	2.83 (m)	3.27 (t)		
R_1	$NHCH_3$ d e	6.2-7.3 (m)	3.80 (t)	1.90 (m)	2.53 (t)	-	2.20 (s)
R_2	Cl	6.8-8.0 (m)	4.03 (t)	1.87 (m)	3.07 (t)		
R_2	$NHCH_3$ d e	6.9-8.2 (m)	4.10 (t)	1.67 (m)	2.23 (t)	-	2.10 (s)
R_2		6.6-10.0 (m)	4.40 (t)	1.94 (m)	2.54 (t)	-	
R_3	Cl	7.0-8.2 (m)	4.47 (t)	2.27 (m)	3.43 (t)		
R_3	$NHCH_3$ d e	6.9-8.1 (m)	4.30 (t)	1.90 (m)	2.37 (t)	-	2.30 (s)

Table 4

NMR Shift Values in Units of δ for

Amino-1,3-dimethyl-5-phenyl Barbituric Acids



Compound		Chemical Shift					
R_1	R_2	Ph	N-CH_3	a	b	c	d
H	CH_3-CH_2-CH_2- (d, c, b)	7.35 (s)	3.33 (s)	2.37 (s)	2.47 (t)	1.50 (m)	0.92 (t)
a							
H	c: CH_2 / CH_2 >CH- (b)	7.33 (s)	3.37 (s)	2.73 (s)	2.07 (m)	0.56 (m)	
a							
H	CH_3O-CH_2-CH_2- (d, c, b)	7.37 (s)	3.33 (s)	2.77 (s)	3.50 (t)	2.87 (t)	3.27 (s)
a							
H	c: benzyl, CH_2- (b)	7.1-7.6 (m)	3.35 (s)	2.77 (s)	3.76 (s)	7.1-7.6 (m)	
a							

Table 4. Con't

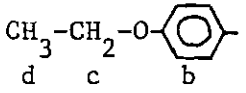
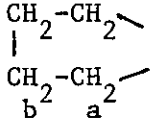
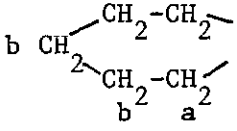
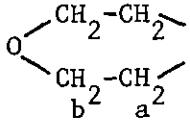
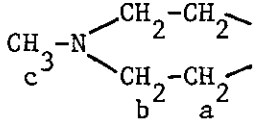
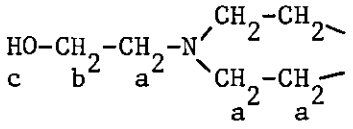
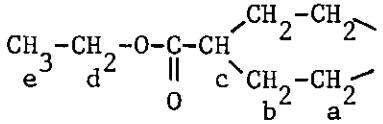
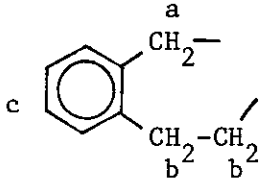
Compound		Chemical Shift					
R_1	R_2	Ph	N-CH_3	a	b	c	d
H a		7.43 (s)	3.37 (s)	3.53 (s)	6.63 (m)	3.95 (q)	1.37 (t)
		7.35 (s)	3.28 (s)	2.82 (m)	1.82 (m)		
b		7.37 (s)	3.30 (s)	2.62 (m)	1.4-1.8 (c)		
		7.37 (s)	3.30 (s)	2.70 (t)	3.70 (t)		
		7.33 (s)	3.27 (s)	2.50 (m)	2.62 (m)	2.27 (s)	

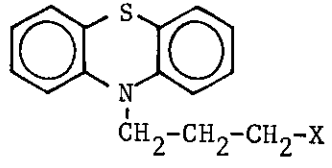
Table 4. Con't

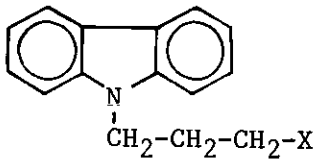
Compound		Chemical Shift						
R_1	R_2	Ph	$N-CH_3$	a	b	c	d	e
		7.40 (s)	3.30 (s)	2.3-2.8 (c)		3.60 (t)	2.90 (s)	
		7.35 (s)	3.28 (s)	2.68 (m)	1.88 (m)	2.27 (m)	4.13 (q)	1.23 (t)
		7.43 (s)	3.33 (s)	3.88 (s)	2.93 (s)	6.8-7.3 (m)		

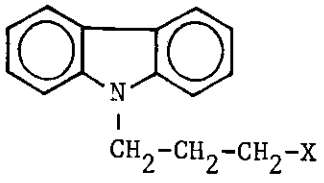
APPENDIX C

MASS SPECTRA

Table 5. Mass Spectral Data of Derivatives of Phenothiazine and Carbazole

$R_1X=$ 

$R_2X=$ 

$R_3X=$ 

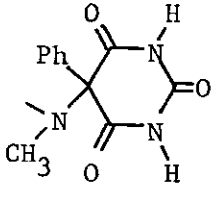
Compound		Mol. Wt.	Data				
R	X						
R_1	Cl	275	275 (10)	229 (9)	212(13)	198(19)	77(7)
			69(11)	63(11)	57(13)	51(12)	44(56)
			40(100)				
R_1	$NH(CH_3)\cdot HCl$	306	207(17)	199(82)	167(50)	154(10)	79(20)
			69(57)	68(100)			
R_2		440	207(15)	199(63)	167(100)	149(12)	139(10)
			99(10)	85(23)	71(45)	57(65)	

Table 5. Con't

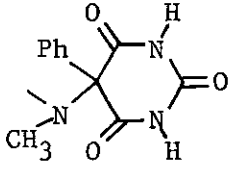
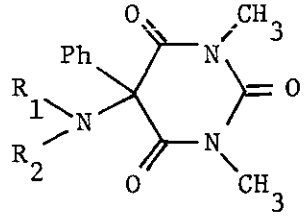
Compound R	X	Mol. Wt.	Data				
R_3	Cl	311	313(8)	311(48)	252(9)	248(100)	
R_3		508	308(18)	307(86)	276(24)	275(33)	263(24)
			249(64)	136(57)	102(57)	86(100)	70(57)

Table 6

Mass Spectral Data of

Amino-1,3-dimethyl-5-phenyl Barbituric Acids



Compound		Mol. Wt.	Data				
R_1	R_2						
H	$CH_3-CH_2-CH_2-$	289	289(1)	260(20)	232(16)	231(21)	203(10)
			146(12)	142(10)	118(35)	104(29)	91(19)
			77(18)	58(100)	57(11)	56(10)	
H		287	287(10)	232(10)	203(15)	196(28)	182(28)
			175(15)	144(17)	130(10)	118(100)	117(17)
			105(13)	104(27)	89(12)	77(22)	56(60)

Table 6. Con't

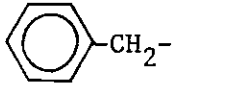
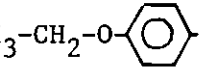
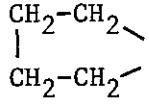
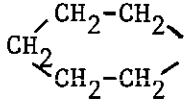
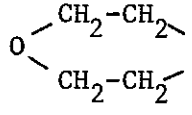
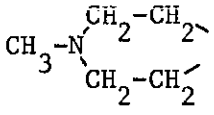
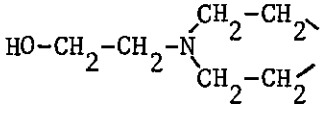
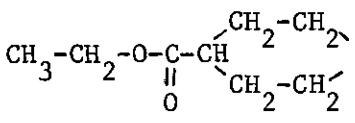
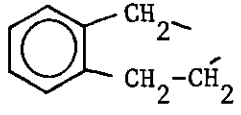
Compound R_1	R_2	Mol. Wt.	Data				
H	$CH_3O-CH_2-CH_2-$	305	305(1)	273(11)	261(16)	260(100)	232(13)
			231(61)	203(14)	118(32)	104(15)	77(16)
H		337	337(1)	232(8)	118(15)	107(10)	106(100)
			104(20)	91(15)	77(16)	65(10)	
H		367	367(28)	232(4)	137(14)	136(96)	118(27)
			109(12)	108(100)	104(8)	81(11)	77(14)
			65(10)				
		301	301(2)	232(12)	203(13)	118(20)	103(12)
			86(10)	84(15)	77(10)	70(100)	
		315	315(1)	232(9)	203(14)	118(25)	117(10)
			104(12)	84(100)	77(12)	56(9)	
		317	317(2)	232(23)	203(17)	175(13)	118(33)
			117(29)	104(9)	89(12)	86(100)	77(20)
			56(19)				

Table 6. Con't

Compound R_1 R_2	Mol. Wt.	Data				
	330	330(7)	232(3)	118(9)	99(100)	70(8)
		58(8)	56(32)			
	360	360(3)	330(16)	329(59)	232(26)	142(30)
		129(32)	119(13)	118(94)	111(20)	99(44)
		98(98)	90(35)	77(20)	58(79)	56(100)
	387	387(<1)	232(15)	203(11)	157(10)	156(100)
		118(19)	82(32)	77(5)	56(5)	
	363	363(1)	232(12)	175(8)	132(100)	118(25)
		104(9)	90(9)	77(10)		

LITERATURE CITED

1. Baeyer, A., Justus Liebigs Ann. Chem., 127, 199 (1863).

2. Baeyer, A., Justus Liebigs Ann. Chem., 130, 129 (1864).

3. Grimaux, E., Ann. Chem., (5) 11, 389 (1876).

4. Grimaux, E., Ann. Chem., (5) 17, 276 (1879).

5. Fischer, E., and Mehring, J. von, Ther. Monatsh., (1903); Chem. Zentralbl., 1903 I, 1155.

6. Fischer, E., and Dilthey, A., Justus Liebigs Ann. Chem., 335, 334 (1904).

7. Friend, D. G., in Adv. Chem. Ser., 45, American Chemical Society, Washington, D. C., p. 154.

8. Doerr, M. L., unpublished Ph.D. Thesis, Georgia Institute of Technology, 1967.

9. Borst, R. C., N. Y. State J. Med., 42, 3 (1942); Biol. Abstr., 16, 16623.

10. Branisteanu, D. and Popovici, G. H., Arch. Int. Pharmacodyn. Ther., 80, 95-8 (1949); Chem. Abstr., 43, 7134 g.

11. Goeres, E., Acta Biol. Med. Ger., 10(5-6), 679-80 (1963); Chem. Abstr., 60, 2216 d.

12. Adams, R., Chiles, H. M., and Rassweiler, C. R., Org. Syn., Coll. Volume I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 10.

13. Barkofer, L. and Storch, I., Chem. Ber., 86, 32 (1953).

14. Bergman, M. and Zervas, L., Ber. Dtsch. Chem. Ges., 65, 1192 (1932).

15. Emery, W. O., Ber. Dtsch. Chem. Ges., 23, 3761 (1880).

16. Peters, J. P. unpublished Ph.D. Thesis, Georgia Institute of Technology, 1974.

17. Bernthsen, A., Ber. Dtsch. Chem. Ges., 16, 2896 (1883).

18. Gaafar, S. M., Garrigus, R. R., and Bennett, D. G., Vet. Med. Small Anim. Clin., 63, 600 (1968); Chem. Abstr., 69, 34606 s.

19. Massie, S. P., Chem. Rev., 54, 797 (1954).

20. Schenker, E. and Herbst, H., Progr. Drug Res., 5, 269 (1963); Chem. Abstr., 59, 12040 a.

21. Pamukeu, A. M., Wattenberg, L. W., Price, J. M., and Bryan, G. T., J. Nat. Cancer Inst., 47, 155 (1971).

22. Lapin, I. P. and Shchelkunov, E. L., Tr. Leningr. Nauchno. Issled. Psikhonevrol. Inst., 45, 130 (1968); Chem. Abstr., 71, 121998 f.

23. Watzman, N., Manian, A. A., Barry, H., and Buckley, J. P., J. Pharm. Sci., 57, 2089 (1968).

24. Frank, G. B. and Jhamandas, K. H., Brit. J. Pharmacol., 39, 696 (1970).

25. Gilman, H. and Ingham, R. K., J. Org. Chem., 19, 560 (1954).

26. England, D. C., Melby, L. R., Dietrich, M. A., and Lindsey, R. V., J. Am. Chem. Soc., 82, 5116 (1960).

27. Reppe, W., Ann. Chem., 601, 128 (1956).

28. Simov, D., Bull. Inst. Chim. Acad. Bulg. Sci., 2, 75 (1953); Chem. Abstr., 49, 6266 e (1955).

29. Massie, S. P. and Kadaba, P. K., J. Org. Chem., 21, 347 (1956).

30. Wheeler, L., unpublished M.S. Thesis, Georgia Institute of Technology, 1974.

31. Walker, J., unpublished Ph.D. Thesis, Georgia Institute of Technology, 1973.

32. Taub, L. and Kropp, W., U.S. Pat. 2,061,114 (1936); Chem. Abstr., 31, 709 (1937).

33. Sandberg, F., Acta Physiol. Scand., 24, 7 (1951); Chem. Abstr., 46, 3154 (1952).

34. Deininger, R., Naunyn Schmiedeberg's Arch. Exp. Pathol. Pharmakol., 222, 193 (1954).

35. Dickey, J. B. and Gray, A. R., Org. Syn., Coll. Volume II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 60.

36. Avdovich, H. W. and Neville, G. A., Can. J. Pharm. Sci., 4, 3 (1969).

37. Voorhes, V. and Skinner, G. S., J. Am. Chem. Soc., 47, 1124 (1925).

38. Wheeler, H. L. and Johnson, T. B., J. Am. Chem. Soc., 24, 680 (1902).

39. Palmer, C. S. and McWherter, P. W., Org. Syn., Coll.Volume I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 245.

40. Zschiedrich, J., Ger. (East), 77491 (Cl. C. 07d), 1970; Chem. Abstr., 75, 98583 p.

41. Gilman, H. and Shirley, D. A., J. Am. Chem. Soc., 66, 888 (1944).

42. Thiel, M. and Stach, K., Manatsh., 93, 1080 (1962).

43. Mihami, A., Morimoto, K., and Murakami, Y., Nippon Kagaku Zasshi, 85, (12), 880 (1964).

44. Forbes, E. J., Stacey, M., Tatlow, J. C., and Wragg, R. T., Tetrahedron, 8, 67 (1960).

45. Snyder, H. R. and Eliel, E. L., J. Am. Chem. Soc., 70, 1703 (1948).

46. Cope, A. C., Heyl, D., Peck, D., Eide, C., and Arroyo, A., J. Am. Chem. Soc., 63, 356 (1941).

47. Dresden, A., Ger., 1,246,743 (1967); Chem. Abstr.,67, 90827 k.

48. Shine, H. J. and Mach, E. E., J. Org. Chem., 30, 2130 (1965).

49. Crosignani, E. and Franzosini, P., Siragusa, G., and Zanotti, L., Arch. Sci., 24, 153 (1961); Chem. Abstr., 61, 9077 h.

50. Lagercrantz, C., Acta Chem. Scand., 15, 1545 (1961).

51. Tuck, L. D. and Schieser, D. W., J. Phys. Chem., 66, 937 (1962).

52. Lhoste, J. M. and Tonnard, F., J. Chem. Phys., 63, 678 (1966).

53. Wood, R. G., McCole, C. H., and Williams, G., Phil. Mag., 31, 79 (1941).

54. Leonard, N. J. and Sutton, L. E., J. Am. Chem. Soc., 70, 1564 (1948).

55. Malrieu, J. P. and Pullman, B., Theor. Chim. Acta, 2, 293 (1964).

56. Sadeghi, D., Therapie, 22, 191 (1967).

57. Julou, L., Ducrot, R., Bardone, M. C., Feo, C., Guymnet, J. C., Loiseau, G., and Pasquet, J., Rev. Farm., 109, 199 (1967); Chem. Abstr., 69, 66046 a.

58. Weissgerber, R., Ber. Dtsh. Chem. Ges., 46, 652 (1913).

59. Buu-Hoi, Justus Liebigs Ann. Chem., 556, 1 (1944).

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In August 1972, she was married to Chia-yeh Chu. They now have a son, Todd, born in December, 1975.