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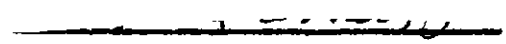

THE STABILITIES OF SOME BARBITURIC ACID DERIVATIVES UNDER HYDROLYTIC CONDITIONS

A THESIS

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TABLE OF CONTENTS

TABLE OF CONTENTS (Continued)

TABLE OF CONTENTS (Continued)

TABLE OF CONTENTS (Continued)

TABLE OF CONTENTS (Continued)

LIST OF TABLES

LIST OF ILLUSTRATIONS

LIST OF ILLUSTRATIONS (Continued)

LIST OF ILLUSTRATIONS (Continued)

SUMMARY

The purpose of this study was to obtain information about the hydrolytic cleavage of the pyrimidine ring in certain derivatives of barbituric acid. This reaction was of interest as a synthetic tool, and the effects of substituents on the course and rate of the cleavage were of interest from a theoretical standpoint. In addition, particular importance was attached to the reaction because of the possibility that the hydrolytic stabilities of barbiturates could be correlated with their hypnotic properties. The theoretical reasons for postulating the existence of such a correlation are discussed in detail.

The compounds of interest in this work included certain spiro-1'-alkyl(or aryl)piperidine-4',5-barbituric acids, spirotetrahydropyran-4',5-barbituric acid, and several common barbiturate hypnotics having two substituents in the 5-position.

When spiro-1'-methylpiperidine-4',5-barbituric acid was subjected to a variety of hydrolyzing conditions, no products were obtained which would have resulted from stepwise hydrolytic degradation of the pyrimidine ring. Instead, ammonium carbonate and some liquid materials were produced. Although these liquids were not definitely identified, tests showed that they contained no tertiary amino group(s). Since

cleavage of the piperidine ring was highly unlikely under the conditions employed, a reinvestigation of the structures of the starting material and other spiro-amino barbituric acids was undertaken. Chemical tests failed to prove or disprove the structure of the 1'-methyl derivative; however, the preparation of a monohydroiodide indicated that only one amino group was present in this compound.

In order to resolve conclusively the problem of their structures, an alternative, unambiguous synthetic route to the spiro-amino barbituric acids was sought. Thus, bis(2-hydroxyethyl)phenylamine was converted to the corresponding ditosylate by treatment with p-toluenesulfonyl chloride in cold, anhydrous pyridine. Condensation of the tosylate with diethyl malonate in refluxing toluene in the presence of two equivalents of sodium gave 1-phenyl-4,4-dicarbethoxypiperidine. This ester was then condensed with urea in the presence of alcoholic sodium ethoxide to afford the sodium salt of spiro-1'-phenylpiperidine-4',5-barbituric acid. An attempt was made to prepare the free acid by dissolving the salt in cold water and carefully acidifying the solution with hydrochloric acid; however, this treatment caused cleavage of the pyrimidine ring, and the only isolable product was 1-phenyl-4-carboxypiperidine-4-carbonylureide. On the other hand, the free barbituric acid could be obtained in good yield by stirring the salt with Amberlite IRC-50 ion-exchange resin in anhydrous ethanol. Spiro-1'-m-tolylpiperidine-4',5-barbituric

acid was prepared by the same reaction sequence starting with bis(2-hydroxyethyl)-m-tolylamine. The use of ion-exchange resins in anhydrous media is recommended as a general technique for liberating easily-hydrolyzed barbituric acids from their sodium salts.

Spiro-1'-phenylpiperidine-4',5-barbituric acid prepared by the new method was not identical with a compound previously reported to have this structure. However, considerable evidence was obtained to indicate that the barbituric acids prepared by the new method did have the correct structures. This evidence included: (a) the unambiguous method of forming the barbituric acid ring; (b) the demonstration of the presence of this ring in the case of the m-tolyl derivative by the production of characteristic barbiturate monoanion absorption at 241 millimicrons upon treatment with one equivalent of aqueous sodium hydroxide; (c) the decrease of this absorption with time--a result readily explained on the basis of hydrolytic pyrimidine ring cleavage; (d) the very rapid cleavage of the pyrimidine ring in the presence of excess base--a typical characteristic of spiro-barbituric acids; (e) the stepwise degradation of the phenyl derivative to give expected hydrolysis products which were isolated and characterized; and, finally, (f) exhaustive hydrolytic degradation of the pyrimidine ring to afford 1-phenyl-4-carboxypiperidine, a known compound.

Attempts to prepare spiro-1'-methylpiperidine-4',5-barbituric acid were not successful. The procedure used for the preparation of the aryl derivatives was not workable in this case because the necessary disulfonic ester could not be prepared from bis(2-hydroxyethyl)methylamine. It was suggested that this ditosylate could not be isolated because it underwent facile polymerization *via* a cyclic immonium salt.

Cursory examination was made of several possible routes to the intermediate ester, 1-methyl-4,4-dicarbethoxypiperidine. It was surmised that this material could be prepared by methylating 4,4-dicarbethoxypiperidine; however, the latter compound could not be prepared by cleavage of 1-*p*-nitrosophenyl-4,4-dicarbethoxypiperidine with sodium bisulfite or sodium ethoxide. Attempts to condense bis(2-chloroethyl)methylamine with diethyl malonate using a variety of bases and conditions were also unsuccessful. Another possible method for preparing 1-methyl-4,4-dicarbethoxypiperidine involved carbethoxylation of 1-methyl-4-carbethoxypiperidine using ethyl chloroformate and a strongly basic catalyst. Phenylsodium was found not to be a satisfactory reagent for effecting this reaction, and the use of triphenylmethylsodium is recommended.

The path of the stepwise hydrolytic degradation of spiro-1'-phenylpiperidine-4',5-barbituric acid under basic conditions was elucidated, and the hydrolysis products were shown to be 1-phenyl-4-carboxypiperidine-4-carbonylureide, 1-phenylpiperidine-4-carbonylureide, 1-phenyl-4,4-dicarboxypiperidine, and 1-phenyl-4-carboxypiperidine. Independent methods of synthesis

were developed for certain of these compounds. For example, it was found that 1-phenyl-4-carboxypiperidine could be readily prepared by decarboxylation of 1-phenyl-4,4-dicarboxypiperidine using heat or aqueous sulfuric acid. Basic hydrolysis of 1-phenyl-4,4-dicarbethoxypiperidine in aqueous ethanol gave excellent yields of the corresponding diacid.

Parallel hydrolysis experiments on spiro-1'-phenylpiperidine-4',5-barbituric acid, spirotetrahydropyran-4',5-barbituric acid, and 5,5-diethylbarbituric acid were undertaken using one or three equivalents of aqueous sodium hydroxide and reflux times of approximately 6 hr. The results indicated that the use of one equivalent of base under such conditions might be a general method of preparing ureides from all types of 5,5-disubstituted barbituric acids. On the other hand, three equivalents of base hydrolyzed the spiro derivatives to the corresponding malonic acids and degraded 5,5-diethylbarbituric acid to diethylmalonamic acid. All of these results could be readily rationalized on the basis of steric hindrance to nucleophilic attack at the carbonyl groups originally present in the 4- and 6-positions of the starting materials.

Methods were investigated for preparing 1-phenyl-4,4-dicarboxamidopiperidine, a compound which theoretically might have resulted from the hydrolysis of spiro-1'-phenylpiperidine-4',5-barbituric acid. Attempts to prepare this diamide from 1-phenyl-4,4-dicarboxypiperidine *via* the intermediate

diacid chloride were not successful. These failures were apparently due to the inability of thionyl chloride to convert the diacid to the required intermediate. However, in a parallel experiment 4,4-dicarboxytetrahydropyran was readily converted to 4,4-dicarboxamidotetrahydropyran by treatment with thionyl chloride and then with concentrated ammonium hydroxide. A trace amount of 1-phenyl-4,4-dicarboxamidopiperidine resulted when the corresponding diester was allowed to stand in contact with concentrated ammonium hydroxide for several days, but the yield could not be improved by running the ammonolysis under more vigorous conditions.

Further attempts were made to prepare the diamide by condensing bis(2-p-toluenesulfonyloxyethyl)phenylamine with malonamide. This method was of particular interest because no previous attempts to alkylate malonamide with sulfonic esters appeared to have been reported, and, for this reason, a thorough study of the reaction employing a variety of bases and conditions was undertaken. In general, the extent of alkylation was found to be small, and the results of the study provided further evidence for the generalization that the methylene group of malonamide is much less reactive than the methylene group of malonic esters. Low yields of 1-phenyl-4,4-dicarboxamidopiperidine and 3,3-dicarboxamidopropyl-2-ethoxyethylphenylamine were obtained when alcoholic sodium ethoxide was used as the basic reagent. Sodium amide in

refluxing dioxane yielded neither of these products but gave, instead, a material believed to be 1,1'-spirobipiperazinium-4,4'-diphenyl p-toluenesulfonate.

A spectrophotometric technique was used to measure the pseudo-first-order hydrolysis rates of several barbituric acids in excess sodium hydroxide. A mathematical analysis is presented which shows that the linearity of the kinetic plot is, in many cases, an excellent indication of the validity of first-order kinetic data.

The hydrolysis rates of the spiro-1'-arylpiperidine-4',5-barbituric acids prepared by the new method were found to be too rapid to measure in excess base. Rate data for several of the compounds designated as spiro-1'-alkylpiperidine-4',5-barbituric acids provided further evidence that the structures of these materials were incorrect.

The hydrolysis rates of several common 5,5-disubstituted barbiturate hypnotics were found to be strongly influenced by the steric effects of the substituents. With few exceptions the hydrolytic stabilities of these compounds could be correlated with their hypnotic efficacies.

CHAPTER I

INTRODUCTION

Since the early years of the twentieth century, it has been recognized that many organic molecules which possess the 2,4,6-triketohexahydropyrimidine ring are endowed with unusual physiological properties. Substances that incorporate this type of heterocyclic structure are commonly referred to as barbituric acids. While the parent compound has no useful physiological activity, many of its derivatives have been found to have pronounced hypnotic (sedative) and anesthetic properties. These substituted barbituric acids are commonly called "barbiturates",[1] and they constitute one of the most important series of drugs used in modern medicine.

One of the more interesting and fundamental aspects of pharmacology is concerned with the mechanisms of action of drugs in living organisms. Exact knowledge about these mechanisms is of considerable importance, not only to pharmacologists and physiologists, but also to chemists concerned with the preparation of new drugs. A considerable amount of research has been directed toward the elucidation of the mechanism of action of hypnotic substances; however, precise studies in this field are rendered extremely difficult because of the enormous com-

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[1] This term is commonly used to designate both the free acids and their salts.

plexities of *in vivo* systems. Therefore, it is not surprising that the way in which barbiturates and other hypnotics exert their depressant actions on the central nervous system is still not fully understood.

Over the years many theories have been presented to account for the mechanism of action of barbiturates. The only theory to receive general acceptance was first proposed in the early 1900's by H. Meyer and Overton and later amplified and restated by K. H. Meyer and Hemmi (1). In its restated form this theory postulates that the depressant activity of any chemical entity is determined solely by its ability to dissolve in the nerve tissues of an organism. When the molar concentration of a material attains a certain definite value in the cell lipids, hypnosis occurs. This value is dependent on the nature of the cell, but it is independent of the nature of the dissolving material, so that the molecular structure and chemical composition of a drug are important only insofar as they influence its solubility properties. Since lipids are fatty substances, it is to be expected that only those materials with appreciable solubility in non-polar or organic type solvents will have hypnotic properties. On the other hand, compounds which are more readily soluble in polar solvents will be unable to penetrate the lipids and will be inactive. Therefore, there should exist a correlation between the hypnotic efficacies of

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(1) W. J. Doran, Medicinal Chemistry, Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1959, p. 17.

substances and their distribution coefficients in a model system such as water and oil.

Experimental tests of the Meyer-Overton theory have shown that there is, indeed, a rough correlation between the solubility properties of substances and their hypnotic potencies; however, the relationship is, at most, only qualitative (2). Nevertheless, the theory is of considerable value because it emphasizes the experimental fact that substances must have appreciable fat solubility to be hypnotically active. The chief objection to the theory would appear to be its total disregard of any fundamental relation of molecular structure to depressant activity.

Besides solubility, several other chemical and physical properties of barbiturates have been examined for the purpose of establishing physiological activity correlations (2-4). However, no generally satisfactory correlations have been reported for any of the properties studied so far. In the absence of a quantitative basis for predicting hypnotic properties certain qualitative generalizations have been used as guides for synthetic work in the barbiturate series. These rules describe the effects of molecular structure on hypnotic potency, and they

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(2) D. L. Tabern and E. F. Shelberg, J. Am. Chem. Soc., 55, 328 (1933).

(3) Doran, op. cit., pp. 18 ff.

(4) R. J. Kuffner, M. T. Bush, and L. J. Bircher, J. Am. Chem. Soc., 79, 1587 (1957).

are based on pharmacological data for several hundred compounds. Exceptions to the rules are known, however.

Following Doran (5), these rules may be stated as follows:

1. For a barbiturate to be hypnotically active, both of the hydrogen atoms in the 5-position must be replaced by substituents--usually alkyl groups.

2. Increasing the length of primary 5-alkyl chains increases the hypnotic potency.

3. Chain branching in primary 5-alkyl substituents increases the hypnotic potency. Branching is even more effective if it occurs on the alpha-carbon atom, so that the alkyl group is secondary rather than primary.

4. Barbiturates with a 5-alicyclic substituent are more active than the corresponding compounds in which the alicyclic group has been replaced by a straight-chain radical containing the same number of carbon atoms.

5. Replacement of an imide hydrogen on the pyrimidine ring by an alkyl group enhances the hypnotic potency.

6. Introduction of halogen (commonly a bromo group) into a 5-alkyl substituent enhances the hypnotic potency.

7. Introduction of an ethylenic linkage into a 5-alkyl substituent enhances the hypnotic potency.

8. Complete loss of hypnotic properties occurs when

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(5) Doran, op. cit., pp. 32-35.

polar and semipolar groups such as hydroxyl, amino, alkylamino, carbonyl, carboxyl, and sulfonyl are present in substituent groups.

As will now be shown, a striking feature of these rules is that most of the structural features tending to increase hypnotic activity are also those which would be predicted to stabilize the pyrimidine ring to certain types of hydrolytic cleavage. For this reason, the hydrolysis of barbituric acid derivatives is of uncommon interest.

If it is assumed that the acid and base-catalyzed hydrolyses of barbiturates proceed by mechanisms analogous to those which are operative in the hydrolysis of simple carbonyl compounds such as esters and amides, then the effects of structure on reactivity will be similar for all three types of compounds. Base-catalyzed ester hydrolysis has been shown to be influenced by both polar and steric effects, while polar effects are usually unimportant in the acid-catalyzed hydrolysis of esters (6).

On the basis of the assumed mechanisms, all of the structural changes suggested in rules 1 through 5 for increasing hypnotic potency would also be expected to increase ring stability in acidic and basic hydrolysis by steric shielding of the 4- and 6-carbonyl groups. The steric effect of a bulky halogen atom (rule 6) would also increase the stability; however, in the case of basic hydrolysis, this factor would be

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(6) J. Hine, Physical Organic Chemistry, McGraw-Hill Book Co., Inc., New York, N. Y., 1956, pp. 274-276.

opposed by a polar inductive effect tending to increase the electrophilicity of the nearest carbonyl functions. The inductive effect would probably be rather small, however, since a halo substituent on a 5-alkyl group must be separated from the nearest reaction center by at least two carbon atoms. The rapid decrease of inductive effects with distance is well-known (7). For the same reason, the inductive effect of unsaturation (rule 7) should also be negligible, while the steric effect associated with this structural feature might be favorable, unfavorable, or negligible, depending on the position of the double bond and the groups attached to it. The polar groups mentioned in rule 8 would also have varying steric factors and would tend to decrease the stability in basic hydrolysis by small inductive effects; however, the hypnotic inactivity of barbiturates containing these groups is probably due almost entirely to the unfavorable solubility properties which they impart.[1]

For basic hydrolysis alkylation of an imide nitrogen (rule 5) might give rise to an important additional effect. In the presence of excess base barbiturates unsubstituted in the pyrimidine ring will be converted largely to dianions (Fig. 1a), while the N-substituted derivatives will exist largely as monoanions (Fig. 1b). The latter species should be much more

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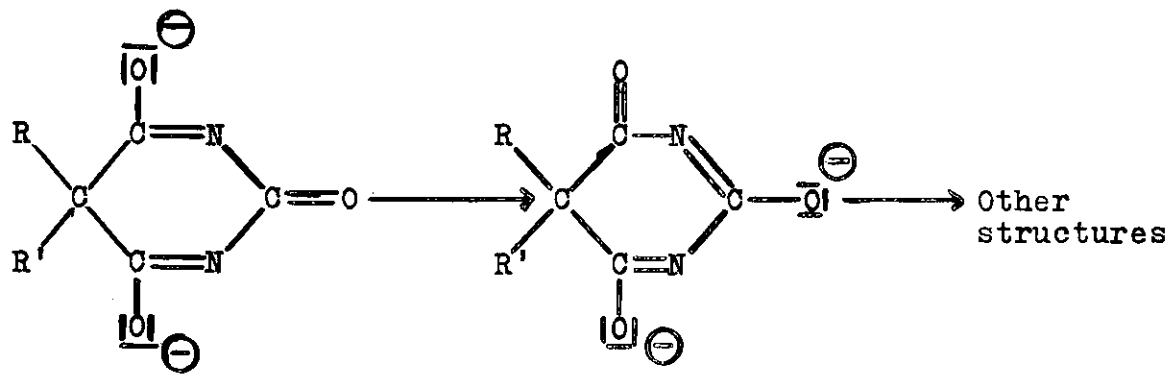
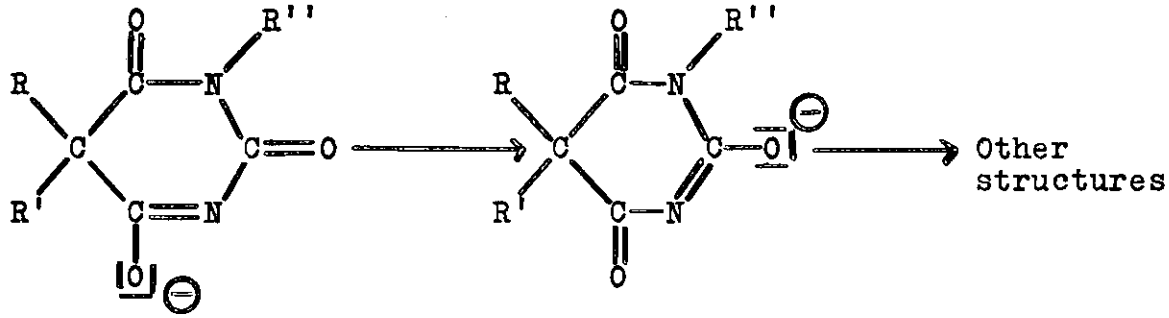
[1] See above, pp. 2-3.

(7) Ibid., p. 68.



a. 5,5-Disubstituted barbituric acid anion



b. 1,5,5-Trisubstituted barbituric acid anion

Figure 1. Anions of Substituted Barbituric Acids

susceptible to nucleophilic attack since it is less highly charged and has less resonance stabilization than the dianion. Therefore, 1-alkyl-5,5-disubstituted barbituric acids should be much more reactive in basic hydrolysis than the corresponding 5,5-disubstituted derivatives. Similar cases involving "protection" of carbonyl-containing substrates toward nucleophilic attack by transforming them to their conjugate bases are well-known (8).

On the basis of the foregoing discussion, it appears that the acid-catalyzed hydrolysis rates of barbiturates could

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(8) See ibid., pp. 294-295, for a critical discussion and important references.

be correlated with their hypnotic potencies. Such a correlation also appears possible for the base-catalyzed rates in cases where the polar effects of substituents are inappreciable. For the base-catalyzed reaction separate correlations would appear to be necessary for the 1,5,5-trisubstituted and the 5,5-disubstituted series because of the ionization effect discussed in the preceding paragraph; however, both of these series should fit into a single correlation in the acid-catalyzed case.

Experimental verification of the stability-activity theory requires quantitative information on both the hydrolysis rates and the hypnotic properties. Unfortunately, pharmacological testing data are influenced by a large number of variables, such as species, strain, age, and sex of the experimental animal(s); temperature of the testing room; and mode of administration of the drug. Moreover, different investigators use different criteria in assessing the results of tests. For these reasons, pharmacological data obtained even under optimum conditions are not strictly quantitative, and comparisons of data obtained by different workers are useful only from a qualitative standpoint.

A good example of some pharmacological data obtained by the same investigators under carefully controlled conditions is that which has been reported for a series of spirocyclopentane-1', 5-barbituric acids (9). With few exceptions the

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(9) Doran, op. cit., p. 130.

predicted stabilities for twenty-five compounds in this series can be correlated with their anesthetic potencies, and it is possible that the exceptions could be rationalized if the detailed stereochemical configurations of the compounds were known. Reliable pharmacological data are also available for some spirocyclohexane-1',5-barbituric acids (10) and for some spirocyclohex-3'-ene-1',5-barbituric acids (10). Good stability-activity correlations also appear possible in both of these series.

If, then, high potency is associated with high hydrolytic stability, it might be expected that the most potent barbiturates would have the longest durations of action. In practice, however, it has been found that the most active derivatives are, in general, the shortest acting. Thus, it follows that hydrolytic cleavage of the pyrimidine ring cannot be one of the principal routes for the in vivo deactivation of barbiturates. This deduction is supported by the observation that only trace amounts of barbiturate hydrolysis products are excreted by the kidneys following administration of these drugs (11). On the contrary, the principal isolable metabolites are found to contain intact pyrimidine rings (12). Moreover, evidence has been obtained which suggests that the common hypnotic,

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(10) Ibid., p. 131.

(11) Ibid., pp. 28-30.

(12) Ibid., pp. 31-32.

barbital, undergoes no metabolic changes at all, and it has also been found that many other common barbiturates are excreted unchanged in appreciable amounts (13).

In view of these facts, it appears that the hydrolysis reaction as such is of minor importance *in vivo*. From the standpoint of the proposed stability-activity correlation, the property which does appear to be of fundamental importance is the degree of steric shielding of the carbonyl groups in the barbituric acid ring. The *in vitro* hydrolysis reaction is simply a convenient tool for measuring this property and is, therefore, related to the physiological activity on purely empirical grounds.

Very few attempts to obtain quantitative data on the hydrolytic stability of barbiturates have been reported. Only one satisfactory method for obtaining such data is available at present, and it was developed only recently (14).

The earliest effort along these lines appears to have been that of Tabern and Shelberg (2). These workers dissolved weighed amounts of the sodium salts of several common 5-substituted-5-ethylbarbituric acids in carbonate-free distilled water and then heated the solutions in sealed tubes at 100°C. for sixteen hours. After cooling, the solutions were acidified

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(13) *Ibid.*, pp. 22 and 31.

(14) P. M. Daugherty, unpublished Ph. D. Thesis, Georgia Institute of Technology, 1957. A discussion of Daugherty's results is postponed until Chapter IV of the present thesis.

with sulfuric acid to liberate carbon dioxide, and the per cent of hydrolysis that had occurred in each case was calculated from the amount of this gas which was evolved. An obvious source of error in this method is that one, two, or three moles of carbon dioxide might be produced, depending on how far the stepwise degradation proceeds in each case. The results, however, are in general accord with the predicted stabilities. Tabern and Shelberg also considered possible relationships between hypnotic properties and hydrolytic stability and noted that the most stable barbiturates were the shortest acting *in vivo*.

Although other isolated reports on barbiturate stability have appeared from time to time in the literature, the only systematic study of the hydrolysis reaction is that undertaken by Aspelund and co-workers (15-21). In this work the products resulting from the hydrolysis in aqueous alkali of a large

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(15) H. Aspelund, *Acta Acad. Aboensis Math. et Phys.*, *20*, No. 3 (1955).

(16) *Ibid.*, No. 12 (1956).

(17) H. Aspelund and O. Backman, *ibid.*, *14*, No. 14 (1944); *C. A.*, *42*, 573 (1948).

(18) H. Aspelund and P. O. Hagberg, *ibid.*, *18*, No. 4 (1952).

(19) H. Aspelund and L. Skoglund, *ibid.*, *10*, No. 10 (1937).

(20) H. Aspelund and S. Stolt, *ibid.*, *20*, No. 4 (1955).

(21) C. Berggardh and H. Aspelund, *Finska Kemistsamfundets Medd.*, *59*, 64 (1950); *C. A.*, *47*, 1607 (1953).

number of 5,5-disubstituted, 1,5,5-trisubstituted, and 1,3,5,5-tetrasubstituted barbiturates were ascertained, and the relative stabilities of the starting materials were estimated from the amounts which could be recovered unreacted. The effects of three reaction variables were studied: base concentration, reaction time, and temperature of reaction. Work-up of the reaction mixtures was along classical lines and involved stepwise acidification to certain definite pH's, followed by solvent extraction and/or filtration of the mixture at each pH. Many of the product fractions obtained by this technique could not be resolved into pure components, however, and for this reason Aspelund's results are only qualitatively correct. The products obtained by Aspelund in the basic hydrolysis of 5,5-disubstituted barbituric acids are depicted in Figure 2. The R and R' groups present were alkyl, aryl, cycloalkyl, aralkyl, or cycloalkenyl. Most of the barbiturates hydrolyzed are useful as drugs.

It was found that cleavage of the ring by hydroxide usually occurred at the 1,6-position, producing malonuric acids (I). However, for certain compounds, excess base and higher reaction temperatures could also induce cleavage at the 1,2-position, producing (presumably) unstable allophanic acids which underwent decarboxylation to yield malonamides (II) as the isolable products. Formation of II to observable extents was found to occur only in cases where attack of hydroxide at the 4- and 6-positions was hindered by the presence of one or

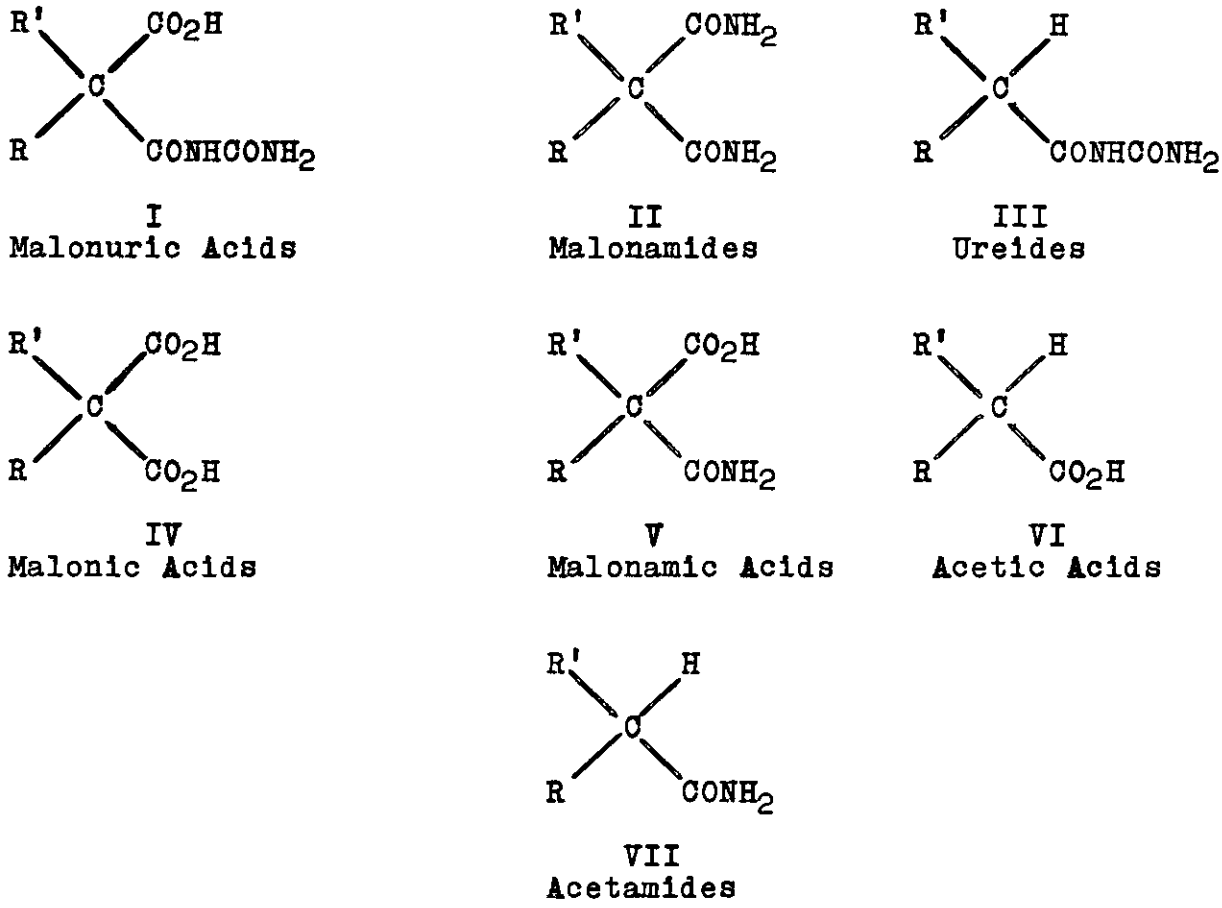

Figure 2. Hydrolysis Products of 5,5-Disubstituted Barbituric Acids

more bulky 5-substituents. The acids (I) could decarboxylate to yield ureides (III) or undergo further hydrolysis to give malonic acids (IV) and/or malonamic acids (V). Formation of IV and V instead of III was favored by lower temperatures and excess base, while the ratio of V to IV was increased when bulky R groups were present. The ureides (III) could hydrolyze to give acetic acids (VI) or acetamides (VII), with VII being favored by bulky R groups. Compounds VI might also have resulted from decarboxylation of IV or hydrolysis of VII, and

VII, in turn, might also have been formed by decarboxylation of V. It was shown in separate experiments that the disubstituted malonamides (II) were remarkably resistant to further basic hydrolysis; hence, II was eliminated as a possible precursor of V. Interestingly, no urea could be isolated from the hydrolysis mixtures; however, this compound would be expected to undergo facile decomposition to carbon dioxide and ammonia under the conditions employed.

The products obtained from the hydrolyses of 1,5,5-tri- and 1,3,5,5,-tetrasubstituted barbituric acids were, in general, analogous to those shown in Figure 2. However, the tri- and tetrasubstituted derivatives showed even less tendency to undergo the 1,2- type of cleavage than did the 5,5-disubstituted compounds. In some cases N-substituted ureas could be isolated as hydrolysis products of the tri- and tetrasubstituted materials.

Aspelund's data on the relative stabilities of barbiturates can be readily rationalized in terms of conventional electronic theory. Steric hindrance to nucleophilic attack at the 4- and 6-positions appears to have been the most important factor governing stability for most of the compounds studied. However, introduction of substituents into the 1- and 3-positions invariably produced great decreases in stability, probably because of the ionization effect discussed earlier.[1]

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[1] See above, pp. 6-7.

Aside from a possible correlation with physiological activity, the hydrolysis of barbituric acid derivatives is attractive as a synthetic method for the products resulting from cleavage of the pyrimidine ring. Moreover, quantitative information about the stability of the ring might prove to be of considerable utility in the preparation of stable solutions of these drugs for administration in vivo. Stability data can also be of value in devising methods of synthesis for the parent compounds, as shown by some recent work on the preparation of spirotetrahydropyran-4',5-barbituric acid (22).

In view of these facts, the principal objectives of the work described in this thesis were: (a) quantitative kinetic studies on the base-catalyzed hydrolysis of barbiturates, and (b) extension of the hydrolysis reaction as a synthetic tool. The recently reported "spiro-amino barbituric acids" (14, 22, 23) depicted in Figure 3 were of particular interest, since practically no qualitative or quantitative data on the hydrolysis of these compounds was available. For purposes of comparison, parallel kinetic and synthetic studies were undertaken on the spiro derivatives and some of the more common barbiturates. Methods of synthesis for hydrolysis products were of especial interest in the spiro-amino series on account of the

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(22) J. A. Stanfield and P. M. Daugherty, J. Am. Chem. Soc., 81, 5167 (1959).

(23) J. Buchi, K. Leuenberger, and R. Lieberherr, Farm. Sci. e tec. (Pavia), 6, 430 (1951).

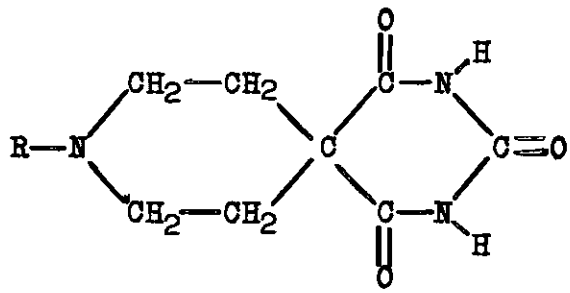

Figure 3. Spiro-amino Barbituric Acids

relative unavailabilities of many 1,4-di- and 1,4,4-trisubstituted piperidine derivatives.

CHAPTER II

METHODS OF ATTACK

The initial step in this investigation was a careful reexamination of the base-catalyzed hydrolysis of 5,5-diethylbarbituric acid (barbital) from a synthetic standpoint. The hydrolysis of barbital had been studied earlier by Aspelund (19, 20); however, as discussed earlier,[1] the results of this work were not wholly definitive due to the procedural difficulties which were encountered. In the present work it was initially thought desirable to examine the ultraviolet spectra of all of the possible hydrolysis products of barbital for the purpose of determining whether or not absorption by any of these materials would interfere with quantitative spectrophotometric measurements of the rate of hydrolysis. Accordingly, the collection of spectral data for these compounds was begun. However, a mathematical analysis[2] showed that valid rate data could be obtained without any knowledge of the absorptions due to these products, so efforts in this direction were discontinued. At any rate, it is worthy of mention that the spectral data obtained in the present work and data

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[1] See above, p. 12.

[2] See Appendix A of this thesis.

previously reported (24) indicated that absorption by products is inappreciable at the wavelength used for the kinetic studies, even if the reaction is near completion.

Synthetic hydrolysis studies were also undertaken on spirotetrahydropyran-4',5-barbituric acid and spiro-1'-methylpiperidine-4',5-barbituric acid. It was found that reaction of the spiro-amino derivative with base gave products other than those which would have been produced if stepwise hydrolytic degradation of the pyrimidine ring had been the only structural change occurring. Although the chief organic product of this reaction was not definitely identified, tests indicated that it contained no tertiary amino group. Therefore, since base-catalyzed cleavage of the piperidine ring was very unlikely, a reexamination of the structures of the spiro-amino barbituric acids was felt to be in order. Chemical tests failed to yield conclusive structural evidence, so it was decided to seek an alternative, unambiguous method of synthesis for these compounds so as to resolve definitely the problem of their structures. Such a method is outlined in Figure 4.

The starting materials for this sequence are the tertiary diethanolamines (I), many of which are commercially available. Treatment of I with p-toluenesulfonyl chloride in cold, anhydrous pyridine should readily yield the disulfonic esters (II), and, in fact, the preparation of some of the compounds in the

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(24) G. R. Jackson, Jr., J. R. Weschler, and R. L. Dannley, Anal. Chem., 26, 1661 (1954).

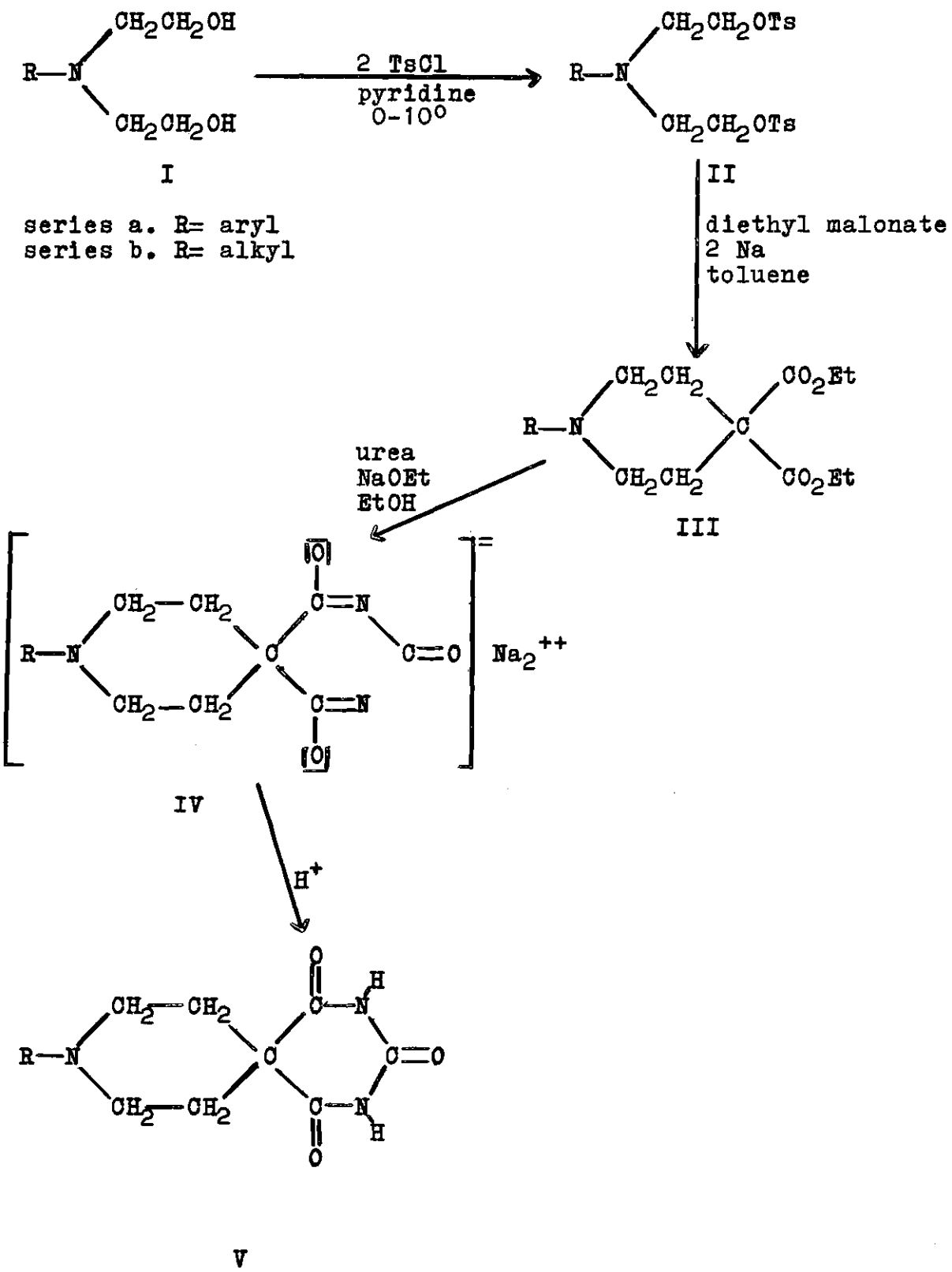

Figure 4. Proposed Synthesis of Spiro-amino Barbituric Acids from Tertiary Diethanolamines

aryl series by this method had already been reported (25). The tosyl derivatives of many simpler alcohols have also been prepared by this technique (26).

The preparation of the 1-substituted-4,4-dicarbethoxypiperidines (III) might be achieved by condensation of II with diethyl malonate in an inert solvent using metallic sodium as the catalyst. This method of piperidine ring closure is exemplified by Skinner's preparation of 1-benzenesulfonyl-4,4-dicarbethoxypiperidine (27). The final step in the procedure would involve condensation of III with urea under sodium alkoxide catalysis to give sodium salts (IV) from which the free barbituric acids (V) might be obtained on acidification. A majority of the barbiturate syntheses reported in the literature have involved pyrimidine ring closure by this method.

An alternative route to IIIb had been suggested by Schmutz et al. and applied successfully to the synthesis of 1-methyl-4,4-dicarbethoxypiperidine (28). However, since this method was quite tedious, a simpler route to IIIb was highly desirable. Another scheme for preparing IIIb is depicted in

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(25) G. M. Timmis, Brit. Patent 662,645 (Dec., 1951); C. A., 46, 11240 (1952).

(26) V. C. Sekera and C. S. Marvel, J. Am. Chem. Soc., 55, 346 (1933).

(27) G. S. Skinner, H. R. Krysiak, and J. A. Perregrino, ibid., 77, 2248 (1955).

(28) J. Schmutz, F. Kunzle, and R. Hirt, Helv. Chim. Acta, 37, 1762 (1954).

Figure 5. This method involves the conversion of the starting alcohols (Ib) into bis(2-chloroethyl)alkylamines (VI), which might then react with diethyl malonate in the presence of two equivalents of a basic reagent to give the desired piperidine esters (IIIb). The preparation of nitrogen mustards (VI) by the action of thionyl chloride on Ib is well-known; however, the use of VI and malonic ester to prepare IIIb appeared rather unpromising in view of several earlier unsuccessful attempts to effect this type of condensation using alkyl nitrogen mustards (22, 23, 28). By way of contrast to these negative results, the reported preparation of 1-phenyl-4,4-dicarbethoxypiperidine by condensation of the corresponding aryl nitrogen mustard with malonic ester is of interest (29). However,

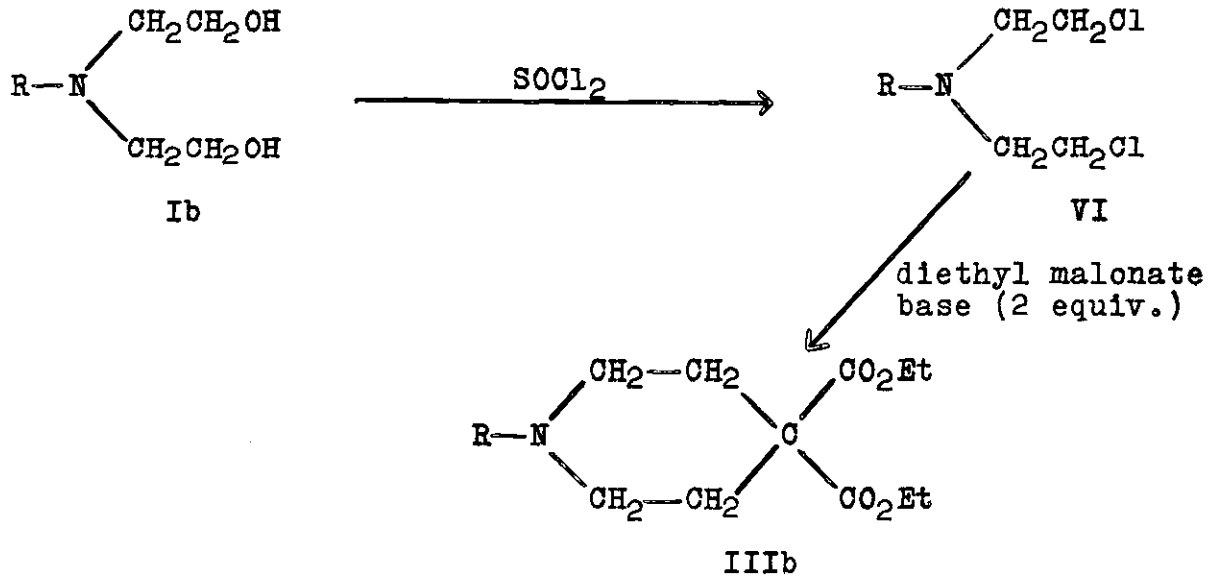

Figure 5. Proposed Alternative Synthesis of 1-Alkyl-4,4-dicarbethoxypiperidines from Tertiary Alkyldiethanolamines

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(29) R. M. Anker, A. H. Cook, and I. M. Heilbron, J. Chem. Soc., 917 (1945).

the published procedure gives low yields, and separation of the product from unreacted starting material has been found to be difficult (30).

Another possible route to 1-alkyl-4,4-dicarbethoxypiperidines is outlined in Figure 6. The starting material in this

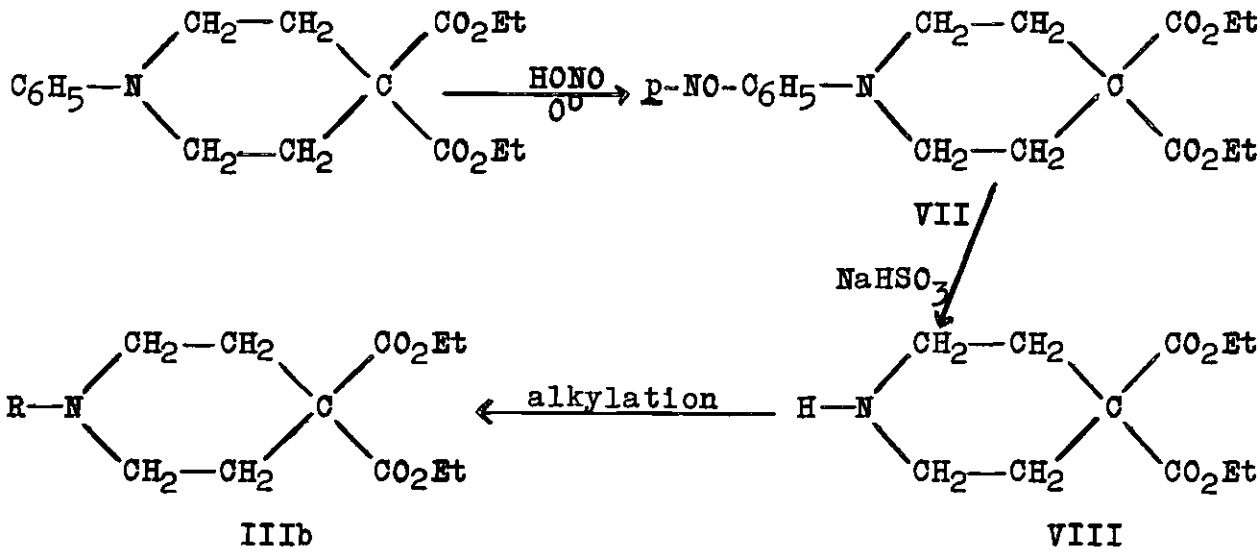

Figure 6. Proposed Alternative Synthesis of 1-Alkyl-4,4-dicarbethoxypiperidines from 1-Phenyl-4,4-dicarbethoxypiperidine

sequence, 1-phenyl-4,4-dicarbethoxypiperidine, is best prepared by the method of Figure 4. This ester is an N,N-dialkylaniline derivative and should, therefore, be readily convertible into a p-nitroso compound (VII) by means of the well-known reaction involving treatment with nitrous acid in the cold. Compound VII might then be cleaved with a nucleophilic reagent to give 4,4-dicarbethoxypiperidine (VIII). This ester (VIII) would

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(30) G. C. Allen, private communication.

then serve as a convenient intermediate from which the desired compounds (IIIb) might be prepared by any of several alkylation techniques. The common method of cleaving p-nitroso-N,N-dialkylanilines requires prolonged treatment with an excess of boiling aqueous alkali and would obviously not be suitable in the present case, since concomitant hydrolysis of the ester groups would undoubtedly occur. The resulting zwitterionic amino acid would be rather difficult to separate from the reaction mixture and would require re-esterification to afford VIII. A more attractive method for effecting this cleavage involved the use of concentrated aqueous sodium bisulfite (31), and, in addition, it seemed likely that sodium ethoxide in boiling ethanol might be capable of effecting the desired transformation.

Another approach to IIIb is outlined in Figure 7. The starting material for this sequence is the readily available pyridine-4-carboxylic acid (IX), commonly called isonicotinic acid. The first step is the conversion of this acid to its ethyl ester (X), either directly, by treatment with excess ethanol and a mineral acid (32, 33, 34), or indirectly, by

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(31) R. Munch, G. T. Thannhauser, and D. L. Cottle, J. Am. Chem. Soc., 68, 1297 (1946).

(32) M. Pailer, K. Schneglberger, and W. Reifschneider, Monatsh., 83, 513 (1952); C. A., 47, 2186 (1953).

(33) M. V. Rubtsov, J. Gen. Chem. U. S. S. R., 13, 702 (1943); C. A., 39, 706 (1945).

(34) H. Gilman and H. S. Broadbent, J. Am. Chem. Soc., 70, 2755 (1948).

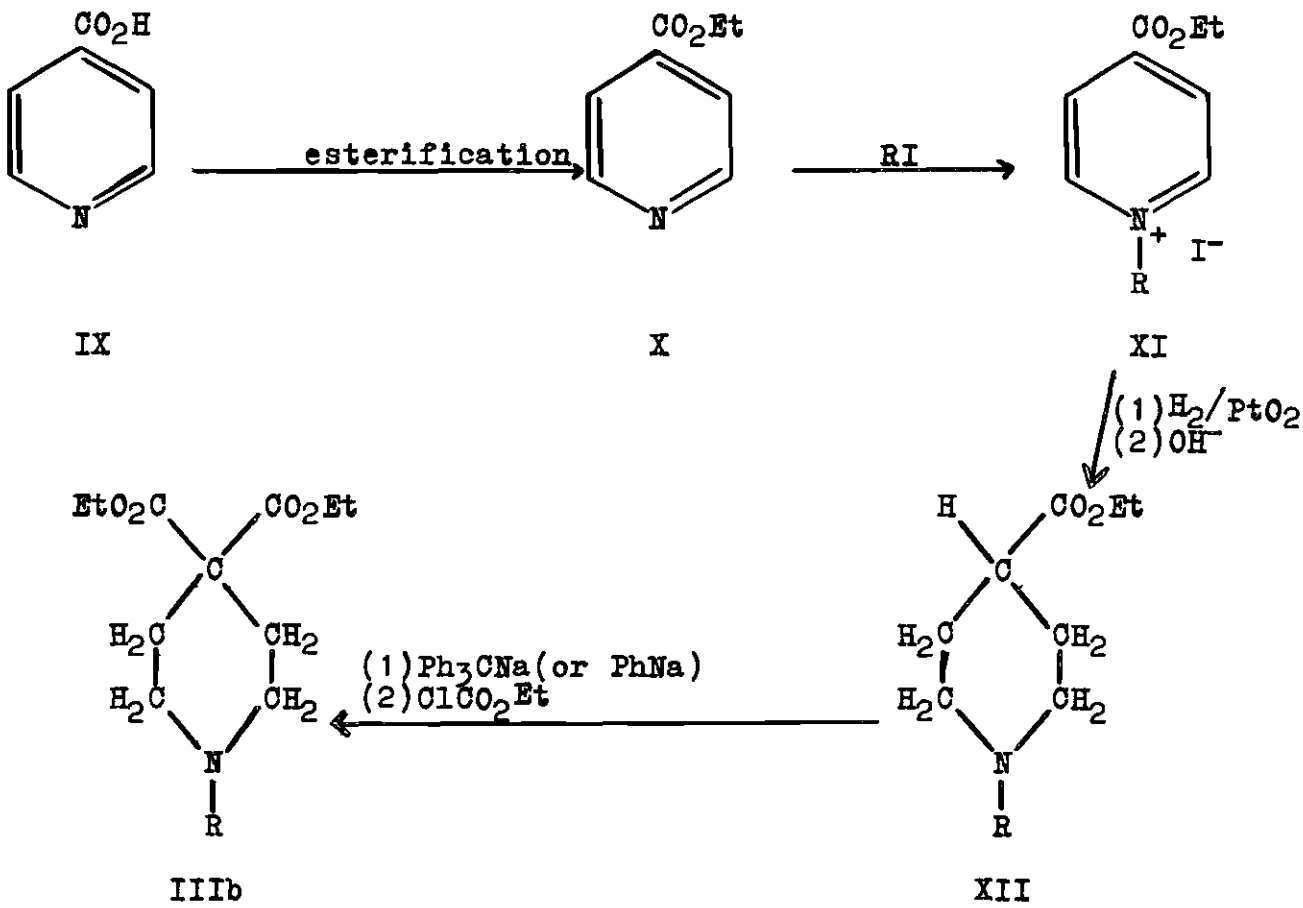

Figure 7. Proposed Alternative Synthesis of 1-Alkyl-4,4-dicarbethoxypiperidines from Isonicotinic Acid

alcoholysis of an intermediate diacid halide obtained from IX and thionyl chloride (35). The alkyl iodides (XI) are then prepared in the usual manner (36) and hydrogenated with platinum oxide under mild conditions to give hydroiodides of the piperidine monoesters. From these the free bases (XII) are

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(35) G. Lock, Pharm. Ind., 14, 366 (1952); C. A., 47, 10531 (1953).

(36) J. Krapcho, U. S. Patent 2,759,942 (Aug., 1956); C. A., 51, 11394 (1957).

obtained in the usual manner (36, 37). The final step is the conversion of XII to IIIb by carbethoxylation of the tertiary carbon atom.

Monoesters with two hydrogens alpha to the ester function are readily converted to the corresponding malonic esters by treatment with diethyl carbonate in the presence of sodium ethoxide (38). However, this reaction fails entirely when one alpha-hydrogen has been replaced by an alkyl substituent. Decreased acidity of the remaining alpha-hydrogen is apparently the principal reason for this failure. Many bases of considerably greater strength than ethoxide have been used in attempts to effect this type of condensation, but at the present time the only reagent known to be effective is triphenylmethylsodium. The serviceability of this very strong base is exemplified by its use in the carbethoxylation of ethyl isobutyrate - the malonic ester derivative is obtained in 75 per cent yield using ethyl chloroformate as the source of the second carbethoxy group (39). Moreover, triphenylmethylsodium readily removes the tertiary hydrogen atom from 1-methyl-4-carbethoxypiperidine, and the resulting enolate anion can be C-alkylated with benzyl halides in good yields

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(37) T. Tsukamoto and T. Komori, Pharm. Bull, (Japan), 3, 243 (1955); C. A., 50, 6565 (1956).

(38) V. H. Wallingford, A. H. Homeyer, and D. M. Jones, J. Am. Chem. Soc., 63, 2056 (1941).

(39) B. E. Hudson, Jr., and C. R. Hauser, ibid., 3156.

(36). In view of these results, it seemed quite possible that this ester and other esters in series XII could be readily carbethoxylated in the 4-position using a similar technique.

Although triphenylmethylsodium is the reagent of choice for the proposed reaction, its method of preparation is tedious, and rather elaborate apparatus is required for its use (39, 40). A possible alternative procedure which seemed worthy of investigation involved the use of another very strong base, phenylsodium, a reagent which could readily be generated in situ by the action of metallic sodium upon chlorobenzene and which would, therefore, present no special handling problems. The use of phenylsodium to form ester anions had apparently not been previously reported. It seemed likely that a complicating factor might be a side reaction involving attack of the base at the ester carbonyl function, a difficulty rarely encountered when triphenylmethylsodium is used. However, phenylsodium shows little tendency to add to nitrile groups, and it has been used with good results in the conversion of dialkylacetonitriles to the corresponding trialkyl derivatives. Recent examples of this reaction which were of particular interest in relation to the present work included the alkylation of 1-methyl-4-cyanopiperidine at the 4-position

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(40) C. R. Hauser and B. E. Hudson, Jr., in Organic Reactions, Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, pp. 286-288.

with propyl bromide (41) and with benzyl bromide (42). In view of these results, an attempt to carbethoxylate XII by phenylsodium catalysis seemed worthwhile.

Spiro-1'-phenylpiperidine-4',5-barbituric acid prepared by the method of Figure 4 was found not to be identical with spiro-1'-phenylpiperidine-4',5-barbituric acid previously reported as the product of the reaction of 5,5-bis(2-iodoethyl)barbituric acid with aniline in the presence of silver oxide (22). However, considerable evidence was obtained in the present investigation to indicate that the compound prepared by the method of Figure 4 had the correct structure.

Synthetic studies on the hydrolysis of spiro-1'-phenylpiperidine-4',5-barbituric acid (prepared by the new method) were undertaken, and several previously unreported materials were obtained as hydrolysis products. Independent syntheses were desirable for certain substances which might theoretically have resulted from hydrolysis, but which were not obtained under the conditions employed. Of prime interest in this connection was 1-phenyl-4,4-dicarboxamidopiperidine, and several possible methods for preparing this compound were investigated.

Surprisingly, several attempts to prepare 1-phenyl-4,4-dicarboxamidopiperidine from the corresponding diacid via the diacid halide were not successful. Reaction of the diacid with

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(41) C. A. Grob and E. Renk, Helv. Chim. Acta, 37, 1672 (1954).

(42) J. Schmutz and F. Künzle, ibid., 38, 925 (1955).

urea according to the procedure of Cherbuliez and Landolt (43) also failed to give the desired product. A trace amount of the diamide did result when the corresponding diester was allowed to stand with an excess of concentrated aqueous ammonium hydroxide over a period of several days; however, the yield could not be increased by running the ammonolysis under more vigorous conditions, and a better method of synthesis was desirable.

A possible direct method for preparing the diamide was alkylation of malonamide with bis(2-p-toluenesulfonyloxyethyl)-phenylamine, as shown in Figure 8. The ditosylate was readily

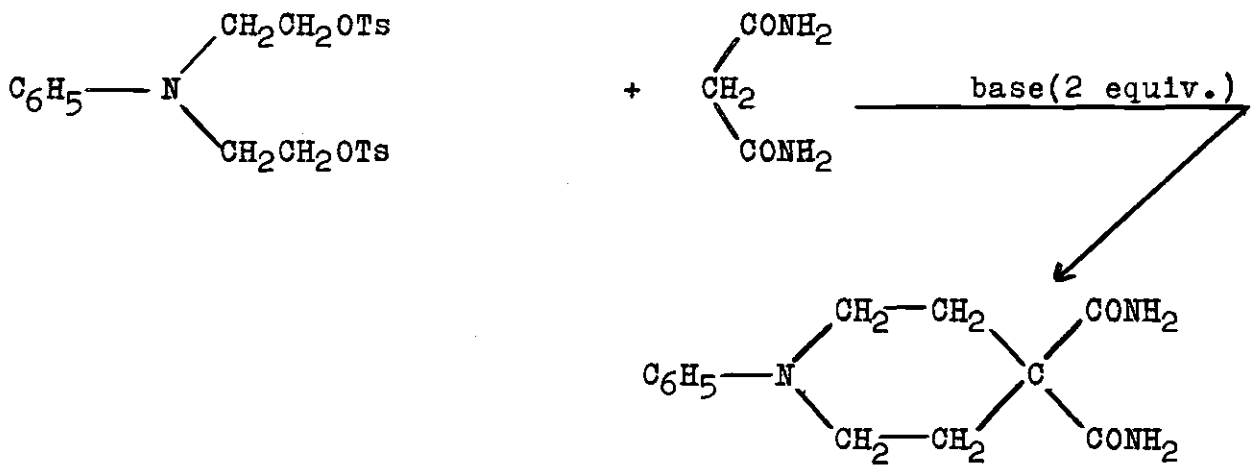

Figure 8. Proposed Synthesis of 1-Phenyl-4,4-dicarboxamidopiperidine

available by the method of Figure 4, and the procedure looked particularly attractive in view of the earlier successful preparation of 1-aryl-4,4-dicarbethoxypiperidines (IIIa) by a

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(43) E. Cherbuliez and F. Landolt, Helv. Chim. Acta, 29, 1438 (1946).

similar reaction shown in Figure 4. However, the methylene hydrogen atoms in malonamide are much less labile than in malonic esters, and C-alkylation of malonamide is known to be rather difficult. Only a few examples of this type of reaction have been reported.

In 1909 Conrad and Schulze were able to prepare 2-methyl- and 2-ethylmalonamide by treatment of the parent compound with methyl or ethyl iodide in the presence of the corresponding sodium alkoxides (44). However, the yields were rather low (39 per cent for the ethyl derivative) even when large excesses of halide and base were employed, and the introduction of a second alkyl group was not possible. The only practical method found for effecting the dialkylation of malonamide was that of Shimo and Wakamatsu (45). This method utilizes alkali hydroxides or amides in liquid ammonia as catalysts and gives satisfactory yields of simple 2-monoalkyl and 2,2-dialkylmalonamides when alkyl halides are used as the alkylating agents. However, the procedure suffers from the disadvantage that elevated pressures are usually required.

A common method for preparing amides involves ammonolysis of the corresponding esters. However, disubstituted malonic esters undergo no appreciable reaction with concentrated ammonium hydroxide under normal conditions (46), and high tempera-

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(44) M. Conrad and A. Schulze, Ber., 42, 729 (1909).

(45) K. Shimo and S. Wakamatsu, J. Org. Chem., 24, 19 (1959).

(46) P. B. Russell, J. Am. Chem. Soc., 72, 1853 (1950).

tures and pressures must be used to obtain satisfactory yields of the corresponding malonamides from these materials.[1]

In view of the above facts, better methods of synthesis for alkyl- (especially dialkyl-) malonamides are clearly desirable. The reaction proposed in Figure 8 was of particular interest in this connection since, apparently, no attempt to alkylate malonamide with a sulfonic ester had been previously reported. Accordingly, a detailed study of this reaction employing a variety of bases and conditions was undertaken.

As the final portion of the program of work, quantitative kinetic studies on the base-catalyzed hydrolysis of barbiturates were undertaken. The necessary data were obtained using a modification of the spectrophotometric method described by Daugherty (14), and the compounds of interest were the spiro-amino barbituric acids and common barbiturate hypnotics.

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[1]However, the discovery of proper conditions is not always easy. See pp. 86-87.

CHAPTER III

EXPERIMENTAL

All boiling points and melting points are uncorrected. The melting points were determined in capillary tubes heated in an aluminum block at a rate of 1-2° per minute, unless otherwise specified. Elemental microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee, or by Drs. Weiler and Strauss, Oxford, England.

Preparation of Spiro-1'-methylpiperidine-4',5-barbituric Acid

4,4-Dicarbethoxytetrahydropyran.--This ester was prepared according to the procedure of Harnest and Burger (47). Duplicate runs on a four-molar scale gave yields of 50 and 51 per cent.

Spirotetrahydropyran-4',5-barbituric acid (monohydrate).--This compound was prepared from 4,4-dicarbethoxytetrahydropyran and urea using the procedure recommended by Stanfield and Daugherty (22). Duplicate runs on a two-molar scale gave yields of 22 and 29 per cent. In the second run 31.8 per cent of the unreacted ester was recovered, so that the yield based on the amount of ester actually consumed during the reaction was 42.5 per cent.

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(47) G. H. Harnest and A. Burger, J. Am. Chem. Soc., 65, 379 (1943).

5,5-Bis(2-iodoethyl)barbituric acid.--This compound was prepared by cleaving spirotetrahydropyran-4',5-barbituric acid with 96 per cent phosphoric acid and potassium iodide. The procedure was essentially the same as that described by Stanfield and Daugherty (22), except that the reaction mixtures were more conveniently agitated by vigorous mechanical stirring rather than by shaking. A maximum yield of 82 per cent was obtained using a reaction time of 17 hr. and recrystallizing the product from dioxane-water. The average yield from several runs using reaction times of 4-6 hr. and aqueous ethanol as the recrystallization solvent was only 49 per cent. The amount of spirotetrahydropyran-4',5-barbituric acid used as starting material in these preparations varied from approximately 0.1 to 0.3 mole, and no correlation between quantity of starting material and percentage yield was observed.

Spiro-1'-methylpiperidine-4',5-barbituric acid.--This compound was prepared according to Stanfield and Daugherty (22), except that the reaction mixtures were stirred mechanically rather than shaken. The average yield of several runs starting with 0.06 to 0.15 mole of 5,5-bis(2-iodoethyl)barbituric acid was 50 per cent. In most of these experiments concentration of the mother liquors from which the pure product had been obtained yielded considerable amounts of an unidentified material, m. p. 136-138°, which failed to react when refluxed at length with excess methyl iodide.

Hydrolysis of 5,5-Diethylbarbituric Acid

Introduction.--In general, work-up of the reaction mixtures was patterned after the procedure described by Aspelund (19). However, certain modifications of this procedure were introduced, so that the chief product fractions obtained in the following experiments do not correspond exactly to those which would have been obtained by Aspelund's original method. Each product fraction obtained in the present work was subjected to an exhaustive series of techniques in efforts to resolve it completely into pure components. Recourse was had to vacuum sublimation, chromatography on silicic acid columns, fractional crystallization, and extraction with a large variety of common solvents. In spite of these intensive efforts, many of the fractions could not be purified; hence, the percentage yields of products reported below do not represent the maximum values obtainable.

In the following résumés the chief modifications introduced into Aspelund's work-up procedure are described, and mention is made of all materials thought to have been obtained in reasonably pure form. Product fractions not specifically discussed may be assumed to have resisted further purification.

Experiment 1. Preparation of 2-ethylbutyrylurea.--In a 500-ml. round-bottomed flask equipped with a reflux condenser were placed 18.4 g. (0.100 mole) of 5,5-diethylbarbituric acid (Merck's U. S. P. grade) and 20.7 ml. (0.100 mole) of 4.83 molar aqueous sodium hydroxide. Two hundred ml. of distilled

water was added, and the mixture was refluxed continuously for 5.5 hr. It was then cooled rapidly to room temperature under the water tap and placed in the refrigerator overnight. On filtering, 3.09 g.[1] of white, crystalline 2-ethylbutyrylurea (A), m. p. 206-207° (lit. (19) m. p. 207-208°), was recovered. An ether extract of the filtrate yielded 0.50 g. of intractable white solid melting over an extremely wide range, and a benzene extract yielded 0.1 g. of material having similar characteristics. The aqueous moiety was then made slightly acidic to litmus with concentrated hydrochloric acid, and the white solid (B) which precipitated was recovered by suction filtration. It weighed 2.55 g. and melted at 188-189.5° alone or upon admixture with an authentic sample of starting material. An additional 2.50 g. of solid (C) was obtained by extracting the acidified filtrate completely with 1150 ml. of ether in five portions. Treatment of C with a small amount of boiling ligroin removed 0.08 g. of material (C-1), most of which melted with sublimation between 95-100°, and which dissolved in water to give a solution weakly acidic to litmus. This fraction could not be further purified by vacuum sublimation or by chromatography on silicic acid, eluting first with chloroform and then with chloroform-methanol. The 2.42 g. of ligroin-insoluble material (C-2) which remained was identified as starting material by means of melting point and mixed melting

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[1]Unless otherwise specified, all product weights recorded in this chapter are of thoroughly air-dried materials.

point determinations. Other attempts to extract the aqueous moiety with common solvents yielded no products. Concentration of the solution to a volume of approximately 25 ml. by boiling and then by warming under aspirator pressure precipitated (after cooling) an additional 3.6 g. of 2-ethylbutyrylurea (D) contaminated with traces of a higher-melting impurity.

The total amount of unreacted barbital recovered (fractions B and C-2) was 4.97 g., or 27 per cent. The total amount of 2-ethylbutyrylurea obtained (fractions A and D) was 6.69 g. This weight corresponds to a yield of 42 per cent, based on the amount of starting material used, or 58 per cent, based on the amount of barbital actually consumed in the reaction.

Another run of this experiment was made using 9.2 g. (0.050 mole) of 5,5-diethylbarbituric acid, 10.35 ml. (0.050 mole) of 4.83 molar aqueous sodium hydroxide, and 100 ml. of distilled water. The reflux period was 5.5 hr., and the work-up was similar to that used in the earlier run. However, a considerable portion of time (several days) elapsed between acidification and concentration of the reaction mixture, and the fraction corresponding to D in the preceding run could not be purified, evidently because of extensive contamination with materials produced by acid-catalyzed hydrolysis. The total yield of 2-ethylbutyrylurea (A) was only 1.8 g., or 23 per cent.

Experiment 2. Preparation of diethylmalonamic acid.--In a 250-ml. round-bottomed flask equipped with a reflux condenser

were placed 18.4 g. (0.100 mole) of 5,5-diethylbarbituric acid and 59 ml. (0.300 mole) of 5.10 molar aqueous sodium hydroxide. The solution was then diluted with 41 ml. of distilled water and refluxed intermittently for a total of 6 hr. during a 24-hr. period. The work-up yielded no unreacted starting material or 2-ethylbutyrylurea, and the only pure product isolable in good yield was diethylmalonamic acid. Most of this material was precipitated from the reaction mixture by adding excess hydrochloric acid. This precipitate (A) weighed 4.1 g. (26 per cent) and had m. p. 133-134° (lit. (20) m. p. 144-145° dec.) with vigorous evolution of a gas. The melt solidified on cooling and remelted at 105-106°.[1] Further purification of diethylmalonamic acid was found to be best accomplished by recrystallizing from ether using approximately 100 ml. per g. of crude solid. The white prisms obtained in this way melted at 143-143.5°. Recrystallization of the crude material from acetone-chloroform gave a product which had m. p. 139.5-140.5° and was also of high purity, as shown by a neutral equivalent determination against aqueous sodium hydroxide using phenolphthalein as the indicator.

Calculated for $C_7H_{13}O_3N$: neutral equivalent, 159.

Found: neutral equivalent, 158.

The other product fractions contained varying amounts of a clear, viscous liquid which was probably 2-ethylbutyric

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[1] The lit. (20) m. p. of 2-ethylbutyramide is 111-112°.

acid. Some of these fractions did yield small amounts of diethylmalonamic acid on further treatment, but the total weight of material obtained in this way was only 0.8 g. This additional amount of product raised the total yield of crude diethylmalonamic acid to 31 per cent.

Extraction of the original reaction mixture (before acidification) with five 50-ml. portions of ether and evaporation of the combined ether extracts to dryness yielded 0.03 g. of a neutral white solid (B) which melted sharply at 222°.[1] The Nujol mull infrared spectrum of B was very similar to the spectrum of 1-phenyl-4,4-dicarboxamidopiperidine (Figure 14) in the region from 2.5 to 6.2 microns, providing evidence for the presence of the diamide function in B.

In an earlier run, 9.2 g. (0.050 mole) of 5,5-diethylbarbituric acid, 30 ml. (0.150 mole) of 4.83 molar aqueous sodium hydroxide, and 80 ml. of distilled water were refluxed intermittently for 5.5 hr. over a 30-hr. period. The larger quantity of water made the separation of products rather difficult. Extraction of the basic reaction mixture with ether gave none of the substance B obtained in the other run, and no solid precipitated when the solution was made strongly acidic to litmus. Concentration of the acidified mixture by boiling to a volume of about 75 ml., followed by cooling, yielded 5.6 g. of white solid (C) which melted over an

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[1] The lit. (46) m. p. of diethylmalonamide is 225°.

extremely wide range. Apparently considerable hydrolysis had occurred during the concentration. All attempts to purify C gave only trace amounts of diethylmalonamic acid. The aqueous filtrate from C was extracted with ether and the ether extracts evaporated to dryness to yield 1.24 g. of solid (D). Chromatography of D on silicic acid using chloroform and then chloroform-methanol as eluents gave small amounts of three fractions with narrow melting point ranges. These were: an acidic material (D-1), m. p. 102-103.5°; an acidic material (D-2), m. p. 127-128° with evolution of a gas; and a neutral material (D-3), m. p. 218-222°. The melting point of D-1 does not correspond to that reported for any of the expected hydrolysis products. Fraction D-2 was probably diethylmalonic acid (lit. (48) m. p. 125°), since the melt failed to solidify on cooling. Fraction D-3 was shown by a comparison of infrared spectra to be identical with compound B obtained in the previously described run of this experiment.

Hydrolysis of Spirotetrahydropyran-4',5-barbituric Acid

Introduction.--The conditions used for the hydrolysis of this compound were roughly parallel to those employed for the hydrolysis of barbital. The work-up procedures were also similar, but not identical, since the hydrolysis products of spirotetrahydropyran-4',5-barbituric acid are more soluble in

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(48) S. B. Speck, J. Am. Chem. Soc., 74, 2876 (1952).

water than the corresponding compounds obtained from the hydrolysis of barbital.

Experiment 1. Preparation of 4,4-dicarboxytetrahydropyran.--In a 50-ml. round-bottomed flask equipped with a reflux condenser were placed 1.08 g. (0.00500 mole) of spirotetrahydropyran-4',5-barbituric acid monohydrate and 13.6 ml. (0.0150 mole) of 1.10 molar aqueous sodium hydroxide. The solution was refluxed for 6.0 hr., then cooled rapidly to room temperature and refrigerated at 0° for approximately an hour. A small amount of light gray, infusible material was filtered off, and the filtrate was extracted with 90 ml. of ether in six portions. Evaporation of the combined extracts afforded only a small amount of solid. The aqueous moiety was treated with hydrochloric acid until acidic to congo red and returned to the refrigerator, but no precipitate separated from the solution, which now had a volume of 35-40 ml. However, complete extraction of this solution with ten 20-ml. portions of ether, followed by treatment of the combined extracts with Drierite and then by removal of the ether under aspirator pressure, afforded 0.81 g. (93 per cent) of pure 4,4-dicarboxytetrahydropyran, m. p. 175-176° with evolution of a gas (lit. (22) m. p. 172-173°). The melt solidified on cooling and remelted at 85-87°.[1] Evaporation of the aqueous portion to dryness under the aspirator left 0.91 g. of white solid as residue. Nothing

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[1] The lit. (22) m. p. of 4-carboxytetrahydropyran is 86.5-87°.

could be extracted from the solid by treatment with boiling acetone or boiling ether; however, it must have been composed largely of sodium chloride, since 0.86 g. of this salt would be produced by complete neutralization of the reaction mixture.

Experiment 2.--In a 50-ml. round-bottomed flask equipped with a reflux condenser were placed 1.08 g. (0.00500 mole) of spiro-tetrahydropyran-4',5-barbituric acid monohydrate, 4.53 ml. (0.00500 mole) of 1.10 molar aqueous sodium hydroxide, and 9.1 ml. of distilled water. The solution was refluxed for 6.0 hr., then rapidly cooled to room temperature and refrigerated overnight. On filtering, 0.10 g. of white needles (A) melting at 229-233° with slight effervescence was obtained. The Nujol mull infrared spectrum of A indicated it was a mixture of tetrahydropyran-4-carbonylureide and 4-carboxytetrahydropyran-4-carbonylureide.[1] Extraction of the filtrate from A with six 15-ml. portions of ether removed only 0.01 g. of solid material, and treatment of the filtrate with hydrochloric acid until it was acidic to congo red paper failed to produce a precipitate. Extraction of the acidic solution with ten 20-ml. portions of ether removed 0.43 g. of white solid (B) which melted over such a wide temperature range (of about 100°) that purification did not appear feasible. Evaporation of the aqueous layer under the aspirator at room temperature left only a small amount of sodium chloride as residue.

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[1] See Figure 24 of reference (14).

The low total weight of the organic fractions is attributed to manipulation losses and/or codistillation of product(s) during evaporation of the acidified solution.

Hydrolysis of Spiro-1'-phenylpiperidine-4',5-barbituric Acid

Introduction.--The only experiments described in this section are those in which samples of spiro-1'-phenylpiperidine-4',5-barbituric acid were used as starting materials. Hydrolysis of this compound also undoubtedly occurred in some of the attempts to prepare it; however, discussion of these results is postponed until a later section.[1]

Experiment 1. Preparation of 1-phenyl-4,4-dicarboxypiperidine.--In a 50-ml. round-bottomed flask equipped with a reflux condenser were placed 1.37 g. (0.00500 mole) of spiro-1'-phenylpiperidine-4',5-barbituric acid and 13.6 ml. (0.0150 mole) of 1.10 molar aqueous sodium hydroxide. The mixture was refluxed for 6.0 hr., rapidly cooled to room temperature, and then refrigerated for several hours. After removal of a small amount of an infusible solid by suction filtration, the solution was extracted with five 20-ml. portions of ether and then carefully adjusted with concentrated hydrochloric acid to a pH of 4.4, as measured by a Beckman "Zeromatic" pH meter.[2] No solid was obtained from the ether extract; but the acidified solution

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[1] See below, pp. 75-77.

[2] All of the pH measurements reported in this chapter were made with this instrument.

deposited a precipitate (A) which was recovered by suction filtration, washed with a few small portions of cold water, and air-dried. Substance A melted at 174-175° with vigorous evolution of a gas and was shown to be 1-phenyl-4,4-dicarboxypiperidine by a mixed melting point determination with an authentic sample of this compound.[1] The yield was 0.24 g. (19 per cent).

Extraction of the mother liquor from A with five 40-ml. portions of ether failed to remove any products. Evaporation of the mother liquor to dryness by boiling left a white solid residue from which no organic products could be extracted using boiling acetone, boiling ether, or boiling absolute ethanol.

Experiment 2. Preparation of 1-phenylpiperidine-4-carbonylureide and 1-phenyl-4,4-dicarboxypiperidine.--In a 50-ml. round-bottomed flask equipped with a reflux condenser were placed 1.37 g. (0.00500 mole) of spiro-1'-phenylpiperidine-4',5-barbituric acid, 4.53 ml. (0.00500 mole) of 1.10 molar aqueous sodium hydroxide, and 9.1 ml. of distilled water. The solution was refluxed for 6.0 hr., then cooled rapidly to room temperature and refrigerated for several hours. The white solid (A) which precipitated was recovered by suction filtration, washed on the filter with several small portions of cold water, and air-dried. This substance melted at 237-238.5° and did not

[1] See below, pp. 78-79.

depress the melting point of an authentic sample of 1-phenylpiperidine-4-carbonylureide.[1] The yield of A was 0.55 g. (45 per cent).

Extraction of the mother liquor from A with six 20-ml. portions of ether yielded no products. The mother liquor was then adjusted to pH 4.4 with concentrated hydrochloric acid and cooled near 0°. Scratching the inner surface of the container with a glass rod induced precipitation, and the precipitate (B) was filtered off, washed with small portions of cold water, and air-dried. The dry solid (B) was pure 1-phenyl-4,4-dicarboxypiperidine, m. p. 178.5-179°. The yield was 0.26 g. (21 per cent).

Extraction of the mother liquor from B with 200 ml. of ether in ten portions yielded no products. The mother liquor was then evaporated to dryness at room temperature under aspirator pressure to give a brownish-white solid (C). Extraction of C with 25-30 ml. of boiling acetone, followed by evaporation of the acetone under aspirator pressure, afforded a tiny amount of material, m. p. (mostly) 132-136°, which was not further investigated. Further extraction of C with acetone in a Soxhlet apparatus for 24 hr., followed by evaporation of the acetone under aspirator pressure, yielded only a trace of amorphous material.

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[1] See below, pp. 77-78.

Experiment 3. Preparation of 1-phenyl-4-carboxypiperidine-4-carbonylureide.--A small, unweighed sample of spiro-1'-phenylpiperidine-4',5-barbituric acid was dissolved in a few ml. of aqueous sodium hydroxide to give a solution of pH 12. After standing at room temperature for 10 min., the solution was carefully adjusted to pH 3.8 by dropwise addition of hydrochloric acid. No precipitation occurred during the acidification, indicating that little, if any, of the barbituric acid was present, since this compound is only slightly soluble at neutral pH's. The solution was partially frozen by placing it in a bath composed of acetone and dry ice. It was then allowed to thaw slowly over a period of 1.5 hr. in the refrigerator at a temperature near 0°. The white precipitate was filtered off, washed sparingly on the filter with fresh portions of cold water, and air-dried. This material was pure 1-phenyl-4-carboxypiperidine-4-carbonylureide, m. p. 229-230° (dec.), mixed m. p. 208-224° with starting material melting at 230.5-231.5°. A mixed melting point determination with an authentic, analytically pure sample of this malonuric acid[1] showed no depression.

Hydrolysis of Spiro-1'-methylpiperidine-4',5-barbituric Acid

Introduction.--The products resulting from the hydrolysis of this compound were found not to be of the type which would have been produced by "normal" stepwise degradation of the pyrimidine

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[1] See below, pp. 75-76.

ring. A diligent search was made for conditions which would lead to some of the "normal" products, but none of these materials were obtained in any of the following experiments.

Experiment 1.--In a 50-ml. round-bottomed flask equipped with a reflux condenser were placed 4.33 g. (0.0206 mole) of spiro-1'-methylpiperidine-4',5-barbituric acid, 4.04 ml. (0.0206 mole) of 5.10 molar aqueous sodium hydroxide, and 26 ml. of distilled water. The mixture was refluxed for 6.0 hr. and then cooled rapidly to room temperature. A white solid (A) present in the lower part of the condenser was washed into the solution with 5-10 ml. of water. The solution was then filtered to remove a small amount of dark material and extracted with 200 ml. of ether in several portions. The combined extracts were dried over Drierite and evaporated under aspirator pressure to give a small amount of a viscous liquid which could not be induced to crystallize. Acidification of the solution with concentrated hydrochloric acid until it gave an acid reaction to bromphenol blue produced no precipitate, and extraction of the acidified solution with 300 ml. of ether in several portions removed no products. However, removal of the water by boiling and then by warming at 80° afforded a residue (B) composed of a crystalline solid and a clear, viscous liquid. This residue was extracted with acetone, and the extract was fractionated under reduced pressure. Most of the distillate was lost due to a leak in the apparatus; however, there was obtained a very small amount of clear liquid (C), b.

p. (approximately) 90-100°/4.5 mm., which failed to solidify on refrigeration. Liquid C had the odor of pyridine, dissolved readily in water to give a strongly basic solution, but was only slightly, if at all, soluble in ether.

The solid (B-1) remaining from the acetone extraction weighed 2.48 g. and was, therefore, not composed entirely of sodium chloride, since the calculated weight of this salt for complete neutralization was only 1.21 g. Extraction of B-1 with 50 ml. of boiling absolute ethanol removed 0.28 g. of solid (B-1a), and left B-1b as residue. No organic materials could be separated from B-1b, and one of the major components of this fraction was undoubtedly ammonium chloride, as shown by its reaction with a boiling ethanolic suspension of freshly prepared silver oxide to liberate copious quantities of ammonia. A small portion of B-1a dissolved in water to give a solution strongly acidic to litmus. This solution deposited a heavy white precipitate upon treatment with aqueous silver nitrate. The remainder of B-1a was dissolved in a few milliliters of water to give a solution whose pH was carefully adjusted to 7.0 with aqueous sodium hydroxide. No material precipitated, but extraction with 250 ml. of ether in several portions, treatment of the combined extracts with Drierite, and evaporation of the ether under aspirator pressure afforded a few milligrams of solid (D) which melted at 208-215° after crystallization from an acetone-water mixture. Insufficient D was obtained to permit further investigation.

Experiment 2.--In a 50-ml. round-bottomed flask equipped with a reflux condenser were placed 2.64 g. (0.0125 mole) of spiro-1'-methylpiperidine-4',5-barbituric acid, 2.45 ml. (0.0125 mole) of 5.10 molar aqueous sodium hydroxide, and 18 ml. of distilled water. The mixture was refluxed for 6.0 hr., cooled rapidly to room temperature, and refrigerated. No precipitate separated; but as in the preceding experiment, a white solid (A) was present in the lower part of the condenser. After having been washed with acetone and allowed to air-dry, A was found to decompose at 90° and was shown to be ammonium carbonate by comparison of the Nujol mull infrared spectrum with the spectrum of an authentic sample. The yield of dried material was 0.41 g., or 34 per cent of theory, assuming one molecule of starting material was required to produce one molecule of ammonium carbonate.

The pH of the reaction mixture was adjusted to 7.0 with concentrated hydrochloric acid, and the mixture was returned to the refrigerator. After standing overnight, the solution had deposited no precipitate, and no products could be extracted with six 50-ml. portions of ether. Removal of the water by warming at 80° afforded a residue (B) composed of white crystals and a clear, viscous liquid. Fraction B was completely insoluble in benzene. Extraction of B with 50 ml. of boiling ether removed only a small quantity of the viscous liquid, but extraction with 30 ml. of absolute methanol at room temperature removed all of the liquid portion and left a solid residue

(B-1) from which nothing could be extracted by treatment with boiling acetone. B-1 decomposed partially when strongly heated in a Bunsen flame, dissolved readily in water to give a solution basic to litmus, and was probably composed largely or entirely of sodium carbonate and sodium chloride, as shown by the results of the next hydrolysis experiment.[1]

The methanolic extract of B was freed of solvent by evaporating under reduced pressure. The clear, viscous liquid (B-2) which remained deposited a few white crystals (B-2a) on cooling to 0°, but the bulk of the material failed to crystallize. B-2a failed to decompose on strong heating in a Bunsen flame and was not further investigated. Treatment of a small portion of B-2 with a few drops of concentrated hydrochloric acid gave a milky suspension. The suspension was treated with several milliliters of methanol, boiled, cooled, and filtered. The white solid (B-2b) that was recovered failed to melt or decompose in a Bunsen flame and was probably sodium chloride. Evaporation of the mother liquor from B-2b left a viscous liquid which was probably unreacted B-2.

All of B-2 was saved for further investigation.[1]

Experiment 3.--A solution containing the same quantities of starting materials used for Experiment 2 was refluxed 6.0 hr., cooled, filtered to remove a few black specks of solid, adjusted to pH 7.0, and evaporated at 80° to give the residue (B)

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[1] See below, p. 49.

obtained in Experiment 2. As in Experiment 2, ammonium carbonate was present in the reflux condenser, and the yield of this material in the present case was 0.38 g., or 32 per cent. Extraction of B with 40 ml. of absolute methanol at room temperature left a solid residue (B-1) which evolved a gas when treated with concentrated hydrochloric acid. The major constituents of B-1 were shown to be sodium carbonate and sodium carbonate monohydrate by comparing the Nujol mull infrared spectrum of B-1 with the spectra of authentic samples of these materials. Removal of the solvent from the methanolic extract of B under aspirator pressure left a liquid (B-2), which was combined with B-2 from Experiment 2. The combined materials were fractionated through a four-inch heated Vigreaux column to give:

fraction 1, b. p. 154-156°/7 mm., 1.64 g.

fraction 2, b. p. 159-170°/7 mm., 0.31 g.

Both fractions possessed faint, amine-like odors. Most of fraction 2 boiled at 159°, and the infrared spectrum of this material was practically identical to that of fraction 1 (Figure 15). A considerable amount of dark material, largely soluble in water, remained in the pot. Extraction of this residue with 40 ml. of boiling acetone removed a few drops of intractable brown liquid.

Further investigations of fractions 1 and 2 are reported on pp. 54-60.

Experiment 4.--A solution containing 2.64 g. (0.0125 mole) of spiro-1'-methylpiperidine-4',5-barbituric acid, 2.45 ml. (0.0125 mole) of 5.10 molar aqueous sodium hydroxide, and 8 ml. of distilled water was allowed to stand at room temperature in a tightly-stoppered flask. An ammonia odor was first noticed after about nine days of standing. After a total standing time of ten days, the solution was frozen in dry ice and allowed to thaw slowly in the refrigerator. The only precipitate was a small amount of brownish powder, which was filtered off and discarded. Extraction of the filtrate with six 25-ml. portions of ether removed no products. When the filtrate was made acidic to litmus with concentrated hydrochloric acid, a considerable amount of gas (presumably carbon dioxide) was evolved. The acid solution yielded no precipitate when it was frozen and then allowed to thaw slowly in the refrigerator. Extraction with six 25-ml. portions of ether removed no products, so the pH of the solution was readjusted to 7.0 with aqueous sodium hydroxide, and the water was removed by warming at 70°. The residue (A) consisted of crystals mixed with a clear, viscous liquid. Some of the liquid (A-1) was removed by extracting with 20 ml. of acetone at room temperature, and the remaining portion of A-1 dissolved when A was extracted with 30 ml. of absolute methanol. The solid fraction (A-2) of A yielded no organic products when extracted continuously with acetone in a Soxhlet apparatus for 21.5 hr.

Liquid A-1 was recovered by evaporating the solvents under aspirator pressure. The infrared spectrum of A-1 (Figure 16) was similar to that of fraction 1, p. 49 (Figure 15); however, the spectrum of the latter material showed a sharp band of high intensity at 5.63 microns which was absent in the spectrum of A-1. A sample of A-1 heated for two hours at 160-170° showed a shoulder at 5.63 microns of very low intensity. Purification of A-1 by distillation was not attempted because of the small amount of material on hand.

Experiment 5.--A solution containing 2.64 g. (0.0125 mole) of spiro-1'-methylpiperidine-4',5-barbituric acid, 2.45 ml. (0.0125 mole) of 5.10 molar aqueous sodium hydroxide, and 8 ml. of distilled water was refluxed for 0.50 hr., cooled rapidly to room temperature, and then refrigerated at 0° for approximately 0.5 hr. The evolution of a basic gas was first noticed after about 15 min. of refluxing, and ammonium carbonate began to form in the condenser at about the same time. As in the earlier experiments, no products could be obtained from the basic reaction mixture either by extracting with ether or by filtering. The mixture also failed to yield products when it was made strongly acidic to litmus with concentrated hydrochloric acid and then treated similarly. Therefore, the pH of the solution was readjusted carefully to 7.0 with sodium hydroxide and the solution then extracted with six 25-ml. portions of sec-butyl alcohol. The combined extracts (A) were dried over anhydrous magnesium sulfate. The water was removed from the aqueous moiety (B) by warming at 75°.

After the magnesium sulfate had been filtered from A, the solvent was removed by warming in a water bath under aspirator pressure. The residue (A-1) was a clear, viscous liquid which failed to crystallize at 0°. An infrared spectrum of A-1 showed that the principal constituent was fraction 1, p. 49. However, in the case of A-1, the band at 5.63 microns appeared only as a weak shoulder on the strong peak at approximately 6 microns. An attempt was made to prepare a methiodide of A-1 by refluxing the material for 20 hr. in the dark in an ethanolic solution containing an excess of C. P. methyl iodide. Evaporation of the excess methyl iodide and ethanol left a reddish-brown gum which was intractable.

The residue from B was a mixture of crystals (B-1) and oily liquid (B-2). The liquid (B-2) was removed by extracting with methanol and, by a comparison of infrared spectra, was shown to contain a considerable amount of fraction 1, p. 49. The band at 5.63 microns was only a weak shoulder in the spectrum of B-2, however.

Extraction of B-1 with acetone for three days in a Soxhlet apparatus failed to remove any material.

Experiment 6.--A solution containing 0.50 g. (0.0024 mole) of spiro-1'-methylpiperidine-4',5-barbituric acid, 0.1 ml. (0.0005 mole) of 5.10 molar aqueous sodium hydroxide, and 10 ml. of distilled water was allowed to evaporate at 60-70° over a period of 27.3 hr. Extraction of the semi-solid residue with 15 ml. of methanol left some crystalline material (A) which was shown

to be composed largely of sodium bicarbonate by comparing its Nujol mull infrared spectrum with that of an authentic sample. Evaporation of the methanolic extract under the aspirator afforded a semi-solid residue (B) having a faint amine-like odor. The infrared spectrum of B (Figure 17) was very similar to that of fraction 1, p. 49; however, a sharp peak was present at 4.60 microns in the spectrum of B.

Experiment 7.--A solution of 0.50 g. of spiro-1'-methylpiperidine-4',5-barbituric acid in 10 ml. of distilled water was allowed to evaporate at 60-70° over a period of 37 hr. The residue was a light brown, viscous liquid (A) whose infrared spectrum (Figure 18) was practically identical with the spectrum of fraction B, Experiment 6.

Experiment 8.--A solution containing 1.00 g. of spiro-1'-methylpiperidine-4',5-barbituric acid, 5 ml. of concentrated hydrochloric acid, and 5 ml. of distilled water was refluxed for 6.75 hr., then cooled rapidly to room temperature and refrigerated overnight at 0°. No precipitate appeared. Approximately one-half (A) of the solution was removed, and the second half (B) was refluxed for an additional 24 hr., during which time an additional 5 ml. of concentrated hydrochloric acid was added. When A was made strongly basic to litmus with 4.3 molar sodium hydroxide, a considerable amount of ammonia was evolved, but no precipitate appeared. Extraction of the basic solution with six 25-ml. portions of ether removed no products. Careful dropwise addition of acetone to the basic

solution until two liquid layers were present failed to produce any turbidity.

Fraction B yielded no precipitate upon cooling or upon being made strongly basic to litmus with 4.3 molar sodium hydroxide; however, the addition of base did liberate a considerable amount of ammonia. The basic solution was re-acidified with concentrated hydrochloric acid and evaporated to dryness at 70° to afford a solid residue (B-1). Extraction of B-1 with 50 ml. of boiling ether removed no products. Extraction with 25 ml. of methanol at room temperature removed only some solid material whose major constituent was shown (by means of the Nujol mull infrared spectrum) to be ammonium chloride.

Characterization of the Liquid Product Obtained in the Hydrolysis of Spiro-1'-methylpiperidine-4',5-barbituric Acid

pH determination.--Two drops of fraction 1, p. 49, in 1-2 ml. of distilled water gave a solution neutral to litmus. However, the pH of a solution containing four drops of fraction 1 in about 20 ml. of distilled water was determined to be 5.6 by means of a pH meter.

Elemental analysis.--Slow distillation of a portion of fraction 1, p. 49, through a four-inch heated Vigreaux column gave the results summarized in Table 1.

The infrared spectrum of cut 1 was identical in every respect with that of fraction 1 prior to re-fractionation.

Table 1. Re-fractionation of Fraction 1, P. 49

Cut	Boiling Point (°C.)	Pressure (mm. Hg)
1	95-97.7	1.7
2	97.7	1.7
3	98-94	1.7

When subjected to qualitative elemental analysis by the sodium fusion method, cut 1 gave a positive Prussian blue test for nitrogen and a negative silver nitrate test for halogen. Quantitative analysis of cut 2 gave: carbon, 54.53 per cent; hydrogen, 9.13 per cent; nitrogen, 8.35 per cent. The empirical formula calculated from these values is $C_{7.58}H_{15.20}N_{1.00}O_{2.90}$.

Attempted reaction with methyl iodide.--Fraction 2, p. 49, dissolved in excess C. P. methyl iodide with no evolution of heat. After standing at room temperature for several minutes, the solution was refluxed briefly. No precipitate appeared after overnight refrigeration. Cooling in a dry ice bath also failed to induce precipitation, and evaporation of the excess methyl iodide left a liquid residue having the odor of fraction 2.

Reaction with acetyl chloride.--When C. P. acetyl chloride was added dropwise to a few drops of fraction 1, p. 49, a vigorous exothermic reaction ensued, indicating that an acetyl derivative could probably be prepared in this way. Accordingly, 0.3 g. of fraction 2, p. 49, was placed in a test tube and treated

dropwise with the reagent until no more heat was evolved. When the contents of the tube were diluted to 5-10 ml. with water and then cooled, no precipitate was obtained. The solution was made slightly basic to litmus with solid sodium bicarbonate, but again there was no precipitate. The solution was then made slightly acidic to litmus with concentrated hydrochloric acid, concentrated, cooled (no precipitate had appeared), and finally evaporated to dryness by warming at 80°. Extraction of the solid residue (A) with 20 ml. of boiling acetone removed only a small amount of intractable, viscous material. The extraction of A was repeated using absolute methanol. Evaporation of the solvent afforded a white, crystalline solid (B) which decomposed when heated in a Bunsen flame, leaving a black, water-insoluble residue (probably carbon). The undissolved portion of A consisted of cubic crystals which failed to decompose in the Bunsen flame and were probably sodium chloride.

B was dissolved in boiling absolute methanol, and the solution was treated with ether slightly past the cloud point and then refrigerated for several days in a tightly-stoppered flask. The precipitate (B-1) was filtered off and determined to be sodium chloride by its failure to decompose in a Bunsen flame and by its positive reaction with aqueous silver nitrate. The mother liquor from B-1 was evaporated to dryness to afford a semi-solid residue (B-2). The Nujol mull infrared spectrum of B-2 was quite different from that of the starting material; however, it was impossible to determine from the spectrum whether or not any acetyl derivative was present.

Reaction with hydrochloric acid.--A 0.22-g. portion of fraction 1, p. 49, was placed in a 50-ml. round-bottomed flask; 15 ml. of concentrated hydrochloric acid was added; and the solution was refluxed for 1.0 hr. At the end of this time, an additional 5-ml. portion of acid was introduced. After another hour of refluxing, the solution was cooled to room temperature, allowed to stand overnight, and then concentrated to a volume of about 2 ml. Acetone was added slightly past the cloud point (30-40 ml. was required), and the mixture was refrigerated for several hours, but only a tiny amount of white powder precipitated. The solvents were then evaporated (partly by warming at 80° and partly by warming at a lower temperature under aspirator pressure), and the clear, light brown, liquid residue (A) was dissolved in the minimum amount of absolute ethanol (a tiny amount of insoluble material was removed by filtering). Careful, dropwise addition of ether precipitated some white crystals (1a) which were recovered by suction filtration. The crystals had m. p. 127-132° and were readily soluble in water to give a solution which was neutral to litmus, but which gave a heavy white precipitate when treated with aqueous silver nitrate. The infrared spectrum of 1a (Figure 19) indicated that it contained little, if any, unreacted starting material. Recrystallization of 1a from ethanol-ether afforded 0.01 g. of off-white crystals, m. p. 132.5-134.5°. This entire sample was dissolved in about 20 ml. of distilled water, and the pH of the solution was determined to be 6.23. The solution was diluted to 50 ml.

and used for the spectral determination described in the next section.

Ultraviolet spectra[1].--A solution (A) containing 0.205 g. of fraction 1, p. 49, and 100 ml. of distilled water absorbed in the ultraviolet at 225 millimicrons. Diluting an aliquot portion of A 1:10 with distilled water gave a solution (B) with absorption at 216 millimicrons (optical density 1.7), and diluting A 1:10 with 1.0 molar aqueous sodium hydroxide gave a solution (C) with a "cutoff" (optical density greater than 2.0) at 217-222.5 millimicrons. An aqueous solution containing about the same weight of 1a as solution B did of fraction 1 showed no ultraviolet absorption from 185 to 350 millimicrons, but a solution having the same weight of 1a in 1.0 molar aqueous sodium hydroxide as solution C did of fraction 1 exhibited a cutoff at 216.5-222.5 millimicrons. Moreover, a solution of 1a in 0.25 molar aqueous sodium hydroxide had a peak at 217 millimicrons with optical density 2.04, and a solution of fraction 1 at the same concentration level (by weight) in 0.25 molar aqueous sodium hydroxide had a peak of optical density 2.03 which was also at 217 millimicrons.

From these data it is postulated that fraction 1 reacted with hydrochloric acid to give a substance (1a) which reverted to starting material when treated with base.

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[1]See p. 121 for a description of the apparatus used to obtain these spectra.

The tertiary amino group of 1-methylpiperidine has been reported to have absorption at 213 millimicrons with an extinction coefficient of approximately 1600 (49); however, many other chromophores also absorb in this region. At any rate, the infrared spectra of fraction 1 (Figure 15) and 1a (Figure 19) indicate that 1a is not simply a hydrochloride of fraction 1.

Reaction with aqueous permanganate.--Approximately 0.1 g. of cut 3, p. 55, was treated dropwise with a freshly-prepared two per cent aqueous solution of reagent grade potassium permanganate. One drop of the reagent was decolorized after 15 sec., and two drops had been decolorized after 60 sec. An additional eighteen drops of the reagent were then added, and 3.5 min. later a heavy precipitate of manganese dioxide was observed. None of the original permanganate color remained after 2-3 min. more of standing. These results are interpreted as a positive Baeyer test (50).

Attempted reaction with picric acid.--Approximately 0.1 g. of cut 1, p. 55, was dissolved in a solution containing approximately 0.5 g. of picric acid. No precipitate appeared, and slow evaporation of the solution at room temperature over a

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(49) N. J. Leonard and D. M. Locke, J. Am. Chem. Soc., 77, 437 (1955).

(50) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, The Systematic Identification of Organic Compounds, fourth ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 133.

period of several days caused the deposition of a yellow solid which was recovered and identified as picric acid.

Characterization of Spiro-1'-alkylpiperidine-4',5-barbituric Acids

Attempted reaction with methyl iodide. Preparation of spiro-1'-methylpiperidine-4',5-barbituric acid hydroiodide.--An analytically pure sample of spiro-1'-methylpiperidine-4',5-barbituric acid failed to react with excess C. P. methyl iodide at room temperature or when kept at the boiling point of the reagent for several minutes. Evaporation of the methyl iodide left only unreacted starting material, which was identified by melting point and mixed melting point determinations. Spiro-1'-ethylpiperidine-4',5-barbituric acid also failed to react with methyl iodide, even though the mixture was kept at reflux temperature for sixteen hours.

Since it was surmised that the failure of spiro-1'-methylpiperidine-4',5-barbituric acid to react might be due to its extreme insolubility in methyl iodide, several attempts were made to prepare a methiodide of this compound in homogeneous ethanolic solution. In a typical experiment, 1.00 g. (0.00474 mole) of the barbituric acid was dissolved in 35 ml. of commercial absolute ethanol by warming gently. Ten ml. of C. P. methyl iodide was added, and the solution was refluxed intermittently in the dark for a total of 4.25 hr. over a two-day period. The reaction flask was then stoppered tightly

and allowed to stand overnight. The white crystals (A) which precipitated were filtered off, washed with fresh absolute ethanol, and air-dried. A weighed 0.42 g. and melted at 167.5-169° with decomposition to give an orange-brown melt. In addition, A gave a positive silver nitrate test for ionic halogen and depressed the melting point of the starting material to 140-154°. Upon refluxing the mother liquor from A intermittently for an additional 4.75 hr. over a period of about a day, a second crop of product weighing 0.41 g. and melting at 165.5-167° was produced. An analytical sample of A, prepared by recrystallizing twice from ethanol-ether, was light yellow in color and melted at 163.5-165.5° with decomposition. The analysis indicated that this material was more likely a monohydroiodide rather than the desired methiodide.

Calculated for the methiodide, $C_{10}H_{16}O_3N_3I$: C, 34.01; H, 4.57; I, 35.93.

Calculated for the hydroiodide, $C_9H_{14}O_3N_3I$: C, 31.87; H, 4.16; I, 37.42.

Found: C, 32.15; H, 4.15; I, 38.25.

The hydrogen iodide must have been produced by solvolysis of the methyl iodide in the commercial absolute ethanol used. Titration of a solution of 10 ml. of methyl iodide in 30 ml. of this ethanol *vs.* standard aqueous sodium hydroxide showed that only 1.33×10^{-5} equivalents of acid were originally present; however, an identical solution was found to contain 102×10^{-5} equivalents of acid after 6.5 hr. of refluxing in the dark.

As further proof that compound A was the hydroiodide, an independent synthesis of this material was desirable. Accordingly, 0.50 g. (0.0024 mole) of spiro-1'-methylpiperidine-4',5-barbituric acid was dissolved in 15 ml. of absolute ethanol by warming gently; then 1.0 g. (0.0040 mole) of freshly-distilled constant-boiling hydroiodic acid (sp. gr. 1.5; b. p. 126°) was added. A white precipitate (B) appeared immediately; and after ten minutes at gentle reflux, this material was filtered off, washed well with fresh portions of solvent, and air-dried. Compound B was shown to be identical with A by means of melting point and mixed melting point determinations and by a comparison of the infrared spectra (Figure 20). The yield of B was 0.57 g. (71 per cent).

All other attempts to prepare a methiodide in commercial absolute ethanol gave only the hydroiodide in yields which varied from 32 to 50 per cent, depending on the time of reflux and the amount of methyl iodide present.

Attempted reaction with acetyl chloride.--Highly-purified samples of spiro-1'-methylpiperidine-4',5-barbituric acid and spiro-1'-ethylpiperidine-4',5-barbituric acid failed to react with C. P. acetyl chloride at the boiling point of the reagent. In a control experiment, 5,5-diethylbarbituric acid also exhibited the expected inertness toward acetyl chloride at room temperature.

Reaction with acetic anhydride.--Approximately 0.1 g. of spiro-1'-methylpiperidine-4',5-barbituric acid failed to react

with a few ml. of acetic anhydride (Eastman, 99-100 per cent pure) at room temperature, so the mixture was refluxed for 1.3 hr. The orange, homogeneous solution which resulted deposited no precipitate on overnight refrigeration or upon cooling in dry ice, and the addition of several ml. of water also failed to produce a precipitate. The excess water and acetic acid were then distilled off. The amorphous residue was entirely soluble in 15-20 ml. of acetone, thus indicating that no starting material remained. Removal of the acetone under aspirator pressure and trituration of the residue with ether caused the separation of a dark green oil that could not be induced to crystallize and was not examined further.

Behavior toward aqueous permanganate.--A solution of 0.10 g. of spiro-1'-methylpiperidine-4',5-barbituric acid (m. p. 161°; light gray in color and, therefore, somewhat impure) in 2.0 ml. of distilled water decolorized only one drop of freshly-prepared two per cent aqueous potassium permanganate after five minutes. At the end of this time, an additional 10-12 drops of the reagent were added, and 25 min. later more decolorization appeared to have occurred. Twenty more drops of reagent were then added, and the solution was allowed to stand for an additional 30 min. with occasional shaking. Slow decolorization of the solution took place throughout this period, but little or no manganese dioxide precipitated. These results are interpreted as a negative test (50).

Potentiometric titration of spiro-1'-methylpiperidine-4',5-barbituric acid.--Thirty ml. of a solution 0.0033 molar in spiro-1'-methylpiperidine-4',5-barbituric acid was titrated with 0.01014 molar carbonate-free aqueous sodium hydroxide added from a burette which could be read accurately to 0.01 ml. After each addition of base, the solution was mixed thoroughly by stirring magnetically. The stirrer was then stopped, and the pH of the solution was read on a Beckman Zeromatic pH meter equipped with standard electrodes and previously standardized with Beckman pH 7.0 buffer solution. A plot of pH vs. ml. base added showed no inflection point, even after a total of 33.00 ml. of the base had been added. A plot of ΔpH/(ml. base) vs. ml. base added showed no maximum. The initial and final pH's were 6.78 and 11.20, respectively.

A potentiometric titration of 5,5-diethylbarbituric acid performed in an identical manner gave the expected rapid change in pH at the equivalence point.

In aqueous solution the spiro-amino barbituric acid would exist largely as a zwitterion with an estimated initial pK_a of about 10-12. Therefore, the results of the potentiometric titration do not necessarily indicate that no barbituric acid ring is present in this compound.

Preparation of Spiro-1'-arylpiperidine-4',5-barbituric Acids

Bis(2-p-toluenesulfonyloxyethyl)phenylamine.--This compound had previously been prepared in 35 per cent yield by a method similar to the following (25).

In a typical experiment, a solution containing 81.0 g. (0.448 mole) of bis(2-hydroxyethyl)phenylamine (Union Carbide product used without further purification) in 450 ml. of anhydrous pyridine was prepared in a liter three-necked round-bottomed flask equipped with an efficient mechanical stirrer, a thermometer, and a powder funnel. The solution was cooled to 6° by means of an ice bath and stirred rapidly while 180 g. (0.942 mole) of p-toluenesulfonyl chloride (Eastman white label) was added portionwise over a period of 55 min. at a rate such that the solution temperature did not rise above 12°. The funnel was then washed down with an additional 35-ml. portion of pyridine and replaced with a calcium chloride drying tube. After an additional 3.0 hr. of stirring in the ice bath, the flask was tightly stoppered and refrigerated overnight. The contents were then poured into a mixture of ice and water weighing approximately one kg. The product separated as a light green oil which crystallized readily upon stirring. The cold mixture was made strongly basic to litmus with 100 ml. of concentrated ammonium hydroxide, and the solid was recovered by filtering with suction. Most of the pyridine was removed from the product by suspending the solid in liter portions of water, stirring well, and then recollecting by suction filtration. After thorough air-drying to remove the water, the solid was suspended in a mixture composed of 1600 ml. of absolute ethanol and 1600 ml. of n-hexane. The product gradually dissolved as the hexane was boiled off, and the resulting solution was refrigerated over-

night. Upon filtering, 100.0 g. (46 per cent) of flat, pale green needles was obtained, m. p. 90.5-92.5° (lit. (25) m. p. 89-90°).

Concentration of the mother liquor by boiling failed to yield any more of the desired product; however, in other runs of this preparation, the addition of more hexane to the mother liquor at this point precipitated several grams of an unidentified material melting at 149-151°.

Similar yields were obtained when the initial period of overnight refrigeration was eliminated. Considerable loss of product occurred during the recrystallization, and a better method of purification is desirable.[1] The success of the preparation was found to be greatly dependent on the purity of the p-toluenesulfonyl chloride: "practical" grade material gave little or none of the desired product. Purification of the bis(2-hydroxyethyl)phenylamine might also have a beneficial effect on the yield.[2]

1-phenyl-4,4-dicarbethoxypiperidine.--In a three-liter three-necked round-bottomed flask equipped with an efficient Teflon-blade mechanical stirrer and a reflux condenser were placed 800 ml. of anhydrous toluene (Eastman practical grade, dried over sodium wire) and 186 ml. (196 g., or 1.22 mole) of diethyl malonate (Eastman white label). Sodium metal (14.8 g., or 0.643

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[1] In this connection, see below, pp. 71-72.

[2] As evidence, compare the yield reported for bis(2-p-toluenesulfonyloxyethyl)-m-tolylamine on p. 71.

g. atom) cut into small pieces was then added, and the mixture was stirred for 0.5 hr. in the absence of moisture. After warming the mixture to reflux and stirring it vigorously over a period of approximately 0.67 hr., all of the sodium appeared to have reacted, so external heating was discontinued. Then 150 g. (0.306 mole) of bis(2-p-toluenesulfonyloxyethyl)phenylamine was added with continued stirring. During this addition a heavy, white precipitate (evidently sodiomalonic ester) appeared, and an additional 600 ml. of anhydrous toluene was added to facilitate mixing. When the mixture was heated back to reflux, the white precipitate dissolved, and a light yellow precipitate of sodium p-toluenesulfonate soon began to separate. After 23 hr. at reflux temperature, the mixture was cooled and poured with good stirring into approximately one liter of cold water. The toluene layer was then separated, and the aqueous portion was extracted with an additional 100 ml. of toluene. The combined toluene layers were dried with Drierite overnight and freed of solvent by boiling. Fractionation of the residue through a six-inch heated Vigreaux column afforded 99.0 g. (51 per cent) of unreacted diethyl malonate and 70.48 g. (75 per cent) of straw-colored liquid, b. p. 165-173°/2 mm. (lit. (29) b. p. 140°/4 mm.). This liquid solidified on cooling and was recrystallized from methanol to give a total of 53.44 g. (57 per cent) of 1-phenyl-4,4-dicarbethoxypiperidine in several crops with melting points ranging from 52.2-54.5° to 51.0-53.5° (lit. (29) m. p. 53°).

Duplicate runs of this preparation on one-half scale gave 61 per cent of the pure product and on one-sixth scale gave 69.5 per cent yield. The boiling points of the products obtained in these runs were 145-146°/2 mm. and 155-158°/3 mm. These distillations were performed in a semi-micro apparatus having a four-inch Vigreaux column and an external thermometer well.

Anhydrous ethanol.--Commercial absolute ethanol was dried using the method of Smith (51). This ethanol is designated as "re-dried" throughout this chapter. "Absolute" ethanol refers to the commercial product used without further treatment.

Spiro-1'-phenylpiperidine-4',5-barbituric acid.--In a 200 ml. three-necked round-bottomed flask equipped with an efficient mechanical stirrer and a reflux condenser containing a calcium chloride drying tube was placed 35 ml. of re-dried ethanol. Sodium metal (1.15 g., or 0.0500 g. atom) cut into small pieces was added, and the mixture was stirred with exclusion of moisture until all of the sodium had reacted. Urea (U. S. P. grade, 2.00 g., or 0.0330 mole) was then added through a powder funnel, and the funnel was washed down with an additional 7.5 ml. of re-dried ethanol. The mixture was warmed with stirring in the absence of moisture until the urea dissolved. Then 5.10 g. (0.0167 mole) of 1-phenyl-4,4-dicar-

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(51) E. L. Smith, J. Chem. Soc., 1289 (1927).

bethoxypiperidine was added, and the powder funnel was again washed down with 7.5 ml. of fresh solvent. When warmed back to reflux temperature, the mixture immediately deposited a heavy, white precipitate. After refluxing with stirring and exclusion of moisture for 12.75 hr., the mixture was cooled to room temperature, refrigerated briefly, and then filtered. While on the filter, the precipitate was washed several times with fresh solvent. It was then suspended in 75 ml. of fresh re-dried ethanol and stirred magnetically in a dry atmosphere for approximately two days with 20 g. of Amberlite IRC-50 (Rohm and Haas) acidic ion-exchange resin.[1] At the end of this time, the mixture was heated to boiling and filtered. The filtrate was saved, and the filter cake was extracted with an additional 50-ml. portion of boiling absolute ethanol. The extract was saved, and the filter cake was suspended in 50 ml. of absolute ethanol and stirred as before for an additional day. The solids were again filtered off, placed in a Soxhlet apparatus, and extracted with the boiling filtrate for six hours. The original filtrate and both ethanolic extracts were then evaporated to dryness under aspirator pressure, and the combined residues were recrystallized from 95 per cent ethanol to give 3.23 g. (71 per cent) of spiro-1'-phenylpiperidine-4',5-barbituric acid, m. p. 229-230.5°. Concentration of the mother liquor yielded 0.32 g. of impure material

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[1] The commercial product contains a considerable amount of water. This was removed by washing the resin repeatedly with acetone and then allowing it to air-dry thoroughly.

melting largely at 208-216°. Two more recrystallizations of the barbituric acid from 95 per cent ethanol afforded an analytical sample as shiny flakes, m. p. 231-232° with very slight decomposition.

Calculated for $C_{14}H_{15}O_3N_3$: C, 61.53; H, 5.53; N, 15.38.

Found: C, 61.82; H, 5.72; N, 15.44.

This compound was essentially insoluble in cold water and could also be recrystallized from hot water with negligible decomposition. Further evidence for its structure was provided by its ability to dissolve in cold concentrated hydrochloric acid or in cold aqueous sodium hydroxide.

Purification of bis(2-hydroxyethyl)-m-tolylamine.--A sample of this material obtained from Antara Chemicals Co. was a dark, viscous liquid which could not be recrystallized from benzene or benzene-hexane mixtures. Fractionation through a six-inch heated Vigreaux column removed a considerable amount of low-boiling forerun and afforded the desired amine as a water-white liquid boiling at 150-153°/1 mm. This material solidified on cooling and was recrystallized from benzene to give a pure product melting at 71.5-73.5° (lit. (52) m. p. 71-72°).

Bis(2-p-toluenesulfonyloxyethyl)-m-tolylamine.--A solution containing 29.3 g. (0.150 mole) of purified bis(2-hydroxyethyl)-m-tolylamine and 150 ml. of anhydrous pyridine was prepared in a 300-ml. round-bottomed three-necked flask equipped

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(52) Beilstein's Handbuch der Organischen Chemie, Erstes Erganzungswerk, Band XII, Julius Springer, Berlin, Ger., 1933, p. 399.

with a thermometer and an efficient mechanical stirrer. The solution was cooled to 3° in an ice bath and stirred vigorously while 60 g. (0.31 mole) of p-toluenesulfonyl chloride (Eastman white label) was added portionwise through a powder funnel during a period of 30 min. at a rate such that the temperature did not rise above 11°. The powder funnel was washed down with an additional 10 ml. of anhydrous pyridine, and the mixture was stirred in the cold for 2.25 hr. with exclusion of moisture. The contents of the flask were then poured into approximately 500 g. of a mixture of ice and water. The product separated as a heavy, light green oil which soon crystallized. Fifty ml. of concentrated ammonium hydroxide was then added with stirring, and the product was filtered off. It was freed of pyridine by stirring repeatedly with fresh portions of cold water, again recovered by filtering, sucked dry, and air-dried overnight. The crude material weighed 69 g. (91 per cent) but afforded only 47.3 g. (63 per cent) of bis(2-p-toluenesulfonyloxyethyl)-m-tolylamine, m. p. 83.5-85.5°, after recrystallization from a mixture of absolute ethanol and hexane (see next paragraph). Addition of more hexane to the mother liquor precipitated 9.8 g. of material, m. p. 116-118.5°, which was not examined further.

The method of performing the recrystallization was found to have considerable influence on the yield of the desired product. Thus, in another run of this preparation, the crude product was first dissolved in hot ethanol; then hexane was added

to the cloud point, and the mixture was refrigerated. The solid that separated had m. p. 83-113° and resisted all further attempts at purification. In the most satisfactory procedure found for the recrystallization, the product was suspended in a 1:2 (by volume) ethanol-hexane mixture (approximately 10 ml. per gram of crude product), and the hexane was gradually boiled off until all of the solid dissolved. Cooling of the solution caused the product to separate as an oil which crystallized on vigorous stirring. Recrystallizing three times according to this procedure afforded an analytical sample as white crystals melting at 86-87°.

Calculated for $C_{25}H_{29}O_6NS_2$: S, 12.73.

Found: S, 12.50.

Duplicate experiments gave crude products melting at 81-84° in yields as high as 96 per cent.

1-m-Tolyl-4,4-dicarbethoxypiperidine.--In a two-liter three-necked round-bottomed flask equipped with an efficient Teflon-blade stirrer and a reflux condenser containing a calcium chloride drying tube were placed 280 ml. of anhydrous toluene (Eastman practical grade, dried over sodium wire) and 60.4 g. (0.377 mole) of diethyl malonate (Eastman white label). The solution was stirred vigorously while 4.55 g. (0.198 g. atom) of sodium metal cut into small pieces was added. After about 0.67 hr. of stirring and warming with exclusion of moisture, all of the sodium had reacted, and an additional 150 ml. of toluene was added to redissolve the white precipitate (evi-

dently sodiomalonic ester) that appeared. Stirring and warming were continued while 47.5 g. (0.0943 mole) of bis(2-p-toluenesulfonyloxyethyl)-m-tolylamine was added rapidly through a powder funnel. The funnel was washed with an additional 20 ml. of anhydrous toluene and replaced by a ground-glass stopper. The mixture was refluxed with vigorous stirring for 23 hr., cooled to room temperature, and poured into 700-800 ml. of ice water with good stirring so as to dissolve the large quantity of sodium p-toluenesulfonate present. The orange toluene layer was separated, and the aqueous layer was extracted twice with 100-ml. portions of fresh toluene. After drying with Drierite overnight, the combined toluene extracts were freed of solvent by boiling, and the residue was fractionated at reduced pressure through a six-inch heated Vigreaux column to give 33.5 g. (55 per cent) of unreacted diethyl malonate and 24.02 g. (80 per cent) of 1-m-tolyl-4,4-dicarbethoxypiperidine as a water-white liquid, b. p. 188°/3 mm. The ester crystallized when the inner surface of the container was scratched with a glass rod, and the crude product was purified by dissolving it in a few ml. of 95 per cent ethanol at room temperature and then refrigerating the solution. The snow-white needles that precipitated weighed 12.13 g. and melted at 43-45°. Concentration of the mother liquor afforded an additional 5.36 g. of product melting at 43-44°, so that the total yield of purified product was 17.49 g., or 58 per cent. In view of the high solubility of the ester in 95 per cent ethanol, a better recrystallization solvent was desirable, but none was found.

An analytical sample prepared by recrystallizing two more times according to the above procedure melted at 43-44°.

Calculated for $C_{18}H_{25}O_4N$: C, 67.69; H, 7.89; N, 4.39.

Found: C, 67.11; H, 8.07; N, 4.74.

Spiro-1'-m-tolylpiperidine-4',5-barbituric acid.--A solution of sodium ethoxide was prepared in the usual manner from 2.62 g. (0.114 g. atom) of sodium and 75 ml. of re-dried ethanol contained in a 200-ml. three-necked round-bottomed flask equipped with a mechanical stirrer and a reflux condenser containing a calcium chloride drying tube. Urea (4.56 g., 0.0760 mole) was added through a powder funnel which was then washed down with an additional 10 ml. of solvent. The mixture was stirred and warmed with exclusion of moisture until the urea dissolved; then 12.1 g. (0.0380 mole) of 1-m-tolyl-4,4-dicarbethoxypiperidine was added, and the powder funnel was washed with 15 more ml. of solvent. The mixture was refluxed with stirring and exclusion of moisture for 6.0 hr. After an additional 16 hr. of standing at room temperature, the sodium salt was filtered off and sucked as dry as possible. It was then suspended in 150 ml. of fresh re-dried ethanol and stirred magnetically in the absence of moisture with 30 g. of dry Amberlite IRC-50 (Rohm and Haas) acidic ion-exchange resin.[1] After 49 hr. of stirring the mixture was heated to boiling and filtered. The filter cake was extracted with an additional

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[1] See footnote 1, p. 69.

150-ml. portion of solvent, and the combined filtrates were concentrated by boiling to a total volume of approximately 200 ml. After a brief period of refrigeration, the free barbituric acid precipitated as fine white needles which were recovered by suction filtration, washed with fresh solvent, and air-dried. The yield was 7.44 g., m. p. 221-223.5°. An additional 1.60 g. of product, m. p. 220-222°, was obtained by extracting the resin with fresh absolute ethanol for 7.7 hr. in a Soxhlet apparatus. Thus the total yield was 9.04 g., or 83 per cent.

An analytical sample melting at 224-225° was prepared by recrystallizing once from 95 per cent ethanol and then twice from absolute ethanol.

Calculated for $C_{15}H_{17}O_3N_3$: C, 62.70; H, 5.96; N, 14.63.
Found: C, 63.06; H, 6.13; N, 14.83.

Attempted Preparations of Spiro-1'-phenylpiperidine-4',5-barbituric Acid. Preparation of 1-Phenyl-4-carboxypiperidine-4-carbonylureide

Prior to the observation that the sodium salt(s) of spiro-1'-phenylpiperidine-4',5-barbituric acid could be readily converted to the free acid in anhydrous ethanol by means of an acidic ion-exchange resin, several attempts were made to prepare the free acid by acidifying aqueous solutions of the salt(s).

In a typical experiment, sodium ethoxide was prepared in the usual manner from 0.69 g. (0.030 g. atom) of sodium and 30 ml. of re-dried ethanol. Urea (U. S. P., 1.20 g., or 0.020 mole) and then 1-phenyl-4,4-dicarbethoxypiperidine (3.05 g., 0.010 mole) were added, rinsing the powder funnel with 10 ml. of solvent after each addition. After 14 hr. of refluxing, the salt was filtered off, washed with fresh solvent, and air-dried. It was then dissolved in distilled water, and the pH of the solution was adjusted to 5.4 with hydrochloric acid. The solution, whose volume was now about 60 ml., was refrigerated briefly. The white, crystalline precipitate was filtered off and washed repeatedly with cold water and then with acetone. An infrared spectrum (Figure 21) showed that this material was not spiro-1'-phenylpiperidine-4',5-barbituric acid. It was, instead, 1-phenyl-4-carboxypiperidine-4-carbonylureide, m. p. 228-230°, and the yield was 1.55 g., or 53 per cent.

No satisfactory solvent for recrystallizing this malonuric acid could be found; however, it was reprecipitated in analytically pure form, m. p. 230-231° with charring and effervescence, by dissolving it in aqueous sodium hydroxide and adjusting the pH of the solution to 4-5 with hydrochloric acid. The neutral equivalent was determined by titrating samples dissolved in 50 per cent (by volume) aqueous acetone with aqueous sodium hydroxide to bromthymol blue end points.

Calculated for $C_{14}H_{17}O_4N_3$: neutral equivalent, 291.

Found: neutral equivalent, 291, 293.

Optimum conditions for preparing this compound were not determined, and it appears that the yield in the present method of preparation could be increased substantially by using a smaller volume of water to dissolve the sodium barbiturate salt(s). Another method for preparing this malonuric acid was described earlier.[1]

In another experiment, addition of a portion of the barbiturate salt(s) to a mixture of cracked ice and concentrated hydrochloric acid caused the precipitation of a new material, m. p. 302-305° with vigorous decomposition. This compound was apparently a hydrochloride of either the malonuric acid or the barbituric acid, since its aqueous solution gave a strong positive silver nitrate test for ionic halogen.

In contrast to this result, treatment of an ethanolic suspension of the barbiturate salt(s) with concentrated hydrochloric acid until the mixture gave a weakly acidic reaction to litmus caused precipitation of a small amount of the free barbituric acid.

Preparation of 1-Phenylpiperidine-4-carbonylureide

When an aqueous suspension of 1-phenyl-4-carboxypiperidine-4-carbonylureide was boiled, decarboxylation occurred, and 1-phenylpiperidine-4-carbonylureide was produced. This material is not appreciably soluble in either hot or cold water and was recovered in essentially quantitative yield by

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[1] See above, p. 44.

filtering the cooled mixture. Recrystallizing three times from absolute ethanol afforded an analytical sample as white flakes, m. p. 238.5-239.5°.

Calculated for $C_{13}H_{17}O_2N_3$: C, 63.14; H, 6.93; N, 16.99.

Found: C, 62.98; H, 6.91; N, 16.84.

The preparation of this ureide starting with spiro-1'-phenylpiperidine-4',5-barbituric acid has already been described.[1]

Preparation of 1-Phenyl-4,4-dicarboxypiperidine

This acid could be obtained by hydrolyzing spiro-1'-phenylpiperidine-4',5-barbituric acid;[2] however, it was more conveniently prepared from the corresponding diester according to the following procedure.

A solution prepared from 5.00 g. (0.0164 mole) of 1-phenyl-4,4-dicarbethoxypiperidine, 41.5 ml. (0.0458 mole) of 1.10 molar aqueous sodium hydroxide, and 41.5 ml. of absolute ethanol was refluxed vigorously for 24 hr., then cooled to room temperature and allowed to stand overnight. The ethanol was removed by extracting with 150 ml. of ether in two portions, and the pH of the aqueous layer was adjusted to 3.5 with concentrated hydrochloric acid. After cooling the mixture in the refrigerator for 0.5 hr., the white crystals of 1-phenyl-4,4-dicarboxypiperidine were filtered off, washed

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[1] See above, pp. 42-43.

[2] See above, pp. 41-43.

repeatedly with fresh portions of cold water, sucked dry, and air-dried overnight. The yield was 3.9 g. (95 per cent). This compound melted at 170° (slow heating) or at 180° (rapid heating) with vigorous evolution of carbon dioxide. The melt resolidified on cooling and remelted at 124-125°, a temperature which corresponds to the melting point of 1-phenyl-4-carboxypiperidine (lit. (53) m. p. 131°).

No satisfactory solvent for recrystallizing this diacid could be found, and it decomposed upon heating in most of the solvents tried. Recrystallization from warm water with considerable loss of material afforded a pure sample as white needles, m. p. 173° (slow heating) with vigorous effervescence. The neutralization equivalent was determined in aqueous ethanol with aqueous sodium hydroxide using phenolphthalein as the indicator.

Calculated for $C_{13}H_{15}O_4N$: neutral equivalent, 125.
Found: neutral equivalent, 130.

Preparation of 1-Phenyl-4-carboxypiperidine (N-Phenylisonipecotic Acid)

From 1-phenylpiperidine-4-carbonylureide.--A suspension of 0.75 g. (0.0030 mole) of 1-phenylpiperidine-4-carbonylureide in a solution prepared from 2.76 ml. (0.0030 mole) of 1.10 molar aqueous sodium hydroxide and 7.2 ml. of distilled water

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(53) V. Prelog and V. Hanousek, Collection Czechoslov. Chem. Communications, 6, 225 (1934).

was refluxed for 6.0 hr., during which time most of the solid gradually dissolved. After cooling, 0.06 g. (8 per cent) of unreacted ureide was filtered off, and the filtrate was extracted with 90 ml. of ether in six portions. The ether extracts failed to yield any products, so the aqueous portion was adjusted to pH 4.3 with concentrated hydrochloric acid and refrigerated briefly. Upon filtering, 0.29 g. of 1-phenyl-4-carboxypiperidine melting at 125.5-127° (lit. (53) m. p. 131°) was recovered. An additional 0.23 g. of this acid, m. p. 125.5-127°, was obtained by extracting the filtrate with 120 ml. of ether, drying the combined extracts over Drierite, and evaporating the solvent under aspirator pressure. The total weight of 0.52 g. represents a yield of 91 per cent, based on the amount of ureide which reacted, or 84 per cent, based on the amount of ureide used as starting material. Evaporation of the acidic solution to dryness left a solid residue from which 0.04 g. of solid melting at 132-135° was extracted by treatment with 25 ml. of boiling acetone. This material was shown to be urea by comparing its Nujol mull infrared spectrum with the spectrum of an authentic sample. The yield of urea was 24 per cent, based on the amount of ureide which was consumed in the reaction.

From 1-phenyl-4,4-dicarboxypiperidine by heating.--Into a 125-ml. Erlenmeyer flask was placed 2.0 g. (0.0080 mole) of 1-phenyl-4,4-dicarboxypiperidine. The solid was distributed as evenly as possible in a thin layer covering the bottom of the vessel,

and the flask was then heated carefully with a low Bunsen flame until no more evolution of gas could be detected. Recrystallization of the residue from approximately 150 ml. of boiling n-hexane afforded 1.30 g. (79 per cent) of N-phenylisonipecotic acid as pale yellow crystalls. The product was obtained in several crops with melting points ranging from 125-127.5° to 126-128.5°.

In an earlier experiment, 0.24 g. (0.00096 mole) of the diacid was placed in a 50-ml. round-bottomed flask, which was then heated in a molten metal bath at 187-190° until no more gas evolution occurred. Recrystallization of the residue from n-hexane afforded 0.14 g. (71 per cent) of the desired monoacid. While the infrared spectrum of this material (A) was identical with the spectrum of the compound prepared by other methods (Figure 22); A failed to melt at the expected temperature and only underwent slow decomposition, with charring, on being heated to approximately 200-250°. A small sample (B) of the monoacid, m. p. 125.5-127°, prepared by hydrolyzing the corresponding ureide, was kept in the metal bath at 175-193° for five minutes, and the cooled melt was then recrystallized from n-hexane. The spectrum of the recovered material (C) was identical to that of B; however, only a portion of this sample melted at 126-127°, and the remainder decomposed with charring at 210-265°. On admixture, A and B partially melted at 125-126°, and the unmelted portion decomposed with charring at 190-260°. A possible explanation for these peculiar results is that A and B represent different allotropic forms.

From 1-phenyl-4,4-dicarboxypiperidine and sulfuric acid via the dihydrogen sulfate.--A solution prepared from 3.9 g. (0.016 mole) of 1-phenyl-4,4-dicarboxypiperidine, 3.5 ml. (0.066 mole) of sulfuric acid (sp. gr. 1.84), and 15 ml. of distilled water was refluxed intermittently for 13.5 hr. during a 29-hr. period and then allowed to stand overnight. After filtering to remove a small amount of infusible solid, the solution was treated dropwise with 20 per cent sodium hydroxide solution while pH changes were observed on a pH meter. A heavy precipitate began to separate at pH 0.3. At pH 0.6 the addition of base was stopped, and the precipitate (A) was recovered by suction filtration. Slow addition of base to the filtrate until it was strongly alkaline failed to cause any additional precipitation.

A weighed 2.75 g. and was not the desired product, since it melted at 189-194° with effervescence. A sample of A was recrystallized from hot water and dried at 130° for 1 hr. This sample melted at 192-195° with effervescence, contained nitrogen and sulfur, and in aqueous solution gave a heavy, white precipitate with 0.1 molar barium chloride solution. These data indicated that A was the dihydrogen sulfate of N-phenylisonipecotic acid, and further evidence for this structural assignment was provided by neutral equivalent determinations, which were performed by titrating samples of the dried material with aqueous sodium hydroxide using bromthymol blue as the indicator.

Calculated for $C_{24}H_{32}O_8N_2S$: neutral equivalent, 127.

Found: neutral equivalent, 130, 134, 137 (avg., 134).

Two more recrystallizations of A from boiling water gave small, flat, off-white needles melting at 192-195° with effervescence. When an air-dried sample of this material was heated at 114° under 1 mm. pressure for two days, the needles changed into a powder(B), m. p. 190-192° without effervescence, and a weight loss corresponding to approximately 1.2 moles of water was observed. This result indicates that A was a hydrate of B and accounts for the discrepancy between the theoretical and observed values of the neutral equivalent (above), since $C_{24}H_{32}O_8N_2S \cdot H_2O$ would have a neutral equivalent of 132. The infrared spectrum of A had bands at 2.77 and 2.95 microns which were probably -O-H stretching absorptions resulting from the presence of water of hydration. These bands were also present in the spectrum of B (Figure 23), but their intensities were greatly diminished. A sulfur analysis of B was in accord with the proposed structure but did not indicate whether or not the compound was hydrated.

Calculated for $C_{24}H_{32}O_8N_2S$: S, 6.31.

Calculated for $C_{24}H_{34}O_9N_2S$: S, 6.09.

Found: S, 6.17.

Conversion of A into N-phenylisonipecotic acid was accomplished by dissolving 0.50 g. (0.0095 mole) of the compound in 25 ml. of water and adjusting the pH of the solution to 4.3 with aqueous sodium hydroxide. The solution was concentrated by boiling and then cooled, whereupon N-phenylisonipecotic acid separated as a clear oil which soon crystallized.

The product was recovered by suction filtration, washed well with fresh portions of water, and air-dried. Further concentration of the mother liquor afforded a second crop of crystals, which was recovered in a similar manner. The melting points of the crops were 127-129° and 126.5-128.5°, respectively, and the total yield was 0.17 g., or 69 per cent.

Preparation of Derivatives of N-Phenylisonipecotic Acid

N-Phenylisonipecotic acid hydrobromide.--Approximately 0.2-0.3 g. of N-phenylisonipecotic acid was warmed briefly with a few drops of constant-boiling hydrobromic acid, and the solution was then evaporated to dryness under aspirator pressure. Two recrystallizations of the residue from ethanol-ether mixtures afforded the hydrobromide as shiny flakes melting at 215-216° (lit. (53) m. p. 218-219°).

N-Phenylisonipecotic acid picrate.--Ten ml. of absolute ethanol containing 0.30 g. (0.0015 mole) of picric acid (reagent grade, 15 per cent water) was added to two ml. of absolute ethanol containing 0.2 g. (0.001 mole) of N-phenylisonipecotic acid. On vigorous shaking, a yellow solid separated, and the mixture was allowed to stand at room temperature until precipitation appeared to be complete. The picrate was recovered by suction filtration, washed with fresh solvent, and recrystallized from absolute methanol. This material decomposed sharply at 203° when placed in a 195° block heated at the rate of 5° per minute (lit. (53) dec. p. 207°).

Preparation of 1-Phenyl-4,4-dicarboxamidopiperidine from 1-Phenyl-4,4-dicarbethoxypiperidine

One g. of 1-phenyl-4,4-dicarbethoxypiperidine and 10 ml. of concentrated ammonium hydroxide were placed in a 25-ml. Erlenmeyer flask which was then stoppered tightly and allowed to stand for 13 days at room temperature with occasional vigorous shaking. The insoluble material (A) was then filtered off, washed with water, and air-dried. The principal component of A was apparently unreacted ester, since most of A melted at 52-54°; however, a small amount of higher-melting material was also present. Treatment of A with 10 ml. of benzene dissolved the low-melting portion and left 0.01-0.02 g. of material (B) melting at 277° with charring. The infrared spectrum of B (Figure 14) showed no ester carbonyl absorption, had bands near 3 and 6 microns indicative of the amido function, and was identical in every respect with the spectrum of a material obtained by condensing malonamide with bis(2-p-toluenesulfonyloxyethyl)phenylamine.[1] Therefore, B was apparently 1-phenyl-4,4-dicarboxamidopiperidine. Unfortunately, there was not enough B on hand to permit the preparation of an analytical sample.

Evaporation of the filtrate from A left only a trace of solid residue.

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[1] See below, pp. 96-97.

Several other attempts to effect the ammonolysis of 1-phenyl-4,4-dicarbethoxypiperidine all failed to yield any of the desired product. Only unreacted starting material was obtained when 0.25 g. of the ester was refluxed for 24 hr. in a solution containing 10 ml. of ethanol and 10 ml. of concentrated ammonium hydroxide. The ester was also recovered unchanged in another experiment in which a solution containing 1.00 g. of ester in 10 ml. of absolute ethanol was cooled to 0°, saturated with gaseous ammonia, and then heated at 64-90° in a pressure reactor for approximately 12 hr.

More vigorous conditions seemed to be required, and another high-pressure run was made using a temperature of 200-203° and a reaction time of approximately four days. Evaporation of the solvent left a viscous, pale green liquid which was nearly all soluble in 20 ml. of benzene. A few mg. of white needles (C) which did not dissolve was collected by filtering and found to melt at 176-179.5°. The Nujol mull infrared spectrum of this material had absorption bands indicative of a primary amido group at 2.89(m), 3.09(m) and 6.05(s) microns, and no ester carbonyl absorption was present. These data indicate that C may have been the previously unreported N-phenylisonipecotamide. Fractionation of the benzene solution through a four-inch Vigreaux column at atmospheric pressure gave a few drops of water-white liquid (D) boiling at approximately 230°. This liquid had characteristic ester carbonyl absorption at 5.78(s) microns but failed to show any absorp-

tion ascribable to an amide carbonyl linkage. However, D was not 1-phenyl-4-carbethoxypiperidine, since absorption was also present at 2.90(m) microns.

In another experiment, one g. of 1-phenyl-4,4-dicarbethoxypiperidine was suspended in 10 ml. of concentrated aqueous ammonia, and the mixture was shaken in the pressure apparatus for approximately three days at 57-66°. When the mixture had cooled, the insoluble material was recovered by filtering and found to melt at 53-195°. This material resisted all attempts at purification. Evaporation of the filtrate under aspirator pressure left a gummy residue which was also intractable.

Attempted Preparations of 1-Phenyl-4,4-dicarboxamidopiperidine from 1-Phenyl-4,4-dicarboxypiperidine

Several attempts were made to prepare 1-phenyl-4,4-dicarboxamidopiperidine from the corresponding diacid via an intermediate diacid chloride, according to the procedure used for the preparation of 4,4-dicarboxamidotetrahydropyran.[1] None of these attempts was successful. Thionyl chloride failed to react appreciably with the diacid at room or slightly elevated temperatures, and when the mixture was heated further, a tarry substance was produced. Removal of the excess thionyl chloride and treatment of the tar with excess concentrated ammonium hydroxide or liquid ammonia failed to yield any of

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[1] See below, p. 103.

the desired product. Evaporation of the solutions to dryness yielded only tar and, in some instances, small amounts of the diammonium salt of 1-phenyl-4,4-dicarboxypiperidine. The identity of this compound was established by its reaction with cold aqueous sodium hydroxide to liberate ammonia and by its conversion to the free acid, which precipitated when aqueous solutions of the salt were adjusted to pH 3.6 with hydrochloric acid.

A single attempt was made to prepare the diamide by heating the diacid with urea according to the procedure of Cherbuliez and Landolt (43). Thus, 0.50 g. (0.0020 mole) of the diacid and 0.24 g. (0.0040 mole) of urea were mixed intimately by grinding them together in a mortar. The mixture was transferred to a 50-ml. round-bottomed flask, and the flask was heated at temperatures up to 210° in an oil bath until gas evolution had nearly ceased. After cooling, the residue, which contained a considerable amount of charred material, was extracted thoroughly with boiling absolute ethanol. When an excess of n-hexane was added to the ethanolic solution, the only material which separated was a dark, mobile liquid which could not be induced to crystallize.

Attempted Preparation of 1-Phenyl-4-carboxamidopiperidine (N-Phenylisonipecotamide) from N-Phenylisonipecotic Acid

Five ml. of thionyl chloride (Eastman white label) and 0.17 g. of N-phenylisonipecotic acid were refluxed briefly

until the mixture became quite dark. The excess thionyl chloride was removed under aspirator pressure, and the oily, dark brown residue was treated with two ml. of concentrated ammonium hydroxide. After 1.5 hr. at room temperature, the solution had deposited no solid, so the water was removed under aspirator pressure. The residue was a brownish gum which resisted all attempts at purification.

Condensation of Bis(2-p-toluenesulfonyloxyethyl)phenylamine with Malonamide Using Various Bases

Sodium metal in toluene.--A suspension of 2.08 g. (0.0204 mole) of malonamide (Eastman white label) in 50 ml. of anhydrous toluene was prepared in a 200-ml. three-necked round-bottomed flask equipped with a Teflon-blade mechanical stirrer and a reflux condenser containing a calcium chloride drying tube. Small pieces of sodium (0.47 g., 0.020 g. atom) were then added, and the mixture was refluxed and stirred rapidly with exclusion of moisture. Approximately one hr. later, bis(2-p-toluenesulfonyloxyethyl)phenylamine (5.00 g., 0.0102 mole) was added through a powder funnel, and the funnel was washed down with an additional 10 ml. of solvent. After one hr. of refluxing with stirring in a moisture-free atmosphere, a considerable amount of yellow-brown solid was present, and an additional 25-ml. portion of toluene was added to facilitate mixing. Heating and stirring were discontinued after a total reaction period of 20 hr., and the solid (A) was removed from the cooled

mixture by filtering. This solid was readily soluble in a small amount of hot water, but the solution deposited no crystals on cooling. Extraction of A with 75 ml. of boiling acetone removed a small amount of yellow, amorphous material (B) which had an unpleasant sulfur odor and which either failed to dissolve or yielded only gummy precipitates on attempted crystallizations from ethanol, ethanol-benzene, and several other solvents and solvent mixtures. Treatment of B with concentrated hydrochloric acid gave a small amount of an unidentified material, m. p. 276-282° with decomposition, which was recovered by filtering.

Extraction of A with 75 ml. of boiling absolute ethanol removed a considerable amount of solid (C) having the unpleasant odor associated with B. On recrystallization from a small amount of ethanol, C afforded a water-soluble solid which partially melted at 127-147° but contained some higher-melting material. After several more recrystallizations from ethanol, the high-melting product was obtained in pure form and identified as sodium p-toluenesulfonate by comparing its Nujol mull infrared spectrum with that of an authentic sample.

Evaporation of the toluene from the original reaction mixture by warming the solution under aspirator pressure left a small amount of brown, viscous oil which could not be induced to crystallize.

Sodium metal in dioxane.--The reaction mixture in the preceding experiment was heterogeneous because of the insolubilities of

malonamide and sodiomalonamide in toluene. It was felt that better results might be obtained under homogeneous conditions, and several other solvents were examined for the purpose of discovering a more suitable medium for carrying out the proposed reaction. Tetrahydrofuran and ethylene glycol diethyl ether failed to dissolve appreciable quantities of malonamide at their respective boiling points. However, both malonamide and the ditosylate dissolved readily in hot dioxane, so this was the solvent which was selected.

A solution containing 1.04 g. (0.0102 mole) of malonamide in 75 ml. of anhydrous dioxane was prepared by heating and stirring the components in a 300-ml. three-necked round-bottomed flask equipped with a Teflon-blade mechanical stirrer and a reflux condenser containing a Drierite drying tube. Vigorous stirring of the hot solution was continued while 0.55 g. (0.024 g. atom) of sodium metal cut into small pieces was added. A solid (probably sodiomalonamide) that soon appeared failed to dissolve when an additional 25 ml. of solvent were added, so the remainder of the experiment had to be conducted under the undesirable heterogeneous conditions. Twelve min. after the addition of the sodium, 5.00 g. (0.0102 mole) of the ditosylate was added, and the mixture was refluxed and stirred with exclusion of moisture for 23 hr. A small amount of light-colored, water-soluble gum was removed from the hot mixture by filtering, and the filtrate was cooled in a mixture of dry ice and acetone until it began to solidify.

On re-warming to room temperature, the mixture contained no precipitate, so the dioxane was removed under aspirator pressure. The residue was a pale orange oil which yielded no solid products on attempted crystallization from several common solvents and solvent mixtures.

Sodium amide in dioxane.--A solution containing 5.00 g. (0.0102 mole) of bis(2-p-toluenesulfonyloxyethyl)phenylamine in 100 ml. of anhydrous dioxane was prepared in a 300-ml. three-necked round-bottomed flask equipped with a Teflon-blade mechanical stirrer and a thermometer. Malonamide (1.04 g., 0.0102 mole) was added, and the stirred suspension was then treated with 0.85 g. (0.022 mole) of powdered sodium amide, which had been weighed out under dioxane. An additional 25 ml. of dioxane was used to wash all of the sodium amide into the reaction mixture; then a reflux condenser equipped with a calcium chloride drying tube was placed in the third neck of the flask, and the mixture was stirred rapidly at 50-52°. A white solid gradually separated, and vigorous evolution of ammonia occurred. After 22 hr. the mixture was heated to the boiling point and maintained at this temperature with continued stirring for 8 hr. After cooling back to room temperature and standing for approximately 20 hr., it was refluxed with stirring for an additional 4.5 hr. and then filtered while hot to remove the light brown solid (A) which was present. On cooling, the filtrate deposited approximately 0.5 g. of tan solid whose principal constituent was shown to be malonamide by means of

a Nujol mull infrared spectrum. Evaporation of the dioxane on the steam bath under aspirator pressure left an intractable reddish-brown syrup.

Fraction A was washed several times with water, and the insoluble material (B) was recovered by filtering. B weighed 0.95 g. and began to melt slowly at 287°. It was recrystallized from water to give snow-white scales melting at 292-292.5° with charring. The infrared spectrum of B (Figure 24) showed no N-H or carbonyl absorption but did exhibit bands at 8.39, 9.65, and 9.87 microns which were also present in the spectrum of an authentic sample of sodium p-toluenesulfonate. Further evidence for the presence of the tosyl group was provided by the strong out-of-plane C-H deformation band occurring at 12.26 microns (54). B dissolved readily in cold aqueous hydrochloric acid and was precipitated unchanged when the solution was made basic with sodium hydroxide. An analytical sample prepared by recrystallizing twice from ethanol melted sharply with charring at 295.5°.

The empirical formula calculated from the analytical data is $C_{27.33}H_{34.97}N_{3.05}O_{3.25}S_{1.00}$. There is no obvious structure for B which corresponds to this formula; however, the analysis also agrees fairly well with the formula $C_{27}H_{33}N_3O_3S$.

Calculated for $C_{27}H_{33}N_3O_3S$: C, 67.63; H, 6.94; N, 8.76; S, 6.69.

Found: C. 66.96; H, 7.19; N, 8.72; S, 6.55.

On the basis of the available data, B is tentatively assigned the structure shown in Figure 9.

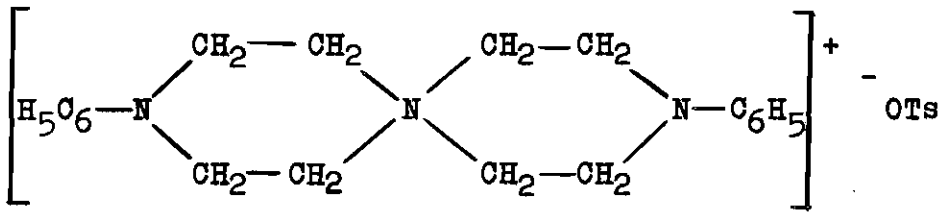

Figure 9. Proposed Structure for B , P. 93

Another possibility is the covalent structure depicted in Figure 10.

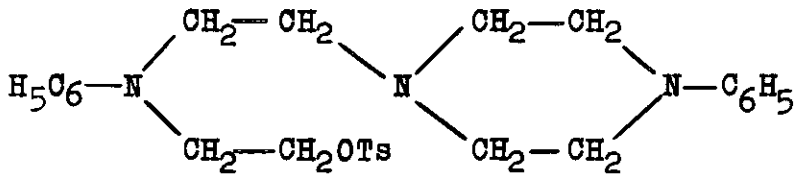

Figure 10. Alternate Structure for B , P. 93

The ionic structure of Figure 9 seems preferable, however, in view of the high melting point, the appreciable water solubility, and the absence of absorption at 7.30-7.41 microns--a region where covalent sulfonates absorb strongly (55).

Sodium amide in liquid ammonia.--A solution containing 0.0230 mole of sodium amide in approximately 50 ml. of liquid ammonia was prepared according to the procedure of Hauser et al. (56) in a 200-ml. round-bottomed three-necked flask equipped with a Teflon-blade mechanical stirrer and a thermometer. The solution was cooled with acetone and dry ice to -56° and stirred

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(54) L. J. Bellamy, The Infra-red Spectra of Complex Molecules, John Wiley and Sons, Inc., New York, N. Y., 1959, p. 78.

(55) Ibid., p. 364.

(56) C. R. Hauser, J. T. Adams, and R. Levine in Organic Syntheses, Coll. Vol. III, John Wiley and Sons, Inc., New. York, N. Y., 1955, p. 291.

while 1.04 g. (0.0102 mole) of malonamide was added. After five min. of stirring, 5.00 g. (0.0102 mole) of the ditosylate was added, and the mixture was then stirred at -42° to -52° for 9.0 hr. The apparatus was then transferred to a hood, and the ammonia was allowed to evaporate at room temperature. The residue was washed several times with water, and the insoluble portion was collected by suction filtration and air-dried. This material was shown to be unreacted ditosylate by means of melting point and mixed melting point determinations. The weight of 4.28 g. represented 86 per cent recovery.

In another experiment using identical quantities of starting materials, the malonamide was added to the sodium amide solution as described above. A solution of the ditosylate in 75 ml. of anhydrous toluene was added, and the mixture was then stirred for 15 hr. while the temperature rose slowly from -60° to -34°. The cooling bath was removed, and the ammonia was allowed to evaporate in the hood while stirring was continued for an additional 2.5 hr. Only a small amount of gummy precipitate was observed in the toluene solution which remained; thus, only traces of malonamide and sodium p-toluenesulfonate could have been present. The gum was filtered off, and the filtrate was evaporated on the steam bath under aspirator pressure to yield 4.16 g. (83 per cent) of unreacted ditosylate.

Sodium ethoxide in ethanol. Preparation of 1-phenyl-4,4-dicarboxamidopiperidine and 3,3-dicarboxamidopropyl-2-ethoxyethylphenylamine.--A solution of sodium ethoxide was prepared by allowing 0.47 g. (0.020 g. atom) of sodium to react with 40 ml. of re-dried ethanol in a 200-ml. three-necked round-bottomed flask equipped with a mechanical stirrer and a reflux condenser protected from moisture with a calcium chloride drying tube. Malonamide (1.14 g., 0.0112 mole) was added through a powder funnel, which was washed down with an additional 5 ml. of solvent and replaced with a stopper; then the mixture was warmed with stirring. When all of the malonamide had dissolved, 5.00 g. (0.0102 mole) of the ditosylate was added through the powder funnel, which was again washed down with 5 ml. of fresh solvent. The flask was then re-stoppered and refluxed with stirring for 20.3 hr., during which time ammonia was evolved, and a pale yellow solid (A) was precipitated. This solid was recovered by filtering the hot mixture, and the filtrate was refrigerated. The solid (A) was shown to be sodium p-toluenesulfonate by comparing its Nujol mull infrared spectrum with the spectrum of an authentic sample. The weight of A was only 2.25 g., as compared to the theoretical weight of 3.96 g.

The cooled filtrate from A deposited 0.11 g. of powdery solid (B) melting at 264-274°. Recrystallization of B from water afforded white needles, m. p. 275-278° with charring, which did not dissolve in 20 per cent aqueous sodium hydroxide. The infrared spectrum of this material was identical in every

respect with the spectrum of B, p. 85, (Figure 14), so it was presumed to be 1-phenyl-4,4-dicarboxamidopiperidine.

Evaporation of the mother liquor from B on the steam bath under aspirator pressure afforded a light yellow, semi-solid residue (C). Treatment of C with cold benzene removed a light orange liquid that could not be induced to crystallize and left 0.37 g. of white solid (D) melting largely at 150-160°. Three recrystallizations of D from water afforded an analytically pure material as fine white needles which melted at 179-180°. The infrared spectrum (Figure 25) showed amide carbonyl absorption at 5.99(s) microns and N-H absorption at 2.93(m) and 3.06(m) microns, but no ester carbonyl absorption was present. These data and the analytical results showed that D was 3,3-dicarboxamidopropyl-2-ethoxyethylphenylamine.

Calculated for $C_{15}H_{23}O_3N_3$: C, 61.41; H, 7.90; N, 14.33.

Found: C, 61.20; H, 8.05; N, 14.42.

A second experiment was performed using 75 ml. of ethanol, 0.70 g. (0.030 g. atom) of sodium, 1.56 g. (0.0153 mole) of malonamide, and 5.00 g. (0.0102 mole) of ditosylate. After a reflux period of 2.0 hr., the mixture was worked up according to the procedure just described to yield 3.33 g. (84 per cent) of sodium p-toluenesulfonate, 0.09 g. (4 per cent) of crude 1-phenyl-4,4-dicarboxamidopiperidine, and 0.55 g. (18 per cent) of crude 3,3-dicarboxamidopropyl-2-ethoxyethylphenylamine.

An experiment designed to improve the yield of the latter compound was undertaken using 50 ml. of ethanol, 0.26 g. (0.011

g. atom) of sodium, 1.04 g. (0.0102 mole) of malonamide, and 5.00 g. (0.0102 mole) of ditosylate. After a reflux period of 1.7 hr., 1.40 g. (64 per cent, based on sodium) of sodium p-toluenesulfonate was filtered from the hot solution. On cooling, the solution deposited an additional 0.19 g. of solid material which dissolved readily in a very small amount of cold water and was, therefore, neither 1-phenyl-4,4-dicarboxamidopiperidine nor 3,3-dicarboxamidopropyl-2-ethoxyethylphenylamine. Evaporation of the ethanol on the steam bath under aspirator pressure left an amorphous residue. This material was also readily soluble in cold water (except for a small oily portion) and was not investigated further.

Another experiment was undertaken using 125 ml. of ethanol, 0.25 g. (0.011 g. atom) of sodium, 5.20 g. (0.0510 mole) of malonamide, and 5.00 g. (0.0102 mole) of ditosylate. After 5 hr. of refluxing, 3.56 g. of material readily soluble in a small amount of cold water was filtered from the hot solution. The theoretical yield of sodium p-toluenesulfonate was only 2.12 g., so it appeared possible that some malonamide was present in this fraction. On cooling the filtrate, an additional 0.69 g. of water-soluble material precipitated and was filtered off. Evaporation of the mother liquor yielded a solid residue which weighed 4.06 g. after thorough extraction with benzene. Treatment of a portion of this solid with cold 20 per cent sodium hydroxide solution caused the evolution of ammonia; hence, one of its constituents may have been ammonium

p-toluenesulfonate. The remainder of the residue was triturated with cold aqueous sodium hydroxide; then the insoluble material was collected by filtering and washed well with small portions of water. This fraction weighed 0.30 g., melted at 152-162°, and was shown by its infrared spectrum to be crude 3,3-dicarboxamidopropyl-2-ethoxyethylphenylamine.

Potassium t-butoxide in t-butyl alcohol.--A solution of potassium t-butoxide in anhydrous t-butyl alcohol was prepared in the usual manner. The solution was stored in a polyethylene bottle under nitrogen, and it was found to be 0.448 molar in base by titrating aliquot portions against 0.0350 molar aqueous perchloric acid.

In the apparatus described in the section immediately preceding were placed 45.6 ml. (0.0204 mole) of the standard t-butoxide solution and 1.04 g. (0.0102 mole) of malonamide. After 15 min. of refluxing with stirring, all of the malonamide had dissolved, and 5.00 g. (0.0102 mole) of the ditosylate was then added through a powder funnel, which was washed down with an additional 10 ml. of solvent. The flask was re-stoppered; then refluxing and stirring were continued. A yellow precipitate soon began to separate, and vigorous ammonia evolution occurred. After one hr. of refluxing, the amount of external heating was reduced, so that the temperature fell to 67° within 0.25 hr. Approximately 1.75 hr. later, the temperature had fallen to 47°. The mixture was then heated briefly back to the boiling point, and the light yellow precipitate (A)

was recovered by filtering. A weighed 4.25 g. (calculated for 0.0204 mole of potassium p-toluenesulfonate, 4.29 g.) and was readily soluble in a few ml. of cold water. On brief refrigeration, the filtrate from A deposited several tenths of a gram (estimated weight) of pale yellow oil which could not be induced to crystallize. Evaporation of the filtrate by warming it on the steam bath under aspirator pressure left a pale yellow, amorphous residue (B) which was extracted with 50 ml. of hot benzene. Concentration of the extract to 10 ml., followed by refrigeration, failed to afford a precipitate. The remainder of B was insoluble in hot water and yielded only a small amount of gum when recrystallization from an ethanol-water mixture was attempted.

In a second experiment using identical quantities of reactants, one-half of the t-butoxide solution and an additional 25 ml. of anhydrous t-butyl alcohol were refluxed with the malonamide for 0.33 hr. External heating was discontinued, and the ditosylate was added through a powder funnel which was then washed down with 5 ml. of fresh solvent. After 0.33 hr. of stirring, during which time the temperature fell to 50°, the second half of the base was added dropwise over a period of 0.45 min. while the temperature was maintained at 47-50°. The mixture was stirred at 47-50° for an additional 1.6 hr. and then filtered. The precipitate (A) weighed 4.08 g. On treatment with 5-10 ml. of cold water, a large portion of A dissolved, and the insoluble fraction (B) was recovered by fil-

tering. After air-drying, B weighed 1.98 g. and was shown by melting point and mixed melting point determinations to be unreacted ditosylate (40 per cent recovery). Evaporation of the filtrate from A by warming it on the steam bath under aspirator pressure afforded an amorphous residue (C). When treated with cold water, all of C dissolved except for several tenths of a gram (estimated weight) of pale yellow oil which was not examined further.

Sodium t-amyloxide in t-amyl alcohol.--Sodium metal (0.43 g., 0.019 g. atom) was added to 25 ml. of anhydrous t-amyl alcohol contained in the apparatus previously described. The mixture was refluxed with stirring for 1.8 hr. and then treated with 0.87 g. (0.0085 mole) of malonamide, using a powder funnel which was washed down afterward with an additional 5-ml. portion of solvent. The malonamide was rather insoluble, and an appreciable portion remained undissolved after 0.25 hr. of vigorous stirring and refluxing. At the end of this time, 4.18 g. (0.00854 mole) of the ditosylate was added and the powder funnel again washed with 5 ml. of fresh solvent. The mixture was refluxed with stirring for 15.25 hr. and then filtered while hot. Except for a trace of yellow, amorphous material, the white filter cake was entirely soluble in cold water, and the reddish filtrate deposited no solid on cooling. Evaporation of the filtrate by warming it on the steam bath at aspirator pressure afforded a reddish, semi-solid residue which was largely soluble in 50 ml. of cold benzene. The insoluble

portion consisted of 0.43 g. of yellow-brown solid, m. p. 144-160°. This solid was not investigated further.

Preparation of 4,4-Dicarboxytetrahydropyran

A solution prepared from 10.87 g. (0.0473 mole) of 4,4-dicarbethoxytetrahydropyran, 3.27 g. (0.142 mole) of sodium hydroxide (C. P. pellets) and 50 ml. of approximately 1:1 (by volume) aqueous ethanol was refluxed for 16 hr. and then allowed to stand at room temperature for an additional 49 hr. The solution was extracted with four 50-ml. portions of ether, and the ether extracts were discarded. (The addition of the first portion of ether caused precipitation of a white solid which redissolved when 20 ml. of water was added.) The aqueous portion was acidified with a large excess of concentrated hydrochloric acid and extracted ten times with 50-ml. portions of ether, which were combined and dried over Drierite. Evaporation of the ether under aspirator pressure afforded 6.55 g. of solid material which melted over a considerable range of temperature. However, recrystallization of the solid from a mixture of hexane and ethyl acetate afforded 3.41 g. (42 per cent) of 4,4-dicarboxytetrahydropyran in several crops of crystals with melting points ranging from 176-178° to 170.5-172.5° (lit. (22) m. p. 172-173°).

The rather low yield of the desired product was surprising in view of the excellent yield of 1-phenyl-4,4-dicarboxypiperidine which could be obtained using this method of

hydrolysis.[1] Incomplete extraction of the aqueous moiety was not the reason, since the last ether extract contained practically no solid material.

The preparation of this diacid from spirotetrahydropyran-4',5-barbituric acid was described earlier.[2]

Preparation of 4,4-Dicarboxamidotetrahydropyran

The diacid chloride of 4,4-dicarboxytetrahydropyran was prepared by refluxing 0.79 g. (0.0045 mole) of this diacid with 3 ml. of thionyl chloride (Eastman white label) for 2 hr. At the end of this time, the excess reagent was removed under aspirator pressure, and the dark green liquid that remained was treated with 4 ml. of concentrated ammonium hydroxide. The mixture was warmed gently until all of the acid chloride dissolved and then refrigerated overnight. The light gray solid which precipitated was collected by filtering and washed sparingly with cold water. An analytical sample prepared by recrystallizing once from 95 per cent ethanol and then twice from absolute ethanol consisted of snow-white crystals, m. p. 225.5-227.5°.

Calculated for $C_7H_{12}O_3N_2$: N, 16.27.

Found: N, 16.16.

This compound had been previously reported to result from ammonolysis of the corresponding diester; however, the

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[1] See above, pp. 78-79.

[2] See above, pp. 39-40.

melting point was given as 156.5-157° (22). A sample (X) of this low-melting "diamide" was obtained,[1] and a re-examination of its structure was undertaken. Compound X was immediately shown not to be 4,4-dicarboxamidotetrahydropyran by the fact that its aqueous solution was acidic to litmus. Furthermore, X evolved a gas at its melting point, then solidified and re-melted at 167-175°, a temperature range which corresponds to the reported melting point for 4-carboxamidotetrahydropyran (lit. (57) m. p. 179°). These data indicated that X is likely to be 4-carboxy-4-carboxamidotetrahydropyran.

Attempted Preparations of 1-Methyl-4,4-dicarbethoxypiperidine from Diethyl Malonate and Bis(2-chloroethyl)methylamine

Bis(2-chloroethyl)methylamine hydrochloride.--This compound was prepared from bis(2-hydroxyethyl)methylamine and thionyl chloride according to the method of Ulrich et al. (58) in 69 per cent yield.

Bis(2-chloroethyl)methylamine.--This nitrogen mustard was obtained by adding an excess of 20 per cent sodium hydroxide to a water solution of the hydrochloride at 5-15°. The basic mixture was extracted thoroughly with benzene; then the com-

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[1] This sample had been prepared by Dr. P. M. Daugherty and was supplied by Dr. J. A. Stanfield.

(57) C. S. Gibson and J. D. A. Johnson, J. Chem. Soc., 2525 (1930).

(58) H. Ulrich, E. Ploetz, and M. Bogemann, U. S. Patent 2,163,181 (June, 1939).

bined extracts were dried over Drierite and distilled to give 80 per cent (based on the hydrochloride) of product, b. p. 57°/4.8 mm. (lit. (22) b. p. 60-70°/2-4 mm.). This rather unstable compound was stored in the refrigerator and either redistilled or filtered (to remove the piperazinium salt resulting from dimerization) immediately before use.

Catalysis by sodium in toluene.--A solution containing 32.0 g. (0.200 mole) of diethyl malonate (Eastman white label) in 100 ml. of anhydrous toluene (Eastman practical grade, dried over sodium wire) was prepared in a 300-ml. three-necked round-bottomed flask equipped with a Teflon-blade mechanical stirrer and a reflux condenser protected from moisture by means of a calcium chloride drying tube. Sodium metal (2.42 g., 0.105 g. atom) cut into small pieces was added, and the mixture was refluxed and stirred until all of the sodium had reacted. The resulting solution of sodiomalonic ester was then maintained near the boiling point and stirred vigorously while a solution containing 7.80 g. (0.0500 mole) of bis(2-chloroethyl)methylamine in 25 ml. of anhydrous toluene was added dropwise from a pressure-equalizing funnel over a period of 70 min. The reaction mixture developed a definite cloudiness during the addition. After all of the amine had been added, the mixture was heated again to reflux and maintained at this temperature for 9 hr. with continuous stirring. It was then cooled and filtered to remove a large amount of white precipitate which was, presumably, sodium chloride, since it

dissolved readily in a small amount of cold water. The toluene solution was washed in a separatory funnel with 75 ml. of water, dried over Drierite, and then freed of solvent by warming at 40° under aspirater pressure. Fractionation of the residue through a six-inch heated Vigreaux column yielded several grams of clear liquid having the odor of diethyl malonate, b. p. 61-62°/4.8 mm.; 4.13 g. of clear liquid, b. p. 89-123°/12.2-12 mm.; and 1.75 g. of clear liquid (A), b. p. (mostly) 145-146°/12 mm. Further heating caused decomposition of the material in the pot so that a considerable amount of non-distillable tar remained. The boiling point of fraction A indicated that it might be the desired 1-methyl-4,4-dicarbethoxypiperidine (lit. (28) b. p. 134-137°/12 mm.), but this possibility was ruled out by the infrared spectrum, which exhibited a strong doublet (poorly resolved) at 2.74-2.84 microns. No further investigation of this material was made because of the small quantity on hand.

Catalysis by sodium amide in toluene.--In a 300-ml. three-necked round-bottomed flask equipped with a mechanical stirrer and a thermometer were placed 50 ml. of anhydrous toluene and 8 g. (0.2 mole) of powdered sodium amide. The mixture was stirred vigorously and cooled in an ice bath while a solution of 16.0 g. (0.100 mole) of diethyl malonate (Eastman white label) in 25 ml. of anhydrous toluene was added dropwise from a pressure-equalizing funnel containing a calcium chloride drying tube. The temperature in the flask rose from 2° to

15° during the 25 min. which were required for the addition. After all of the ester solution had been added, the temperature rapidly fell back to 3°. A solution containing 15.9 g. (0.102 mole) of bis(2-chloroethyl)methylamine in 50 ml. of anhydrous toluene was now added slowly with continued cooling and stirring during a period of 15 min. The cooling bath was then removed and the mixture stirred at room temperature for 9 hr. A considerable volume of ammonia was evolved during this period, but only a small amount of precipitate appeared. The mixture was allowed to stand at room temperature for 3 more hr.; then the thermometer was replaced by a reflux condenser, and the mixture was refluxed vigorously with stirring until no more ammonia was evolved. A considerable amount of solid precipitated during the reflux period, which was 1.7 hr. After cooling to room temperature, the mixture was treated with 250 ml. of water, and the toluene layer was separated. The aqueous layer was extracted with 150 ml. of ether, and the ether extract was combined with the toluene layer. After thorough drying over Drierite, the combined organic layers were freed of ether and toluene by warming under aspirator pressure. The residue was fractionated through a six-inch heated Vigreaux column to give 6.09 g. (38 per cent recovery) of unreacted amine (identified by its characteristic odor and by its deposition of a white precipitate on standing), b. p. 76-78°/12 mm., and 5.60 g. of pale yellow liquid (A), b. p. 85-117°/12-14 mm. Extensive decomposition of pot material occurred during the

collection of the higher-boiling fraction, and a large amount of undistillable tar remained. Fraction A was re-fractionated through a four-inch heated Vigreaux column to give the fractions described in Table 2. Very little decomposition of pot

Table 2. Re-fractionation of A, P. 108

Cut No.	Pressure (mm. Hg)	B. P. (^{o}C.)	Weight (g.)
1	12.4	70-84 (mostly 80-84)	1.31
2	12.4	80-88	0.20
3	12.4	90-120 (mostly 110-120)	0.50
4	12.4	120-127 (mostly 123.5)	1.22
5	12.4	128-131	0.29

material occurred, even though the pot temperature rose to 210^{o}. The infrared spectra of cuts 3, 4, and 5 were similar. All showed a pronounced doublet at 2.7-2.9 microns, perhaps indicative of a primary amino group, and a strong carbonyl doublet at 5.74-5.84 microns. Cuts 3 and 4 had spectra very similar to that of A, p. 106. The spectrum of cut 5 differed somewhat from the spectra of cuts 3 and 4 in the region from 7 to 15 microns and did not show a sharp peak at 6.25 microns which was present in these spectra. Cut 5 gave no crystalline product when boiled for 20 min. with an excess of methyl iodide (C. P.). In contrast, 1-methyl-4,4-dicarbethoxypiperidine has

been reported to give a crystalline methiodide, m. p. 148-149° (28).

A second experiment was performed using 12 g. (0.30 mole) of sodium amide, 16.0 g. (0.100 mole) of malonic ester, and 15.6 g. (0.100 mole) of the amine. The ester and then the amine were added to the sodium amide suspension as before. After the addition of the amine, the mixture was stirred at 5-33° for 1.5 hr., at 53-56° for 25 hr., and then at reflux temperature for 3.5 hr. After standing overnight, the mixture was treated with approximately one kg. of a mixture of cracked ice and water. The toluene layer was then separated, filtered to remove a small amount of tar, dried, concentrated, and distilled to give 1.88 g. of water-white liquid, b. p. 82-115°/12.5 mm., and 1.80 g. of straw-colored liquid, b. p. 124-131° (mostly at 131°)/10 mm. The spectrum of the higher-boiling fraction was essentially identical to that of cut 3, Table 2.

Catalysis by sodium amide in a mixture of liquid ammonia and toluene.--A solution of sodium amide was prepared from 3.08 g. (0.134 g. atom) of sodium metal and approximately 50 ml. of liquid ammonia according to the procedure of Hauser et al. (56). The solution was maintained at -46° to -56° and stirred well while 10.75 g. (0.0670 mole) of diethyl malonate (Eastman white label) dissolved in 40 ml. of anhydrous toluene was added dropwise during 1 hr. from a pressure-equalizing funnel equipped with a calcium chloride drying tube. Stirring was continued for 40 min. at -61° to -58° while a solution con-

taining 10.45 g. (0.0670 mole) of bis(2-chloroethyl)methylamine in 25 ml. of anhydrous toluene was added. After the mixture had been allowed to stand at -58° to -50° for 8 hr. with intermittent stirring, the cooling bath was removed, and the ammonia was allowed to evaporate under a hood. No precipitate was present in the pale orange toluene solution which remained; hence it appeared that the desired reaction had not occurred. However, when the solution was heated to reflux temperature, a white solid began to separate. After 9.7 hr. of refluxing and stirring, the reaction mixture was worked up according to the procedure described in the previous section. The fractionation yielded 2.26 g. (22 per cent recovery) of unreacted amine, b. p. 57°/5.5 mm.; 2.17 g. of straw-colored liquid, b. p. 106-114°/11 mm.; and 0.96 g. of yellow liquid, b. p. 116-140°(mostly at 127°)/10 mm. The infrared spectra of the two higher-boiling fractions showed that these materials were identical with the unidentified liquids obtained in earlier experiments.

Attempted Preparations of Bis(2-p-toluenesulfonyloxyethyl)methylamine

Several attempts were made to prepare this sulfonate from bis(2-hydroxyethyl)methylamine (Union Carbide) and p-toluenesulfonyl chloride (Eastman white label) in pyridine solution using a procedure exactly like that described earlier for the preparation of the ditosylates of bis(2-hydroxyethyl)phenyl-

amine and bis(2-hydroxyethyl)-m-tolylamine.[1] When water and excess ammonium hydroxide were added to the reaction mixture, a red oil separated; but this material could neither be induced to crystallize nor extracted with any of the several common solvents which were tried. In one attempt at purification, the aqueous layer was decanted off, and the oil was washed thoroughly with ether by decantation; then it was dissolved in ethanol. After thorough drying over Drierite, the ethanol solution was filtered to remove a small amount of white solid (which failed to melt or decompose in a Bunsen flame) and then concentrated by boiling. When fractionation of the residue at reduced pressure was attempted, decomposition occurred; and only a few drops of distillate could be collected. The extremely viscous, tarry residue left in the pot could not be induced to crystallize. Several other work-up procedures similar to that just described gave varying amounts of oily materials which invariably decomposed on attempted distillation.

In other attempted preparations, equivalent quantities of p-toluenesulfonyl chloride and bis(2-hydroxyethyl)methylamine were mixed and heated together for various periods of time at various temperatures. Tars were invariably produced which could not be crystallized or distilled. Similar negative results were obtained when solutions of the reactants in benzene or toluene were refluxed for extended periods.

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[1] See above, pp. 64-66 and pp. 70-72.

In another attempt, the amine was dissolved in chloroform and the solution was then treated with an excess of gaseous hydrogen chloride. The resultant cloudy mixture was heated to gentle reflux and stirred while two equivalents of p-toluenesulfonyl chloride dissolved in chloroform was added dropwise. The mixture was then refluxed and stirred for several hours, and the solvent was evaporated. The tarry residue was intractable.

Attempted Preparations of 4,4-Dicarbethoxypiperidine

By cleavage of 1-p-nitrosophenyl-4,4-dicarbethoxypiperidine with sodium bisulfite.--Ten g. (0.0305 mole) of 1-phenyl-4,4-dicarbethoxypiperidine was dissolved at 0° in a solution prepared from 50 ml. of concentrated hydrochloric acid and 50 ml. of water. The solution was stirred manually with a thermometer and treated dropwise with a solution containing 2.30 g. (0.0336 mole) of sodium nitrite in 20 ml. of water during a period of 35 min. Approximately 50-75 g. of cracked ice was also added during this period to keep the temperature of the mixture at -5° to 0°. The cold mixture was allowed to stand for 25 min., and the large quantity of yellow-green precipitate (presumably 1-p-nitrosophenyl-4,4-dicarbethoxypiperidine hydrochloride) was then collected by filtering with suction and transferred to a 300-ml. three-necked round-bottomed flask equipped with a mechanical stirrer and a thermometer. Enough water to dissolve the solid was added, and the solution was

cooled in an ice bath at 0-4° and stirred while excess 20 per cent sodium hydroxide was added. This treatment caused the precipitation of a green solid, presumably 1-p-nitrosophenyl-4,4-dicarbethoxypiperidine. The supernatant liquid was removed by means of a filter stick; then 100 ml. of 25 per cent aqueous sodium bisulfite was added, and the contents of the flask were stirred vigorously at room temperature for 16 hr.[1] The resulting reddish-brown mixture was warmed briefly to 75° and then cooled in an ice bath at 4-7° while excess 20 per cent sodium hydroxide was added. Repeated extraction of the mixture with ether removed only a small amount of green solid, probably unreacted 1-p-nitrosophenyl-4,4-dicarbethoxypiperidine, and the clear aqueous moiety failed to exhibit any cloudiness on further treatment with sodium hydroxide solution. The desired compound, 4,4-dicarbethoxypiperidine, is readily soluble in ether and only slightly soluble in water (59).

In a second experiment, the green solid presumed to be the free p-nitroso compound was prepared in a similar manner, recovered by suction filtration, washed several times by suspending it in fresh portions of water, and then thoroughly air-dried to give 3.75 g. (0.0112 mole) of product melting at 55-57°. This material was refluxed for 30 min. with 28 g. (0.067 mole) of the 25 per cent sodium bisulfite solution.

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[1] This procedure was patterned after the method of Munch et al. (31).

(59) J. G. Thweatt, private communication.

Upon cooling, the mixture deposited a green oil which could not be induced to crystallize and which largely dissolved when the cooled mixture was treated with excess 20 per cent sodium hydroxide. The basic mixture had a strong ammonia odor and contained a considerable amount of opaque oil which remained largely undissolved when the mixture was extracted with five 100-ml. portions of ether. Evaporation of the combined ether extracts left only a small amount of light green solid, and extractions of the aqueous moiety with chloroform and then with benzene failed to remove any products.

By cleavage of 1-p-nitrosophenyl-4,4-dicarbethoxypiperidine with sodium ethoxide.--The yellow-green precipitate thought to be the hydrochloride of 1-p-nitrosophenyl-4,4-dicarbethoxypiperidine was prepared as described in the preceding section, recovered by suction filtration, and freed of excess acid by washing repeatedly with acetone. A solution containing 0.10 mole of sodium ethoxide in 50 ml. of re-dried ethanol was prepared by the usual procedure in a 200-ml. round-bottomed three-necked flask equipped with a mechanical stirrer and a reflux condenser containing a calcium chloride drying tube. To this solution was added 5.83 g. (0.0157 mole) of the supposed hydrochloride, and the reaction mixture was then refluxed vigorously with stirring for 26.25 hr. It was then filtered to remove a brownish, water-soluble powder and evaporated to dryness under aspirator pressure. The residue was a green solid, presumably 1-p-nitrosophenyl-4,4-dicarbethoxypiperidine, since it failed to dissolve when treated with cold sodium hydroxide solution.

Preparation of 4-Carbethoxypyridine (Ethyl Isonicotinate)

The following method of preparing this ester is similar to that described by Rubtsov (33).

A suspension of 100 g. of isonicotinic acid (Reilly) in 300 ml. of absolute ethanol was warmed to reflux and stirred vigorously while 150 g. of concentrated sulfuric acid was added dropwise during 40 min. The rate of addition and the amount of external heating were such that the mixture continued to reflux gently throughout the addition period. (The mixture became homogeneous after approximately three-fourths of the sulfuric acid had been added.) The solution was refluxed with stirring for 15 min. after the addition was completed and then poured over several hundred g. of cracked ice. The cold mixture was made alkaline to litmus with 20 per cent aqueous sodium hydroxide and then extracted with 1500 ml. of ether in three portions. The combined extracts were dried over Drierite, and the ether was distilled off at atmospheric pressure. Fractionation of the residue through a six-inch Vigreaux column gave 58.6 g. (48 per cent) of ethyl isonicotinate, b. p. 80-83.5°/6 mm. (lit. (32) b. p. 115°/12 mm.).

Another preparation of this ester performed according to the method of Pailer *et al.* (32) gave only 32 per cent of the product, b. p. 94-96°/11 mm.

Preparation of Ethyl Isonicotinate Methiodide

A solution containing 48.16 g. (0.319 mole) of ethyl isonicotinate and 120 g. (0.845 mole) of methyl iodide (Baker's

C. P.) in 150 ml. of absolute ethanol was refluxed 16.7 hr. in the dark. Most of the excess methyl iodide and ethanol were then distilled off, and the orange solid which remained was washed repeatedly with ether until the washings were pale yellow in color. Recrystallization of the residue from a mixture of absolute ethanol and ether afforded 84.1 g. (90 per cent) of the methiodide as brilliant yellow crystals melting at 122-124° (lit. (36, 37) m. p. 122-124°). An identical run using 10.0 g. (0.0662 mole) of the ester and 25 g. (0.18 mole) of methyl iodide yielded 17.3 g. (89 per cent) of the purified product.

Preparation of 1-Methyl-4-carbethoxypiperidine

A solution containing 17.3 g. (0.0590 mole) of ethyl isonicotinate methiodide in 150 ml. of absolute ethanol was hydrogenated by shaking in a Parr apparatus with 0.40 g. of platinum oxide at 24-27°. The initial hydrogen pressure was 49.90 p. s. i. After 144 min., 88.5 per cent of the theoretical quantity of hydrogen had been absorbed; and after a total reaction time of 303 min., the amount of hydrogen absorbed was 91.2 per cent of the theoretical. The hydrogenation was stopped at this point. Enough water was added to dissolve the white precipitate of 1-methyl-4-carbethoxypiperidine hydroiodide which was present, and the catalyst was removed by filtering the mixture through a fritted glass funnel of medium porosity. The ethanol was removed from the

filtrate under aspirator pressure, and the solution was then made strongly basic to litmus using a few ml. of 10 per cent aqueous sodium hydroxide and a large excess of saturated aqueous sodium carbonate. The oily top layer which appeared was removed by extracting with 350 ml. of ether in three portions. After drying the combined extracts over Drierite, the ether was distilled off and the residue fractionated at reduced pressure through a four-inch heated Vigreaux column to give 8.95 g. of water-white liquid, b. p. 90-100°/11 mm. (lit. (28) b. p. 94-96°/12 mm.). The yield was 89 per cent, based on the starting methiodide, or 98 per cent, based on hydrogen uptake.

The product rapidly darkened on standing. Re-distillation of the combined products from several runs through a six-inch heated Vigreaux column gave a large amount of colorless liquid, b. p. 89°/9 mm., and a smaller amount of straw-colored liquid, b. p. 90-93°(mostly at 93°)/7-8 mm. A methiodide was prepared from the lower-boiling fraction by cautious treatment with a slight excess of methyl iodide. The excess reagent was evaporated and the residue recrystallized from absolute ethanol to give white crystals melting at 148-149° (lit. (28) m. p. 149-150°).

In a later experiment, the aqueous ethanolic solutions of 1-methyl-4-carbethoxypiperidine hydroiodide resulting from several hydrogenation runs were combined and allowed to stand for several days in the refrigerator. The free base was then obtained in the usual manner and fractionated as before, but

the yield of product boiling at 94.5-101°/11 mm. was only 32 per cent of the theoretical (based on the total weight of methiodide which was hydrogenated). Apparently a considerable amount of the ester had undergone hydrolysis during the long period of standing.

The hydrogenation of ethyl isonicotinate methiodide using a platinum oxide catalyst had been reported earlier (36, 37).

Attempted Preparation of 1-Methyl-4,4-dicarbethoxypiperidine from 1-Methyl-4-carbethoxypiperidine

This experiment was patterned after published procedures for alkylating 1-methyl-4-cyanopiperidine in the 4-position (41, 42).

Sodium sand (4.03 g., 0.175 g. atom) was prepared by rapidly stirring a suspension of the metal in 100 ml. of anhydrous, refluxing toluene (Eastman practical grade, dried over sodium wire) contained in a 500-ml. three-necked round-bottomed flask which was equipped with an efficient Teflon-blade mechanical stirrer and a reflux condenser containing a calcium chloride drying tube. Most of the toluene was decanted, and the sand was washed three times by decantation with 25-ml. portions of anhydrous, thiophene-free benzene (dried over sodium wire, gave negative indophenin test) to remove the toluene which remained. After the third washing, the sodium was covered with 50 ml. of the benzene, and a tightly-fitting

cork bearing a nitrogen inlet tube and a thermometer was inserted into the third neck of the flask. The condenser was replaced with a pressure-equalizing dropping funnel containing 9.85 g. (0.0875 mole) of re-distilled chlorobenzene. While the chlorobenzene was added rapidly to the flask with stirring, admission of nitrogen was begun and was continued throughout the remainder of the experiment.

The rapidly stirred mixture was warmed slowly by the external application of heat. At 35° a mildly exothermic reaction began, and the mixture gradually became jet black. It was stirred at 30-35° for approximately 2 hr., and additional benzene was added to replace that which evaporated. Stirring was then stopped and the suspension of phenylsodium allowed to stand overnight. A solution containing 14.13 g. (0.0825 mole) of 1-methyl-4-carbethoxypiperidine, b. p. 89°/9 mm.,[1] in 20 ml. of benzene was then added during five min. at 15-25° to the rapidly stirred mixture. The mixture was stirred at 15-25° for 1.5 hr. and then cooled to 6°. A solution containing 8.96 g. (0.0825 mole) of ethyl chloroformate (Eastman) in 30 ml. of benzene was now added during 20 min. while the temperature was maintained below 15° by external cooling. After an additional 4.7 hr. of stirring at room temperature, the mixture was cooled to 5° and treated with 20 ml. of absolute ethanol, then with 125 ml. of water. The contents of the

[1] The fraction reported as having this boiling point on p. 117 was the material which was used.

flask were then transferred to a separatory funnel, and the benzene layer was separated. The water layer was extracted with two 50-ml. portions of benzene and two 100-ml. portions of ether. These extracts were combined, dried thoroughly over Drierite, concentrated, and fractionated at reduced pressure through a six-inch heated Vigreaux column to give 4.11 g. (29 per cent) of unreacted 1-methyl-4-carbethoxypiperidine, b. p. 94-95°/12 mm., and 5.57 g. of material, b.p. (mostly) 180-190°/12-8 mm. No fraction having the correct boiling point for 1-methyl-4,4-dicarbethoxypiperidine (lit. (28) b. p. 134-137°/12 mm.) was obtained.

The higher-boiling cut was a very viscous, yellow liquid having the odor of crude triphenylcarbinol. This material partially crystallized when cooled in a dry ice bath and was readily soluble in benzene or benzene-hexane mixtures. No further examination of the material was made.

Infrared Spectra

All of the infrared spectra were recorded on a Perkin-Elmer Model 137 Infracord spectrophotometer equipped with sodium chloride optics. Liquids were examined between sodium chloride plates as films of approximately 0.02 mm. thickness, and solid samples were also conveniently examined between these plates as Nujol or hexachlorobutadiene mulls. The strong polystyrene band at 6.24 microns was recorded on every spectrum and used as the reference mark for the wavelength calibration.

A linear correction from this peak was assumed to apply throughout the wavelength range studied. Appendix B contains the spectra of all of the new compounds which were prepared and certain other spectra of particular interest in relation to the text.

Ultraviolet Spectra

These spectra were obtained with a Beckman Model DK-1 recording spectrophotometer using 1 cm. quartz cells. Certain U-V spectral data have already been mentioned in the text, and the data on 1'-aryl spiro-amino barbituric acids is discussed on pp. 127-129. The remaining U-V data are presented in Tables 7 and 8.

No attempts were made to determine exact extinction coefficients for any of the compounds listed in Table 7. However, it was noted that the extinction coefficients of the absorption maxima in basic solution were, in general, somewhat higher for the spiro-amino barbituric acids than for the 5,5-disubstituted open-chain derivatives.

It will be noted from Table 8 that 2-ethylbutyrylurea and diethylmalonamic acid had only "tail" absorption at 220-223 millimicrons in the wavelength region that was studied. This absorption decreased rapidly with increasing wavelength in both cases, so that the absorption of these substances was essentially equal to zero at the wavelength used for the kinetic runs on 5,5-diethylbarbituric acid.

Kinetic Studies

The procedure of Daugherty (14), modified to some extent, was used to measure the hydrolysis rates of several spiro-amino barbituric acids and some of the more common barbiturate hypnotics. The validity of first-order kinetic data, in general, is examined critically in Appendix A.

Materials and Apparatus.--All of the necessary solutions were prepared with distilled water which had been boiled for at least 30 min. Nitrogen was bubbled through the water as it cooled, and the water was then transferred to a large glass bottle connected by means of polyethylene tubing to the two-way stopcock of a burette. This arrangement allowed the burette to be refilled conveniently by siphoning. The entire apparatus was protected from atmospheric carbon dioxide by soda lime tubes. The capacity of the burette was 25 ml., and it could be read to 0.01 ml.

A 50 per cent solution of sodium hydroxide, prepared from reagent grade pellets and distilled water, was filtered with suction through a fritted glass funnel to remove carbonate and then diluted with distilled water to give a large volume of stock solution approximately 1.1 molar in base. This solution was stored in a large polyethylene bottle and dispensed from a 50-ml. burette which could be read to 0.01 ml. The burette assembly was similar to that of the water burette and prevented contamination of the base by carbon dioxide. The base was standardized against accurately weighed samples of

potassium acid phthalate (primary standard grade) using phenolphthalein as the indicator.

The samples of the spiro-amino barbituric acids were free acids of analytical purity. Other barbiturates studied were commercial materials obtained either in the form of the free acid or the monosodium salt. The free acids were recrystallized until their melting points agreed with literature values, while the sodium salts were used without further purification.

Stock solutions, 1.00×10^{-3} molar in barbiturate, were prepared from samples weighed accurately to 2×10^{-4} g. on a Mettler balance capable of being read to 1×10^{-6} g. Each sample was transferred quantitatively to a 500-ml. or 1000-ml. volumetric flask, and distilled water was then added to the calibration mark. The solutions of the sodium salts were used at once to minimize possible losses due to hydrolysis. Immediate use of the free acid solutions was unnecessary since these solutions were quite stable.

All of the optical density readings were taken on a Beckman DK-1 spectrophotometer equipped with a thermostatted cell compartment. At 65° a short-stemmed mercury thermometer placed in the thermometer well of this compartment showed cyclic fluctuations of approximately plus and minus 1° from the mean temperature;[1] however, the actual temperature change of the solutions in the compartment was probably not nearly

[1] Approximately five minutes was required for completion of a cycle.

this large since the heat capacities of mercury and water are dissimilar. This conclusion is supported by the high precision observed for the runs carried out in the compartment and by the observation that the kinetic points for these runs showed only very slight deviations from the straight-line plots.[1] The actual temperature variation in these runs is estimated to be plus or minus 0.5°.

The water baths in which the reactions at 34.7° and 50.4° were run were capable of maintaining the desired temperatures with a maximum fluctuation of plus or minus 0.1°, while the 65° bath exhibited a temperature fluctuation of plus or minus 0.5°. All of the bath temperatures were determined accurately with short-stemmed mercury thermometers.

Procedures.--For each run at 34.7° or 50.4°, and for the 65.0° runs on 5-allyl-5-(1-methylbutyl)- and 5-ethyl-5-(1-cyclohexenyl)barbituric acid, 90.00 ml. of standard 1.1 molar sodium hydroxide and 10.00 ml. (pipetted) of barbiturate stock solution were placed in separate 100-ml. screw-cap polyethylene bottles and thermostatted at the reaction temperature for 1-2 hr. During this time the spectrophotometer was allowed to warm up, and the thermostatted cell compartment was set at the temperature of the reaction. The solutions were then rapidly mixed, and the time of mixing was recorded and taken

[1] See Figure 50 of reference (14) for sample kinetic plots.

as zero time.[1] The reaction mixture was quickly returned to the bath. Aliquots were then withdrawn periodically, placed in 1 cm. quartz cells, and the optical densities read at the predetermined wavelength compared to a distilled water blank. Care was taken to rinse the sample cell several times with the solution before taking the actual sample. The time which elapsed between withdrawal of a sample and reading of its optical density was of the order of 2-3 min.; however, the rates of the reactions were sufficiently slow so that any errors arising from this source were negligible. The instant at which the optical density was read was the time recorded for each kinetic point. Errors arising from zero drift of the spectrophotometer were minimized by re-setting the zero and one hundred per cent controls immediately before each point was taken, using distilled water in the sample cell.

At 65° most of the reactions were too rapid to follow by means of the technique just described. For each rapid run at this temperature 90.00 ml. of base and 10.00 ml. of barbiturate stock solution were thermostatted separately for 1-2 hr. in a water bath maintained at a temperature of 65±2°, while the thermostatted cell compartment was carefully set at the desired temperature. The solutions were then mixed thoroughly, and a representative aliquot of the mixture was placed in the

[1] Volume changes due to mixing and to temperature effects were determined at each temperature in separate experiments and found to be inappreciable.

sample cell. The cell was returned to the compartment and allowed to stand 5-15 min. for the purpose of attaining thermal equilibrium. A stopwatch was then started, and the optical density was recorded at regular intervals without removing the sample from the cell compartment. Zero time was taken as the time the watch was started. The caustic solutions caused no observable damage to the sample cell under these conditions in runs lasting as long as two hours.

Calculations.--The sodium hydroxide solution used had slight but appreciable absorption at all of the kinetic wavelengths. The extent of this absorption at each wavelength was determined from a spectrum of sodium hydroxide solution against a distilled water blank. The values thus obtained were subtracted from the observed optical densities obtained in the kinetic experiments to give corrected optical density values whose logarithms were plotted vs. time.

All of the reactions gave good straight-line kinetic plots from zero to approximately sixty per cent of reaction. No attempts were made to follow any of the reactions to completion. The points for the runs carried out in constant-temperature baths tended to scatter somewhat, so the data were fitted by the method of least squares to eliminate the subjective factor in plotting. Rate constants which did not agree with the average value to within five per cent were assumed to be in error. Usually, however, the rate constants were reproducible to within a few tenths of a per cent. The points for

the runs carried out in the spectrophotometer showed very little tendency to scatter; however, for consistency the data in these runs were also subjected to the least-squares treatment.

In cases where rate data were obtained at more than one temperature, plots of ln k *vs.* 1/T were used to calculate activation energies and entropies according to the equation[1] (60)

$$\ln K = -E_a/RT + S_a/R + \ln (\underline{k}T/h) + 1$$

where: k is the specific reaction rate constant in sec^{-1}
E_a is the activation energy in cal $mole^{-1}$
S_a is the activation entropy in cal deg^{-1} $mole^{-1}$
T is the absolute temperature in ^{o}K.
R is the gas constant in cal deg^{-1} $mole^{-1}$
h is Planck's constant in erg sec $molecule^{-1}$
$\underline{k}$ is the Boltzmann constant in erg deg^{-1} $molecule^{-1}$.

These data were also fitted by the method of least squares, even though satisfactory straight-line plots were obtained in every case.[2]

Measurements on spiro-1'-arylpiperidine-4',5-barbituric acids.-- Ultraviolet spectral and kinetic studies were undertaken on the material (X) previously reported to be "spiro-1'-phenylpiperidine-4',5-barbituric acid" (22) in an efford to shed some light on the actual structure of this compound. A solution 10^{-4} molar

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[1] The term $\ln(\underline{k}T/h)$ was assumed to be constant for the calculation of E_a; thus the values of E_a obtained are Arrhenius activation energies. For the calculation of S_a T was taken as 323.1^{o} K.

[2] See Figure 13 for sample plots.

(60) F. Daniels and R. A. Alberty, Physical Chemistry, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 356.

in X was scanned in a 1 cm. quartz cell against a water blank in the 210-360 millimicrons region and found to have an absorption maximum at 278 millimicrons with optical density 1.3. In the same wavelength region a solution 10^{-4} molar in X and 0.97 molar in sodium hydroxide exhibited a maximum of optical density 0.9 at 258 millimicrons. An attempt was made to measure the basic hydrolysis rate of X by following the rate of decrease of the absorption at 258 millimicrons. At 34.7° this absorption did decrease slowly with time, but the kinetic plot showed a very pronounced upward curvature, so that no valid rate constant could be calculated from the data. After about 25 hr. at 34.7°, the solution was again scanned in the 210-360 millimicrons region. The only peak observed was at 240 millimicrons, and it had an optical density of about 1.2. Since this peak was not present originally, it must have been due to absorption by a hydrolysis product. "Tail" absorption from the peak was obviously the source of the interference at 258 millimicrons.

In contrast to the foregoing results, authentic samples of spiro-1'-phenylpiperidine-4',5-barbituric acid and spiro-1'-m-tolylpiperidine-4',5-barbituric acid in essentially neutral solution exhibited the expected absorptions characteristic of the N,N-dialkylaniline chromophore at 239 and 241 millimicrons, respectively; and no maxima were observed at higher wavelengths in either case. A solution of the m-tolyl derivative containing one equivalent of sodium hydroxide had an absorption at 241 millimicrons approximately 1.6 times as great as that of a

neutral solution having the same concentration of substrate. The peak absorption of the basic solution decreased with time until it reached a constant value equal to the peak absorption of the neutral solution.

Both of the spiro-1'-arylpiperidine-4',5-barbituric acids hydrolyzed so rapidly in excess base at room temperature that quantitative rate measurements were not possible under these conditions.[1]

[1] See above, p. 44.

CHAPTER IV

DISCUSSION OF RESULTS

The conditions used for the parallel hydrolysis studies are given in Table 3, and the results are summarized in Table 4. The spiro compounds are seen to be less stable than the

Table 3. Conditions for Parallel Hydrolysis Experiments

Run No.	Barbituric Acid	Acid con. (moles/liter)	NaOH con. (moles/liter)	Reflux Time(hr.)
1	5,5-diethyl-	0.45	0.45	5.5
2	5,5-diethyl-	1.00	3.00	6.0
3	spirotetrahydropyran-4',5-	0.365	0.365	6.0
4	spirotetrahydropyran-4',5-	0.365	1.095	6.0
5	spiro-1'-phenylpiperidine-4',5-	0.365	0.365	6.0
6	spiro-1'-phenylpiperidine-4',5-	0.365	1.095	6.0

open-chain derivative, and it is suggested that this decrease in stability is caused by decreased steric hindrance to nucleophilic attack at the 4- and 6-positions of the spiro compounds. The product-isolation techniques obviously left much to be desired, and the percentages given in Table 4 probably do not represent the maximum yields obtainable under these conditions;

Table 4. Results of Parallel Hydrolysis Experiments

Run No.	Products Recovered (%)			
	Barbituric Acid	Ureide	Malonic Acid	Malonamic Acid
1	33	42	0	0
2	0	0	trace	32
3	0	trace	0	0
4	0	0	93	0
5	0	45	21	0
6	0	0	20	0

however, the results are of some interest from the synthetic standpoint.

It appears that the hydrolysis of 5,5-disubstituted barbituric acids using one equivalent of base may be a general synthetic method for ureides, regardless of the nature of the 5,5-substituents. In the case of the spiro derivatives, hydrolysis with three equivalents of base is of use as a method of synthesis for malonic acids. On the other hand, run 2 indicates that hydrolysis with three equivalents of base may be useful for synthesizing malonamic acids when spiro rings are not present. It should be emphasized, however, that no attempts were made to find the optimum conditions for producing particular compounds.

The hydrolysis experiments on spiro-1'-methylpiperidine-4',5-barbituric acid were not definitive, and the only

firm conclusion that can be safely drawn from the results is that this compound certainly does not react under hydrolytic conditions like any of the other 5,5-disubstituted barbituric acids that have been studied to date. None of the "normal" products resulting from stepwise hydrolytic degradation of the pyrimidine ring were found, and the formation of ammonium carbonate was a result which had not heretofore been observed in barbiturate hydrolyses. The liquid hydrolysis products were not definitely identified; however, the data obtained on these materials appears to show rather conclusively that they do not contain a 1-methylpiperidine ring. Thus, if this is the case, the only possible explanations for the results of these experiments are (a) a very remarkable hydrolytic fission of the piperidine ring occurred, or (b) the structure given for spiro-1'-methylpiperidine-4',5-barbituric acid is erroneous.

Chemical tests failed to prove or disprove the structure of this compound, although the synthesis of its hydroiodide showed that a single basic amino group was present. The fact that spiro-1'-methylpiperidine-4',5-barbituric acid fails to yield a methiodide under ordinary conditions indicates that this amino group may not be tertiary; however, the protonated amino group of a zwitterionic molecule would be expected to have greatly decreased reactivity toward methyl iodide. On the other hand, the amino group may actually be secondary, and the failure to react with acetyl chloride may be due to zwitterionic protonation. In any event, the struc-

ture of spiro-1'-methylpiperidine-4',5-barbituric acid must be regarded as open to question.

All of the 1'-alkyl spiro-amino barbituric acids have absorption maxima in neutral solution at approximately 265 millimicrons and in strongly basic solution at approximately 245 millimicrons[1] (14). Because of the fact that other 5,5-disubstituted barbituric acids invariably have no ultraviolet maximum in neutral solution (14, 61, 62), the absorption of the 1'-alkyl spiro-amino compounds under these conditions can only be explained by assuming it to be due to the presence of zwitterionic species (14). According to this argument, aryl-amino barbituric acids, in general, would not have barbiturate ring absorption in neutral solution, since these compounds would certainly not be expected to be zwitterionic. Thus, the fact that compound X , previously reported to be "spiro-1'-phenylpiperidine-4',5-barbituric acid" (22), does absorb at 278 millimicrons in neutral solution can be taken as evidence that this material is not an aryl-amino barbituric acid of any sort. The only type of absorption expected in neutral solution for a compound such as spiro-1'-phenylpiperidine-4',5-barbituric acid would be that due to the N,N-dialkylaniline chromophore; however, this maximum is in the neighborhood of

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[1] See Table 7.

(61) R. E. Stuckey, Quart. J. Pharm. Pharmacol., 15, 377, (1942).

(62) W. F. Elvidge, ibid., 13, 219 (1941).

240 millimicrons;[1] and since X has no maximum at this wavelength, it is concluded that such a chromophore is not present in this compound. Considerable evidence was amassed to indicate that the spiro-1'-arylpiperidine-4',5-barbituric acids prepared by the method described in this thesis do have the correct structures. This evidence includes (a) the manner of forming the barbituric acid ring, which, on the basis of the many barbiturate syntheses reported in the literature, is apparently an unambiguous synthetic method; (b) the demonstration of the presence of this ring in the case of the m-tolyl compound by the production of characteristic barbiturate monoanion absorption at 241 millimicrons;[2] (c) the decrease of this absorption with time,[2] which is readily explained on the basis of hydrolytic pyrimidine ring cleavage; (d) the very rapid cleavage of the pyrimidine ring in the presence of excess base--a typical characteristic of spirobarbituric acids;[3] (e) the stepwise degradation of the phenyl compound to give "normal" hydrolysis products which were isolated and characterized; and, finally (f) exhaustive hydrolytic degradation of the pyrimidine ring to afford N-phenylisonipecotic acid, a known compound.

The course of the stepwise degradation of spiro-1'-phenylpiperidine-4',5-barbituric acid is outlined in Figure 11.

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[1] Note the absorption maxima of the hydrolysis products of spiro-1'-phenylpiperidine-4',5-barbituric acid, Table 8.

[2] See above, p. 128.

[3] See Table 3 of reference (14).

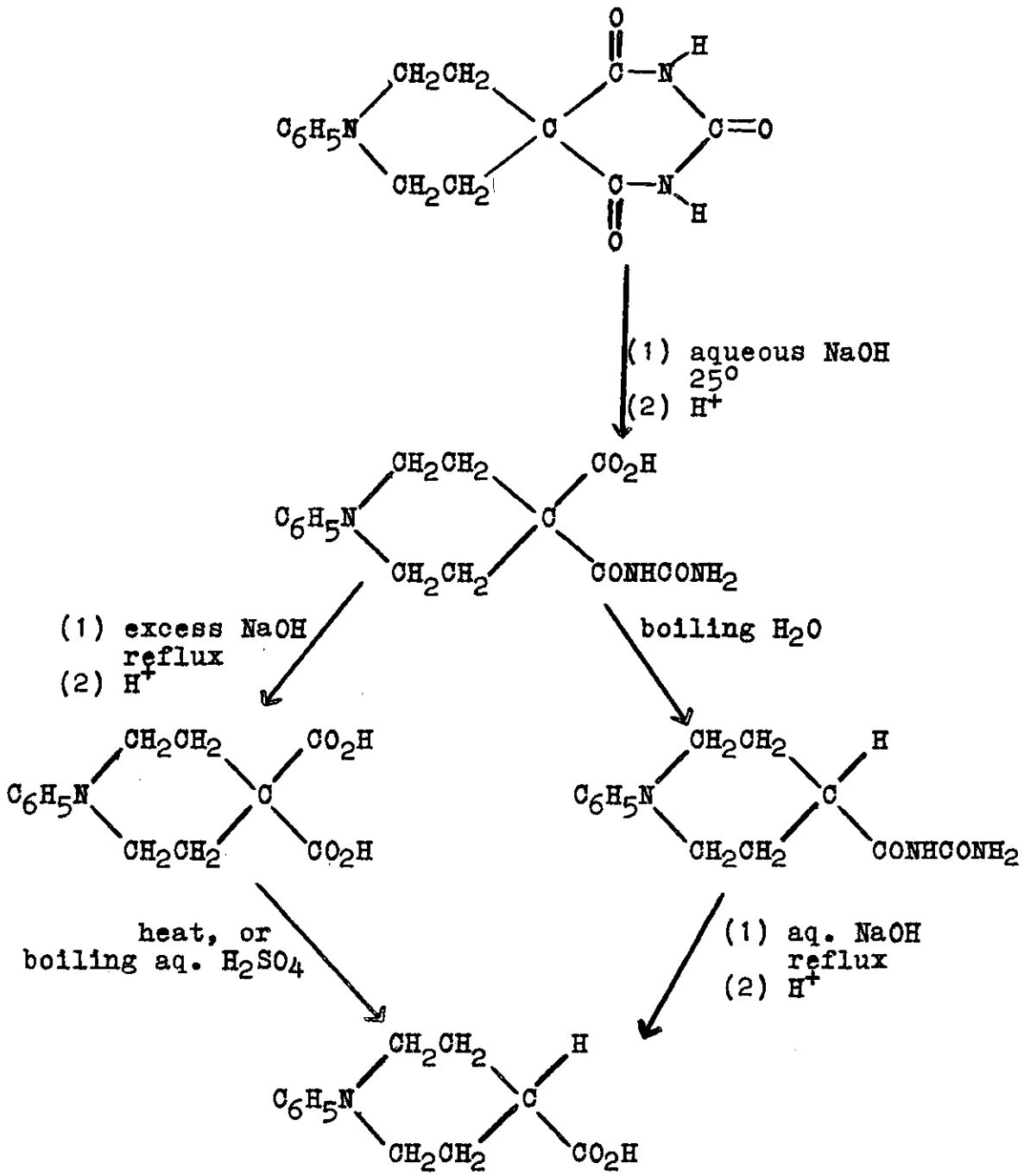

Figure 11. Hydrolytic Degradation of Spiro-1'-phenyl-piperidine-4',5-barbituric Acid

The failure of the hydrolysis to yield a malonamide, a malonamic acid, or a monoamide is explained by the small steric hindrance to nucleophilic attack at the carbonyl groups originally present at the 4- and 6-positions of the parent compound. It is suggested that this behavior on hydrolysis may be general for barbituric acids incorporating spiro rings of six or fewer atoms; that is, if these rings are not too heavily substituted in the positions nearest the 4- and 6-carbonyl groups.

The attempts to condense bis(2-p-toluenesulfonyloxyethyl)phenylamine with malonamide indicate that the alkylation of malonamide with sulfonic esters may be of some synthetic utility when the introduction of only one alkyl group is desired. The method does not appear to be very practical for the simultaneous introduction of two alkyl groups, however. In general, the results of these experiments are additional evidence that the methylene group of malonamide is much less reactive than the methylene group of malonic esters. It is possible that the extent of monoalkylation was actually much greater than indicated by the amount of 3,3-dicarboxamidopropyl-2-ethoxyethylphenylamine which was isolated since, in many of these experiments, all of the product fractions were not completely identified. In this connection, it is noteworthy that no 3,3-dicarboxamidopropyl-(2-p-toluenesulfonyloxyethyl)phenylamine was isolated, although a considerable amount of this material may have been present.

The attempts to develop a better synthesis for 1-methyl-4,4-dicarbethoxypiperidine were not exhaustively pursued, and the suggested alternative routes to this compound cannot be assumed to be ineffective on the basis of the few experiments which were run. As a matter of fact, the synthesis of 1-methyl-4,4-dicarbethoxypiperidine has recently been accomplished using the monoester, ethyl chloroformate, and triphenylmethylsodium, according to the method suggested above[1] (63). Moreover, 4,4-dicarbethoxypiperidine has also recently been prepared by cleavage of 1-benzenesulfonyl-4,4-dicarbethoxypiperidine with a mixture of hydrobromic and acetic acids, and attempts to alkylate this ester to give 1-alkyl-4,4-dicarbethoxypiperidines are now under way (64).

The failure to prepare bis(2-p-toluenesulfonyloxyethyl)-methylamine by the method used for the N-aryl analogues was not entirely unexpected in view of a published report stating that compounds of this type are too unstable to be isolated (65). This instability is probably due to the formation of cyclic immonium salts (Figure 12) which react rapidly with other molecules of the base to give piperazinium dimers or polymers. The inability to condense bis(2-chloroethyl)methylamine with

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[1] See above, pp. 25-26.

(63) G. C. Allen, private communication.

(64) J. G. Thweatt, private communication.

(65) J. M. Sprague, D. Hill, and E. L. Engelhardt, U. S. Patent 2,671,105 (May, 1954).

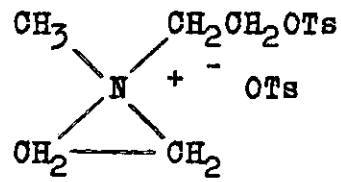

Figure 12. Immonium Salt from Bis(2-p-toluenesulfonyloxyethyl)methylamine

diethyl malonate may also be related to the well-known tendency of this nitrogen mustard to undergo self-condensation in this manner.

The hydrolysis rate data are summarized in Table 5, and the activation energies and entropies calculated using the mean values of k at each temperature are given in Table 6. By

Table 5. Pseudo-first-order Rate Constants for the Hydrolysis of Barbituric Acids in 0.9738 Molar NaOH

Barbituric Acid[a]	$k(min^{-1}) \times 10^{-4}$		
	34.7±0.1°C.	50.4±0.1°C.	65.0±0.50°C.
spiro-1'-methyl-piperidine-4',5-	5.79 5.79	38.2 42.5	226 215
spiro-1'-isopropyl-piperidine-4',5-	5.65 6.03	39.6 38.4	256 258
spiro-1'-cyclohexyl-piperidine-4',5-	6.30 6.22	46.1 49.9	278 266
spiro-1'-benzyl-piperidine-4',5-	4.84 4.91	44.4 44.2	218 233 224
5-allyl-5-(1-methyl-butyl)-	--	--	3.1[b]

(Continued on next page)

Table 5. (continued)

Barbituric Acid[a]	k(min^{-1}) x 10^4		
	34.7±0.1°C.	50.4±0.1°C.	65.0±0.5°C.
5-ethyl-5-(1-cyclo-hexenyl)-	--	--	4.0[b] 5.0[b]
5-allyl-5-isobutyl-	--	--	37.6 39.2
5-ethyl-5-isoamyl-	--	--	40.3 41.1
5-ethyl-5-n-butyl-	--	--	45.4 46.4
5,5-diethyl-	3.22 3.51	14.9 15.6	52.1 52.4
5-ethyl-5-phenyl-	--	--	87.9 88.3
5-allyl-5-n-butyl-	--	--	131 138
5-allyl-5-phenyl-	--	--	194 195
5,5-diallyl-	--	--	377 384
5-methyl-5-phenyl-	--	--	2310 2410

[a]Acid concentration 1.00 x 10^{-4} molar in every case.

[b]Points in these runs scattered rather badly, so that the values of k may be in error by as much as a factor of two.

Table 6. Activation Energies and Entropies for the Hydrolysis of Barbituric Acids in 0.9738 Molar NaOH

Barbituric Acid	E_a(kcal/mole)	S_a(cal mole^{-1} deg^{-1})
spiro-1'-methyl-piperidine-4',5-	24.8	1.6
spiro-1'-isopropyl-piperidine-4',5-	25.8	4.7
spiro-1'-cyclohexyl-piperidine-4',5-	25.8	4.8
spiro-1'-benzyl-piperidine-4',5-	26.2	5.8
5,5-diethyl-	18.7	(-)19.2

means of the Arrhenius equation, for 5,5-diethylbarbituric acid at 40.2° in 0.9738 molar sodium hydroxide k is calculated to be 5.92 x 10^{-4} min^{-1}, a value which corresponds reasonably well to Daugherty's value of 6.22 x $10^{-4}$$min^{-1}$ at this temperature in 0.9505 molar base.[1] On the other hand, Daugherty finds k to be 5.35 x 10^{-4} min^{-1} for spiro-1'-methylpiperidine-4',5-barbituric acid in 0.9505 molar base at 40.2°,[1] while the value calculated from the data of Table 6 for this temperature is 11.8 x 10^{-4} min^{-1}.

The relatively slow hydrolysis rates of the spiro-amino barbituric acids are surprising in view of the extremely rapid rates which have been reported for other spiro-barbiturates.

[1] See Table 3 of reference (14).

For example, according to Daugherty's data,[1] the rate constant for spirotetrahydropyran-4',5-barbituric acid is more than 400 times greater than the rate constant for spiro-1'-methylpiperidine-4'5-barbituric acid in 0.9505 molar base at 40°. These results may be taken as additional evidence for (a) the occurrence of a different type of reaction in the case of the spiro-amino compounds, or/and (b) the incorrectness of the structures assigned to these materials.

Although a 5,5-disubstituted barbiturate is largely converted to its conjugate dianion in strongly basic solution, small equilibrium concentrations of the monoanion and the neutral species must also be present. The two charged forms, especially the dianion, are more highly stabilized by resonance than the neutral molecule, so that cleavage of the pyrimidine ring in these entities would be expected to require a considerably higher activation energy than cleavage of the ring in the neutral species. The electrostatic repulsion between hydroxide ion and the charged species will also tend to increase the activation energy in these cases; however, electrostatic contributions to the activation energies of ionic reactions are ordinarily small (66). On the other hand, electrostatic contributions to activation entropies are very large, and reactions between ions of like sign are found to have high

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[1] See Table 3 of reference (14).

(66) A. A. Frost and R. G. Pearson, Kinetics and Mechanism, John Wiley and Sons, Inc., New York, N. Y., 1958, p. 133.

negative entropies of activation, an effect which is thought to be due to the fact that the transition state complex is more highly solvated than the less highly charged reactants (67). Therefore, the high negative activation entropy obtained for the hydrolysis of 5,5-diethylbarbituric acid may be taken to indicate that the major portion of this reaction occurs by attack of hydroxide on monoanion and/or dianion. Moreover, the activation energies for reaction of each of these species with hydroxide would be expected to differ appreciably, so that if both species contributed appreciably to the overall reaction, the overall activation energy E_a would not be expected to remain constant with changing temperature. Thus, the fact that E_a does remain constant indicates that most, or all, of the reaction occurs *via* only one ionic species over the temperature range studied.

The activation energies for the hydrolysis of the spiro-amino barbituric acids are considerably higher than expected. By way of comparison, the activation energy for the hydrolysis of spirotetrahydropyran-4',5-barbituric acid in 0.8272 molar aqueous sodium hydroxide is only 11.6 kcal/mole.[1] The high activation energies for the spiro-amino compounds may be taken to indicate that the reaction occurs *via* an ionic species highly stabilized by resonance; but, on the other hand, the

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[1]Datum from p. 23, reference (14).

(67) *Ibid.*, p. 132.

entropies of activation for these hydrolyses are certainly inconsistent with the values expected for a reaction between oppositely charged ions. In contrast, using Daugherty's data,[1] S_a for the hydrolysis of spirotetrahydropyran-4',5-barbituric acid in 0.8272 molar sodium hydroxide is calculated to be (-)27.6 cal $deg^{-1}mole^{-1}$. A possible, but unlikely, explanation for these anomalous results is that, in the case of the spiro-amino compounds, the actual nucleophilic reagent is a water molecule rather than hydroxide ion.

If the hydrolysis of the spiro-amino compounds proceeded by way of the neutral molecule or the monoanion, then a correlation between reaction rate and basicity of the amino group would be expected because of the supposed zwitterionic nature of both of these species. The compounds having the more basic amino nitrogens would tend to be more zwitterionic in character and might, therefore, hydrolyze slower, since a negative charge in the barbiturate ring should decrease the reactivity toward nucleophiles. The data show that no such correlation can be made, and, in fact, the hydrolysis rates for all of the spiro-amino compounds are seen to be very nearly the same. Indeed, it seems that the only firm inference to be made on the basis of the results with the spiro-amino compounds is that the substituent groups are too far away from the reaction site to have much influence on the

[1] See Table 4 of reference (14).

hydrolysis rates. It does not seem wise to attempt a more complete interpretation of these data until the problem of the structures of the spiro-amino barbituric acids has been conclusively resolved.

The hydrolysis rates of the 5,5-disubstituted barbituric acids which do not incorporate a spiro carbon atom can be rationalized in terms of the steric and polar effects of the substituents. Steric effects seem to be particularly pronounced, and a striking illustration of their importance is provided by the data for the 5-ethyl-5-phenyl- and 5-methyl-5-phenyl- derivatives. The low stability of the methyl compound suggests that a reported failure (61) of 5,5-dimethylbarbituric acid to exhibit characteristic barbiturate dianion absorption in 0.1 molar aqueous sodium hydroxide may have been due to the occurrence of a rapid base-catalyzed pyrimidine ring cleavage. The stability of the 5-allyl-5-isobutyl- derivative relative to that of the 5-allyl-5-n-butyl- isomer shows that chain branching on the beta-carbon atom of a 5-substituent also exerts an important steric effect on the rate.

A comparison of rates for appropriate pairs of compounds in Table 6 shows that replacement of 5-ethyl by 5-allyl groups invariably caused large decreases in stability. Since three carbon atoms are interposed between the double bond of an allyl group and the reaction center, the inductive effect of this bond would not be expected to enhance the reactivity to a major extent. Therefore, it appears that the destabilizing

effect of the allyl radical may also be largely steric in nature.

The occurrence of a large steric effect in these reactions may be rationalized by assuming that the pyrimidine ring of the ionic species undergoing nucleophilic attack is essentially planar--a condition which is necessary for maximum resonance stabilization by pi orbital overlap. The nucleophilic reagent will tend to attack the 4-carbonyl group in a direction perpendicular to the plane of the ring. Because of the ring structure, the 5-substituents will tend to be more or less in the line of attack and would therefore be expected to exert large F strain effects.

The foregoing discussion is based on the assumption that the chief effect of 5-substituents is on the activation energy of the hydrolysis. It should be realized, however, that it is impossible to determine from rate data at only one temperature whether the effect is on the activation energy, on the activation entropy, or on both of these quantities.

Published physiological activity data[1] are available for many of the compounds in Table 5. These data indicate that, in general, the compounds having the greatest hydrolytic stability also possess the greatest hypnotic activity. The correlation is not exact, but it is surprisingly good in view

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[1] See references (1) and (4) and other references cited therein.

of the inaccuracies associated with pharmacological data[1] and the probability that the solubility properties of these compounds are also important in determining their hypnotic potencies.[2]

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[1] See above, p. 8.

[2] See above, pp. 2-3.

CHAPTER V

RECOMMENDATIONS

One of the more interesting aspects of the synthetic work described in this thesis is the use of an ion-exchange resin in anhydrous ethanol to convert the sodium salts of barbiturates to the free acids. In view of the results obtained so far, it seems that this might be a good general method for preparing barbiturates which are readily hydrolyzed in aqueous media. Since the low yields reported in the syntheses of many of the more common barbiturates may be largely due to hydrolysis, it is suggested that the use of ion-exchange resins in the preparation of these compounds be investigated. For the synthesis of barbiturates which do not contain basic functional groups, very strongly acidic resins, such as the sulfonic acid types, might prove to be more effective than the carboxylic acid type used in the present work. In view of the extensive use of barbiturates as drugs, even slight improvements in their preparation might prove to be of considerable commercial value.

The simplicity of the scheme outlined in Figure 5 for the preparation of 1-methyl-4,4-dicarbethoxypiperidine would appear to make further work on this sequence desirable. It has been shown recently that the rates of alkylation of enolate anions are greatly enhanced when the reactions are run in

the dimethyl ethers of ethylene glycol and diethylene glycol (monoglyme and diglyme) (68). Therefore, it is recommended that further attempts to condense bis(2-chloroethyl)alkylamines with sodiomalonic ester be made using monoglyme or diglyme as solvents.

The effects of structure on the reactivity of barbiturates in basic hydrolysis are of theoretical interest. More work should be done along these lines, and the mechanism of this reaction should be subjected to a detailed kinetic study. The relative stabilities of barbiturates under basic conditions are also of continued interest from the standpoint of a correlation with hypnotic activity; however, as discussed in Chapter I,[1] it seems that the stabilities under acidic conditions might furnish a better basis for such a correlation. The acid-catalyzed hydrolysis should be studied thoroughly, and it seems that the method outlined by Daugherty (14) would be suitable for this purpose.

Further work on the spiro-amino barbituric acids should be deferred until the problem of their structures has been definitely resolved.

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[1] See above, pp. 5-8.

(68) H. D. Zook and T. J. Russo, J. Am. Chem. Soc., 82, 1258 (1960).

APPENDIX A

APPENDIX A

The straight-line criterion as a test of the validity of first-order kinetic data.--All reactions that show a simple first-order kinetic dependence upon reactant concentration are described by the well-known equation

$$(R)_t = (R)_o e^{-kt} \qquad (1)$$

where: $(R)_t$ is the reactant concentration at time t;
$(R)_o$ is the reactant concentration at zero time;
k is the rate constant.

The logarithmic form of equation 1,

$$-\ln(R)_t = kt - \ln(R)_o, \qquad (1a)$$

shows that k can be obtained by plotting values of $-\ln(R)_t$ vs. t and determining the slope of the resulting straight line.

Many common techniques for collecting first-order kinetic data involve the measurement at various times of some physical property of the reaction system which is always directly proportional to reactant concentration. A general physical property, Z, which exhibit such a proportionality may be defined by the equations

$$(Z_R)_t = a_r(R)_t; \qquad (Z_R)_o = a_r(R)_o \qquad (2)$$

where: $(Z_R)_t$ is the contribution to Z from reactant molecules at time t;
$(Z_R)_o$ is the contribution to Z from reactant molecules at zero time;
a_r is the proportionality constant.

Substituting the values of $(R)_t$ and $(R)_o$ from these equations into equations 1 and 1a gives

$$(Z_R)_t = (Z_R)_o e^{-kt} \tag{3}$$

and

$$-\ln(Z_R)_t = kt - \ln(Z_R)_o. \tag{3a}$$

From equation 3a it follows that a plot of $-\ln(Z_R)_t$ vs. t will also give a straight line of slope equal to k.

In practice, it is frequently found that certain products P_Z of a reaction also have finite values of Z, so that the total, measured value of Z is greater than the desired quantity, $(Z_R)_t$. That is,

$$(Z_R)_t = (Z_T)_t - (Z_{PZ})_t \tag{4}$$

where: $(Z_T)_t$ is the total value of Z at time t;
$(Z_{PZ})_t$ is the contribution to Z from product molecules at time t.

If

$$(P_Z)_t = (p_{z1})_t + (p_{z2})_t + \cdots + (p_{zn})_t = \sum_{i=1}^{n} (p_{zi})_t. \tag{5}$$

where: $(P_Z)_t$ is the total concentration at time t of product molecules having Z values;
$(p_{z1})_t, (p_{z2})_t, \ldots, (p_{zn})_t$ are the concentrations of individual molecular species having Z values;

and $b_{z1}, b_{z2}, \ldots, b_{zn}$ are proportionality constants characteristic of the individual molecular species; then

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[1] The concentrations of molecular species which do not contribute to $(Z_T)_t$ may also be included in the sum, $(P_Z)_t$, as long as $(P_Z)_t$ satisfies the relationship expressed in equation 9 (see p. 153).

$$(Z_{PZ})_t = b_{z1}(p_{z1})_t + b_{z2}(p_{z2})_t + \cdots + b_{zn}(p_{zn}) = \sum_{i=1}^{n} b_{zi}(p_{zi})_t. \quad (6)$$

A composite proportionality factor a_p may be defined by the relationship

$$a_p(P_Z)_t = (Z_{PZ})_t, \quad (7)$$

and it follows from equations 5, 6, and 7 that

$$a_p = \sum_{i=1}^{n} b_{zi}(p_{zi})_t \Big/ \sum_{i=1}^{n} (p_{zi})_t. \quad (8)$$

If b_{zi} has the same value for all of the individual molecular species, then equation 8 reduces to $a_p = b_{zi}$. On the other hand, if the molecular species have different b_{zi} values, it is possible for a_p to vary with time.

The calculation of $(Z_R)_t$ from equations 4 and 6 has the practical disadvantages that : (a) the concentrations $(p_{zi})_t$ must be known, and (b) independent determinations of b_{zi} must be made. Moreover, in certain cases, all of the isolable products of a reaction may not include all of the products with finite values of Z (or b_{zi}). Therefore, there is an inherent uncertainty in values of $(Z_R)_t$; and, for this reason, there must also be an uncertainty in the value of k calculated by equation 3a. In view of these difficulties, the establishment of an independent criterion for checking the validity of first-order kinetic data, in general, is clearly desirable.

For a great many first-order reactions the following relationship holds:

$$(R)_o = (R)_t + c(P_Z)_t \qquad (9)$$

where: c is a dimensionless constant.

In all of the cases described by equation 9, it is proposed to show that the linearity of the kinetic plot is an excellent criterion for the validity of k. In other words, when the plot of $-\ln(Z_T)_t$ vs. t is linear, then $(Z_T)_t = (Z_R)_t$, and the slope of the plot must be the true value of k.

In order to be able to discuss a situation which has physical significance and is, therefore, readily visualized; the proof of this statement will be given in terms of the case where a spectrophotometric technique is used to obtain the kinetic data. The Lambert-Beer law (69) will be assumed to apply to all of the molecular species present, and the thickness of the absorbing solution will be taken as unity. Thus,

$$(Z_T)_t = (D_T)_t; \quad (Z_R)_t = (D_R)_t; \quad (Z_{PZ})_t = (D_{PZ})_t; \qquad (10)$$

where: $(D_T)_t$, $(D_R)_t$, and $(D_{PZ})_t$ are optical densities;

and

$$(D_R)_t = \epsilon_r(R)_t; \qquad (D_{PZ})_t = \epsilon_p(P_Z)_t; \qquad (11)$$

where: ϵ_r is the extinction coefficient for reactant molecules, and ϵ_p is a composite extinction coefficient for P_Z.

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(69) F. Daniels and R. A. Alberty, Physical Chemistry, John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 69-70.

(Since ϵ_p is equivalent to a_p of equations 7 and 8, it follows that ϵ_p may either be a constant or vary with time.)

In order to establish the proposed criterion of linearity, it is necessary to show that it is impossible for a plot of $-\ln(D_T)_t$ *vs.* t to result in a straight line whose slope is unequal to k. That is, it must be shown that a straight-line plot described by

$$-\ln(D_T)_t = k't - \ln[\epsilon_r(R)_o] \qquad (12)$$

where: $k' \neq k$

cannot be constructed from the experimental data.

Equations 1 and 9 may be combined to give

$$(P_Z)_t = \frac{(R)_o}{c}(1 - e^{-kt}). \qquad (13)$$

From equations 11 and 13 it follows that

$$(D_{PZ})_t = \frac{\epsilon_p(R)_o}{c}(1 - e^{-kt}), \qquad (14)$$

and from equations 1 and 11

$$(D_R)_t = \epsilon_r(R)_o e^{-kt}. \qquad (15)$$

Adding equations 14 and 15 and equating the sum of $(D_{PZ})_t$ and $(D_R)_t$ to $(D_T)_t$ (see equations 4 and 10) gives

$$(D_T)_t = \frac{\epsilon_p(R)_o}{c}(1 - e^{-kt}) + \epsilon_r(R)_o e^{-kt}. \qquad (16)$$

Equating the logarithm of the right-hand side of equation 16 to the negative of the right-hand side of equation 12 gives, after algebraic manipulation

$$k' = \frac{\ln\epsilon_r - \ln\left[\epsilon_r e^{-kt} - (\epsilon_p/c)e^{-kt} + (\epsilon_p/c)\right]}{t}. \qquad (17)$$

Equation 17 shows that when ϵ_r is greater than ϵ_p/c, and ϵ_p has a constant value greater than zero; then k' must be a function of time. Hence a plot of $-\ln(D_T)_t$ vs. t can never be linear under these conditions. Equation 17 reduces to $k' = k$ when $\epsilon_p = 0$, and this is the only possible case where $-\ln(D_T)_t$ vs. t will yield a straight line of positive slope. Thus, if the experimental plot is linear, then $-\ln(D_T)_t = -\ln(D_R)_t$ at all times; and the slope of the plot must be the true rate constant.

The other case to be considered is that where ϵ_p is a function of time ($\epsilon_p = f(t)$). One type of reaction scheme where this behavior might be observed and which satisfies the restriction imposed by equation 9, as well, is

$$R \longrightarrow P_{z1} \longrightarrow P_{z2} \longrightarrow \cdots \longrightarrow P_{zn}$$

where the extinction coefficients of the products are such that

$$\epsilon_{z1} \neq \epsilon_{z2} \neq \cdots \neq \epsilon_{zn}.$$

It should be noted that the stepwise hydrolytic degradation of 5,5-disubstituted barbituric acids must fit either into this category or into the category previously discussed; viz., ϵ_p = a constant.

Again it is necessary to show that a straight-line plot described by equation 12 cannot be constructed. Substituting $(D_R)_t + (D_{PZ})_t$ for $(D_T)_t$ in equation 12 and rewriting the result in exponential form gives

$$(D_R)_t + (D_P)_t = e^{-(k't + d)} \qquad (18)$$

where: $d = -\ln[\epsilon_r(R)_o]$,

and from equations 3a, 10, and 11 it is readily shown that

$$(D_R)_t = e^{-(kt + d)}. \qquad (19)$$

Combining equations 18 and 19 so as to eliminate $(D_R)_t$, introducing $(D_{PZ})_t = \epsilon_p(P_Z)_t$ (see equations 11), and rearranging gives

$$(P_Z)_t = \frac{e^{-(k't + d)} - e^{-(kt + d)}}{\epsilon_p}. \qquad (20)$$

Differentiating equation 1 with respect to time gives

$$-\frac{d(R)_t}{dt} = k(R)_o e^{-kt}, \qquad (21)$$

and differentiation of equation 9 with respect to time gives

$$-\frac{d(R)_t}{dt} = c \cdot \frac{d(P_Z)_t}{dt} . \tag{22}$$

Combining equations 21 and 22 gives

$$\frac{d(P_Z)_t}{dt} = \frac{k}{c} (R)_o e^{-kt}. \tag{23}$$

Differentiation of equation 20, remembering that $\epsilon_p = f(t)$, gives

$$\frac{d(P_Z)_t}{dt} = -\left[\frac{e^{-(k't + d)} - e^{-(kt + d)}}{\epsilon_p^2}\right]\frac{d\epsilon_p}{dt} - \left[\frac{k'e^{-(k't + d)} - ke^{-(kt+d)}}{\epsilon_p}\right] . \tag{24}$$

Combining equations 23 and 24 and rearranging so as to separate the variables gives

$$-\left[\frac{e^{-(k't + d)} - e^{-(kt + d)}}{\epsilon_p^2}\right] d\epsilon_p - \left[\frac{k'e^{-(k't + d)} - ke^{-(kt + d)}}{\epsilon_p} + \frac{k}{c}(R)_o e^{-kt}\right] dt = 0 \tag{25}$$

Equation 25 is of the form

$$M d\epsilon_p + N dt = 0,$$

and it is readily shown that

$$\left(\frac{dM}{dt}\right)_{\epsilon_p} = \left(\frac{dN}{d\epsilon_p}\right)_t.$$

Thus,

$$M d\epsilon_p + N dt = df(\epsilon_p, t),$$

and

$$M = \left(\frac{df(\epsilon_p, t)}{d\epsilon_p}\right)_t ; \quad N = \left(\frac{df(\epsilon_p, t)}{dt}\right)_{\epsilon_p} ;$$

so that

$$\left(\frac{df(\epsilon_p, t)}{d\epsilon_p}\right)_t = \frac{-e^{-(k't + d)} + e^{-(kt + d)}}{\epsilon_p^2},$$

and

$$f(\epsilon_p, t) = \frac{e^{-(k't + d)} - e^{-(kt + d)}}{\epsilon_p} + g(t).$$

Since

$$\left(\frac{df(\epsilon_p, t)}{dt}\right)_{\epsilon_p} = \frac{-k'e^{-(k't + d)} + ke^{-(kt + d)}}{\epsilon_p} + \frac{dg(t)}{dt} = N,$$

it follows that

$$\frac{dg(t)}{dt} = -\frac{k}{c}(R)_o e^{-kt};$$

$$g(t) = \frac{(R)_o}{c} e^{-kt};$$

and (70)

$$\frac{e^{-(k't + d)} - e^{-(kt + d)}}{\epsilon_p} = -\frac{(R)_o}{c} e^{-kt}. \qquad (26)$$

Combining equations 13 and 20 gives

$$\epsilon_p = c \left[\frac{e^{-(k't + d)} - e^{-(kt + d)}}{(R)_o(1 - e^{-kt})} \right]. \qquad (27)$$

Combining equations 26 and 27 so as to eliminate ϵ_p/c, cancelling out $(R)_o$, and rearranging gives

$$(1 - e^{-kt}) \left[e^{-(k't + d)} - e^{-(kt + d)} \right] = - \left[e^{-(k't + d)} - e^{-(kt + d)} \right] e^{-kt}. \qquad (28)$$

Solving equation 28 for k' gives, as the only possible solution, $k' = k$. Therefore, since the straight-line criterion is also applicable to this case, it is applicable to all of the possible cases where equation 9 is in effect.

King has described a spectrophotometric technique for determining first-order rate constants in cases where ϵ_p does not vary with time (71).

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(70) This method of integrating equations like 25 is discussed in: L. M. Kells, Calculus, second ed., Prentice-Hall, Inc., New York, N. Y., 1950, pp. 424-425.

(71) E. L. King, J. Am. Chem. Soc., 74, 563 (1952).

APPENDIX B

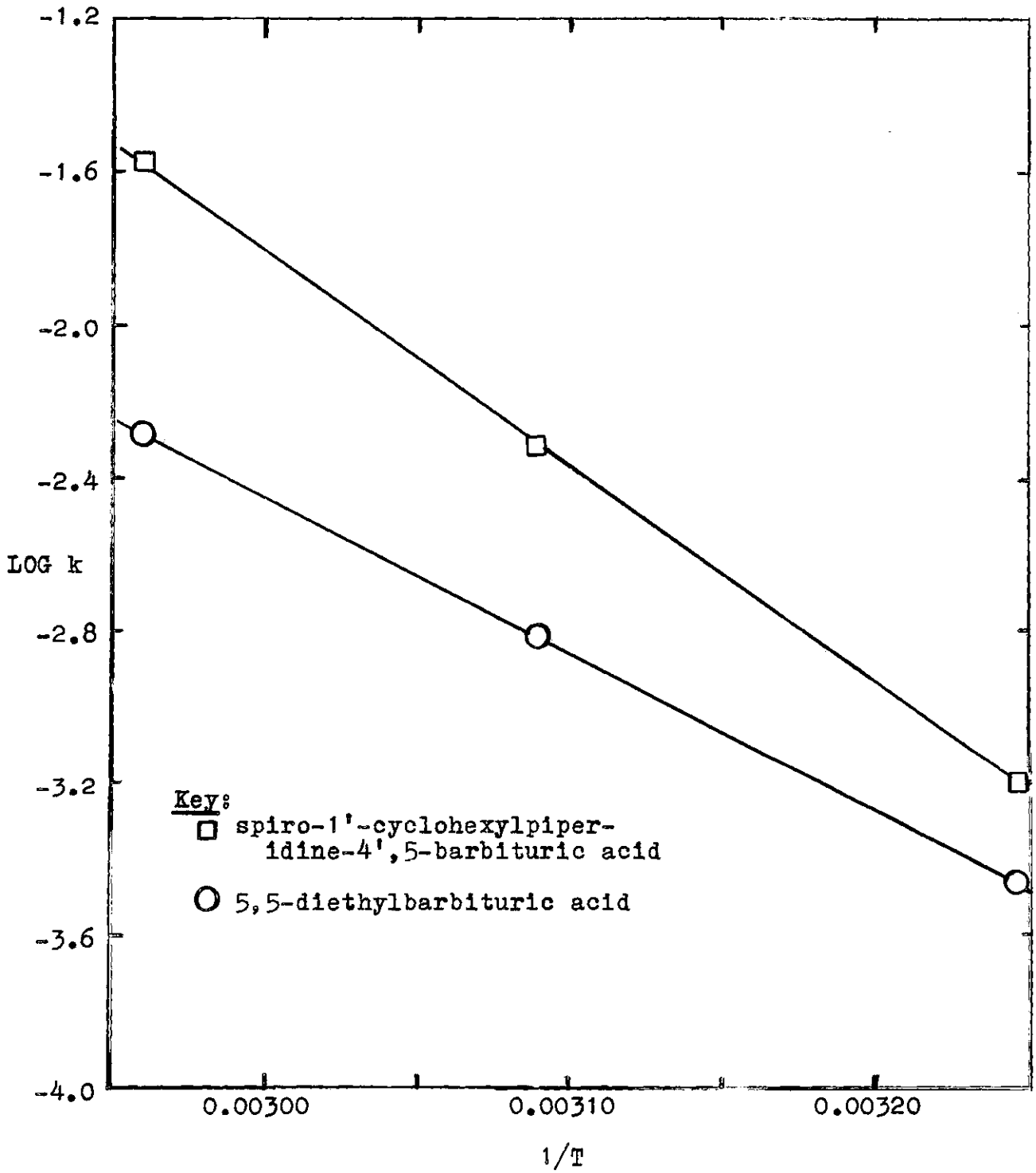

Figure 13. Sample Plots of Log k vs. 1/T for the Hydrolysis of Barbituric Acids in 0.9738 Molar NaOH

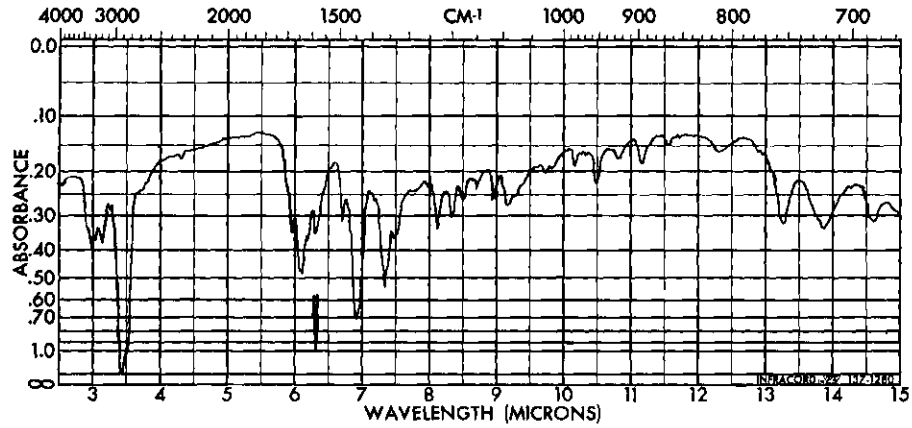

Figure 14. Infrared Spectrum of 1-Phenyl-4, 4-dicarboxamidopiperidine (Nujol Mull).

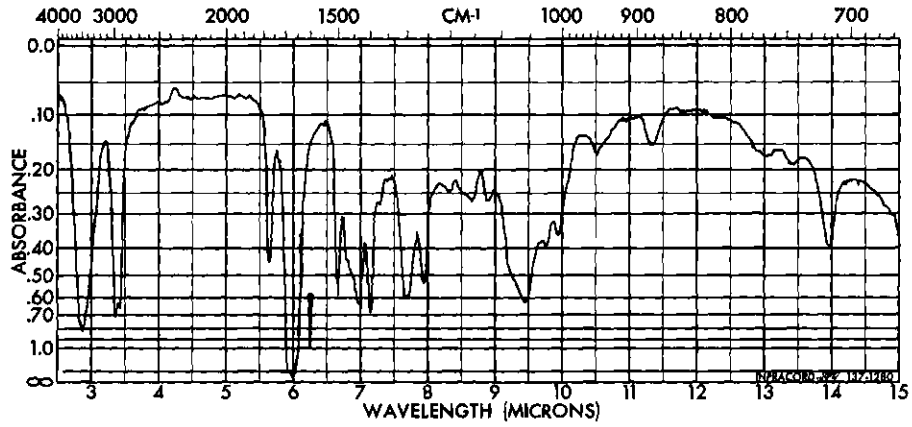

Figure 15. Infrared Spectrum of Fraction 1, P. 49 (Nujol Mull).

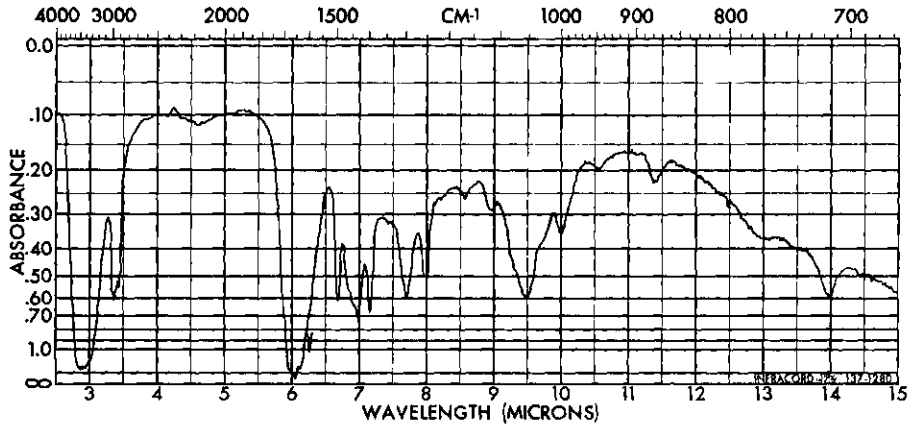

Figure 16. Infrared Spectrum of A1, P. 51 (Liquid Film).

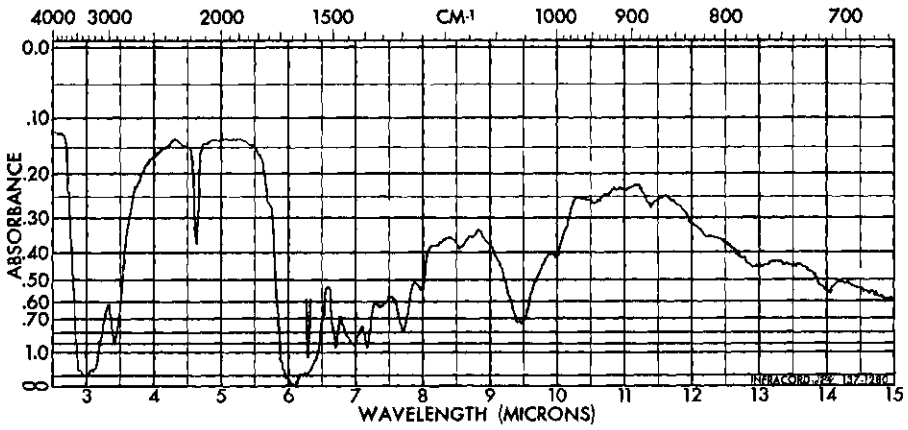

Figure 17. Infrared Spectrum of B, P. 53 (Liquid Film).

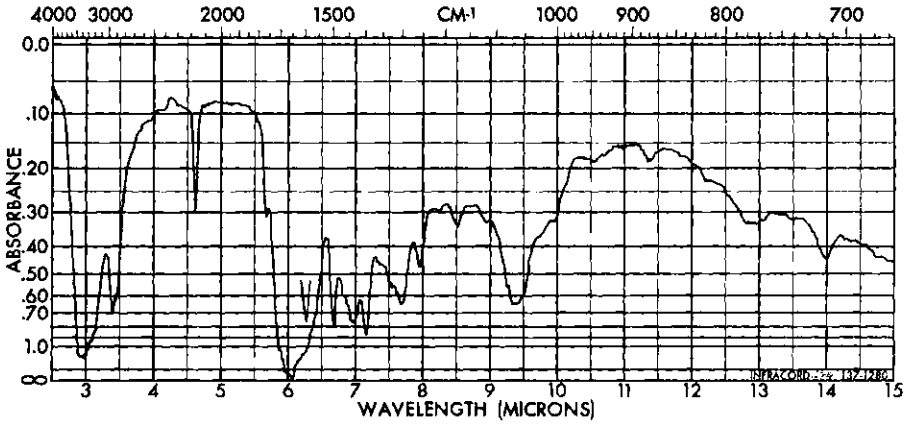

Figure 18. Infrared Spectrum of A, P. 53 (Liquid Film).

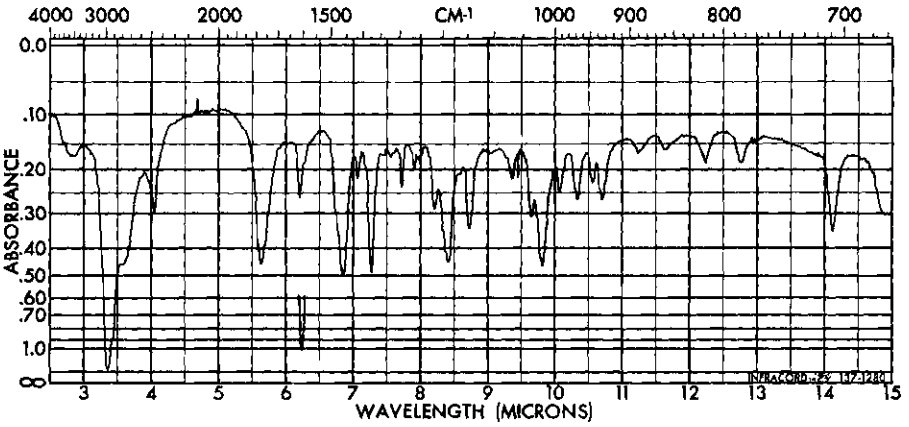

Figure 19. Infrared Spectrum of 1a, P. 57 (Nujol Mull).

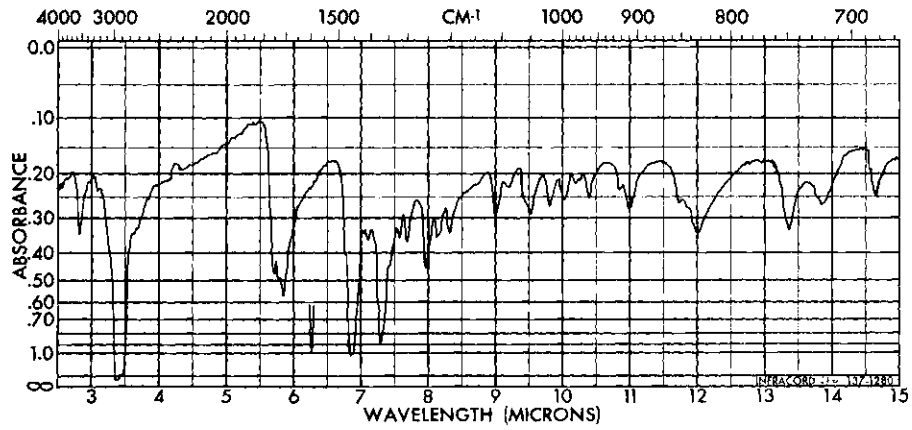

Figure 20. Infrared Spectrum of Spiro-1'-methylpiperidine-4', 5-barbituric Acid Hydroiodide (Nujol Mull).

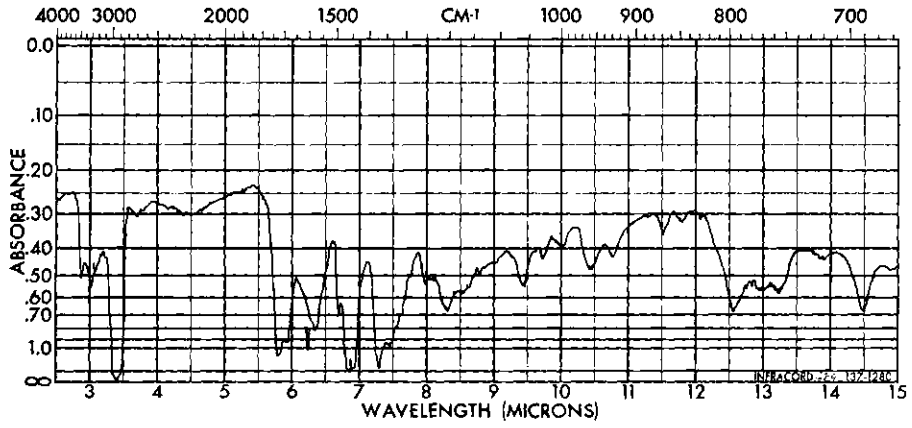

Figure 21. Infrared Spectrum of 1-Phenyl-4-carboxypiperidine-4-carbonylureide (Nujol Mull).

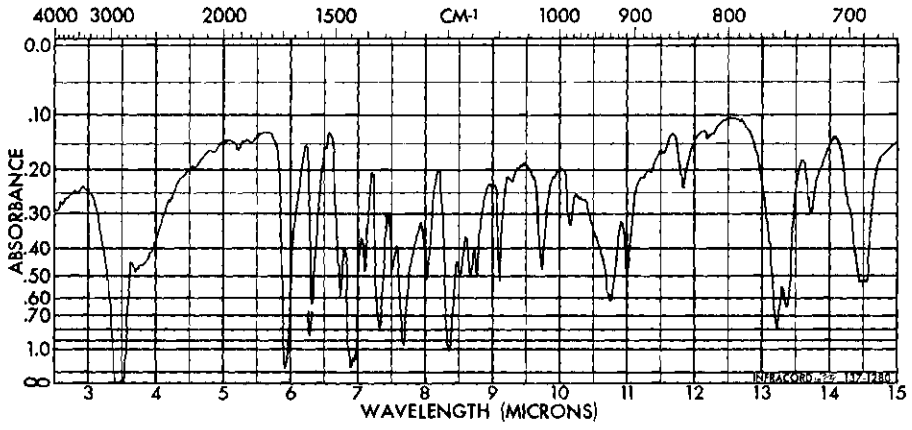

Figure 22. Infrared Spectrum of N-Phenylisonipecotic Acid (Nujol Mull).

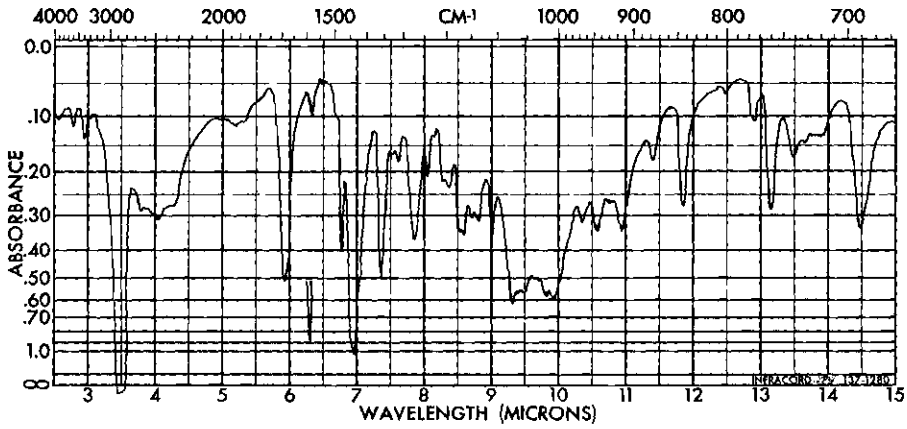

Figure 23. Infrared Spectrum of N-Phenylisonipecotic Acid Dihydrogen Sulfate (Nujol Mull).

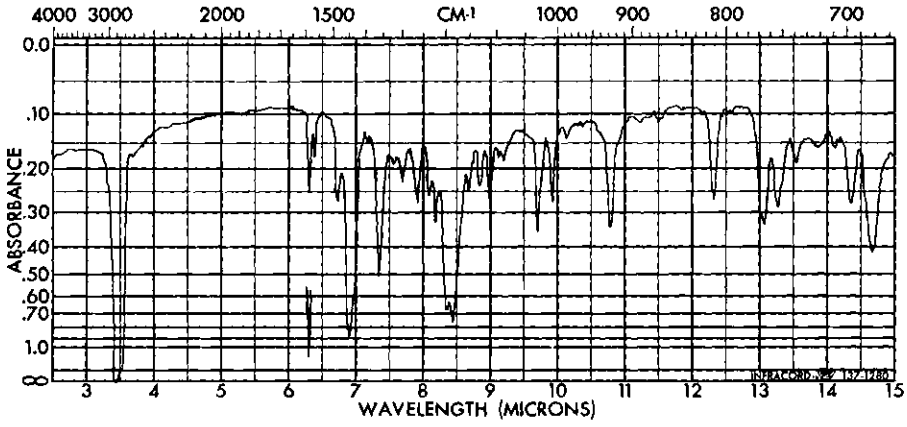

Figure 24. Infrared Spectrum of B, P. 93 (Nujol Mull).

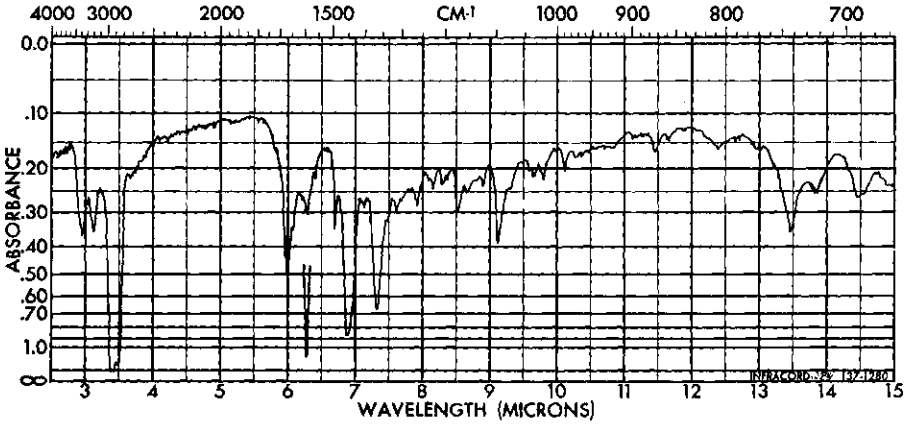

Figure 25. Infrared Spectrum of 3, 3-Dicarboxamidopropyl-2-ethoxyethylphenylamine (Nujol Mull).

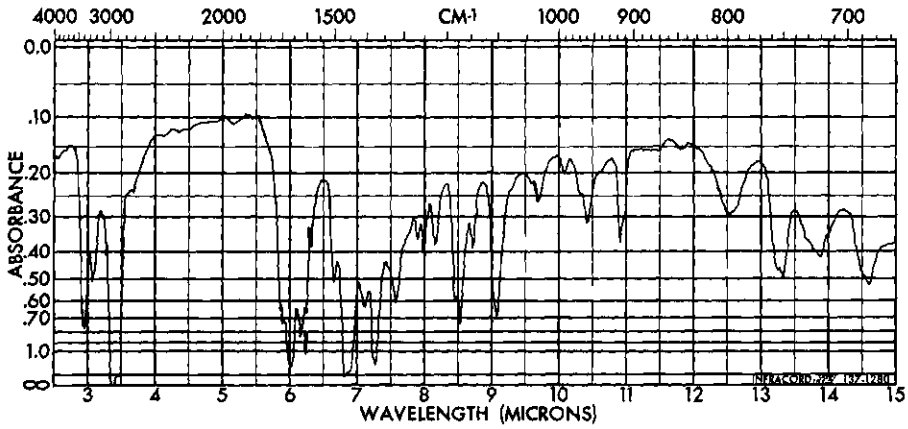

Figure 26. Infrared Spectrum of 1-Phenylpiperidine-4-carbonylureide (Nujol Mull).

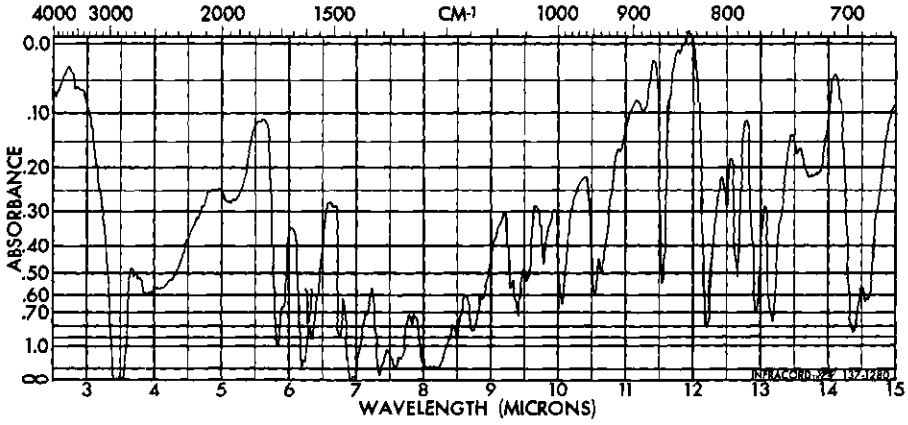

Figure 27. Infrared Spectrum of 1-Phenyl-4,4-dicarboxypiperidine (Nujol Mull).

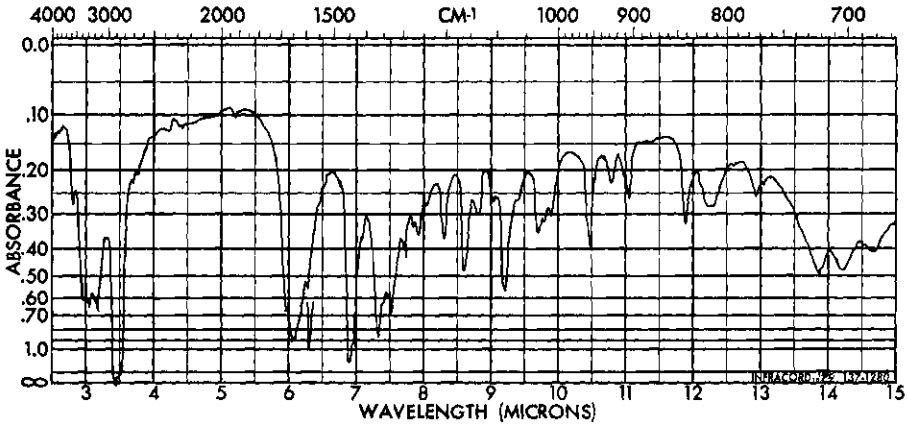

Figure 28. Infrared Spectrum of 4, 4-Dicarboxamidotetrahydropyran (Nujol Mull).

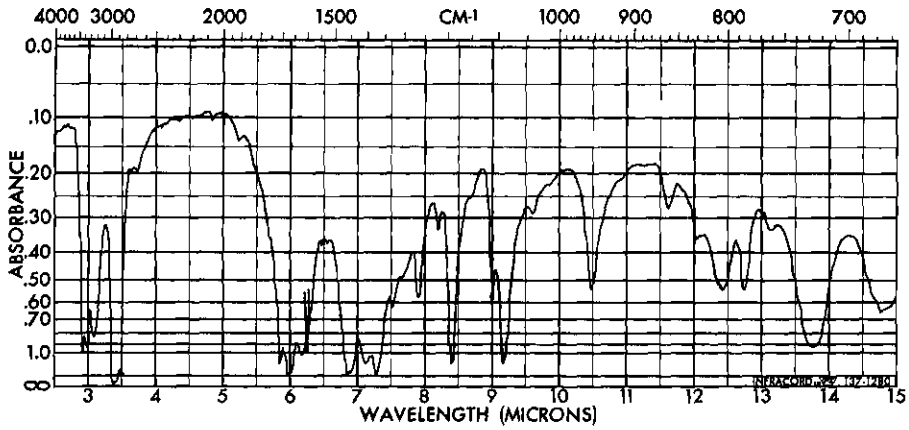

Figure 29. Infrared Spectrum of 2-Ethylbutyrylurea (Nujol Mull).

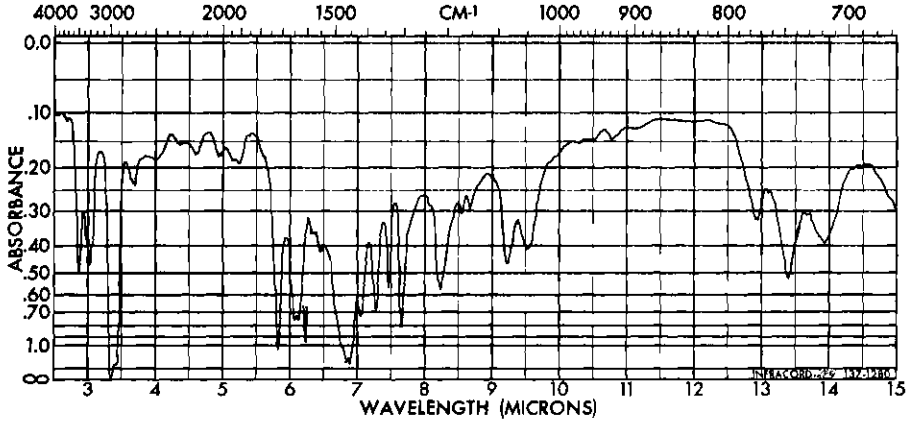

Figure 30. Infrared Spectrum of Diethylmalonamic Acid (Nujol Mull).

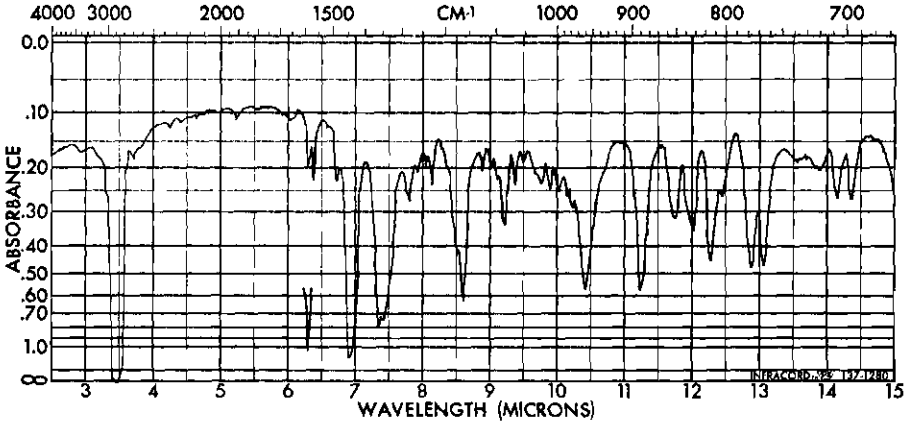

Figure 31. Infrared Spectrum of Bis(2-p-toluenesulfonyloxy-ethyl)-m-tolylamine (Nujol Mull).

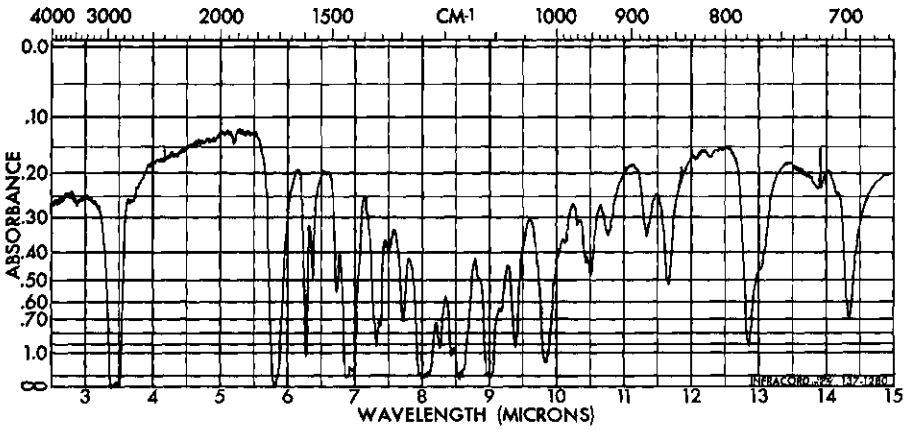

Figure 32. Infrared Spectrum of 1-m-Tolyl-4,4-dicarbethoxypiperidine (Nujol Mull).

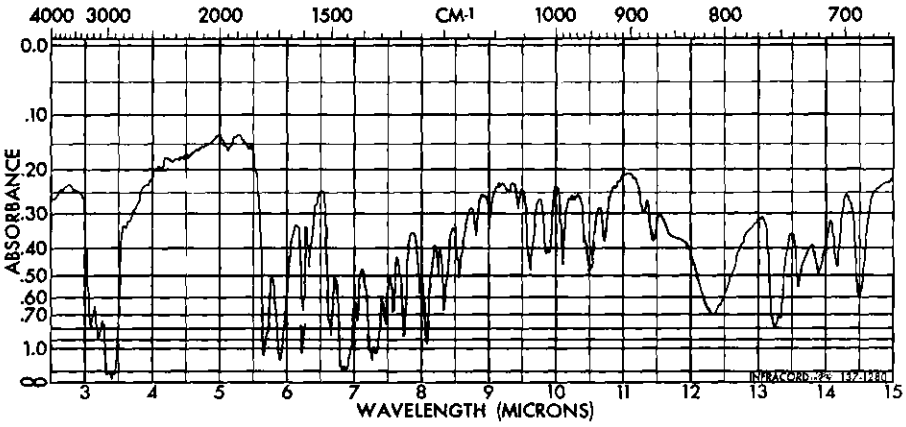

Figure 33. Infrared Spectrum of Spiro-1'-phenylpiperidine-4',5-barbituric Acid (Nujol Mull).

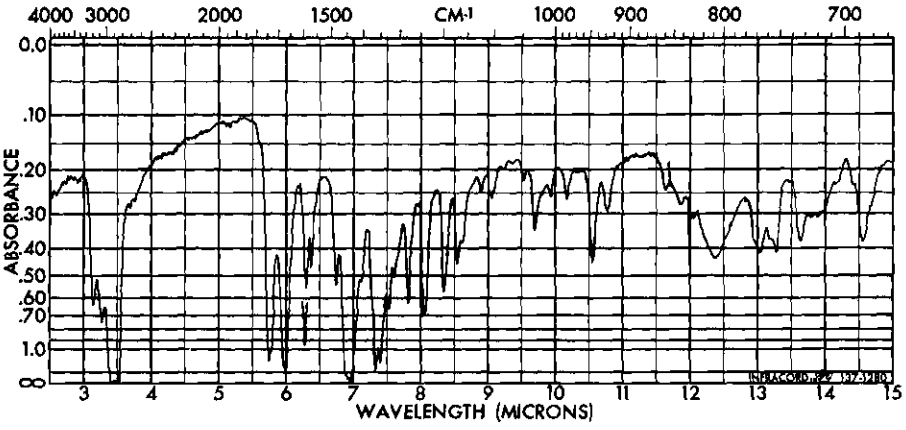

Figure 34. Infrared Spectrum of Spiro-1'-tolylpiperidine-4',5-barbituric Acid (Nujol Mull).

Table 7. Ultraviolet Absorption of Barbituric Acids Studied Kinetically

Barbituric acid[a]	Absorption maximum (mμ) in[b] water	0.9738 molar NaOH
spiro-1'-methyl-piperidine-4',5-	263	243.5
spiro-1'-isopropyl-piperidine-4',5-	264	246.5
spiro-1'-cyclohexyl-piperidine-4',5-	266.5	247
spiro-1'-benzyl-piperidine-4',5-	265.5	246
5-allyl-5-(1-methyl-butyl)-	--	256
5-ethyl-5-(1-cyclo-hexenyl)-	--	255.5
5-allyl-5-isobutyl-	--	255
5-ethyl-5-isoamyl-	--	254
5-ethyl-5-n-butyl-	--	254.5
5,5-diethyl-	--	254
5-ethyl-5-phenyl-	--	256
5-allyl-5-n-butyl-	--	255
5-allyl-5-phenyl-	--	256
5,5-diallyl-	--	255
5-methyl-5-phenyl-	--	256

[a]See references (14), (61), and (62) for additional U-V spectral data on 5,5-disubstituted barbituric acids.

[b]The regions scanned were 220-350 mμ for the spiro-amino compounds and 250-260 mμ for the other materials. Extinction coefficients (defined according to reference (69) had values within the approximate range: 8,000--12,000.

Table 8. Ultraviolet Absorption Data for Miscellaneous Compounds

Compound	Conc. (moles/l.)	Solvent	Abs. max. (mμ)[a]	O.D.[b]
2-ethylbutyryl-urea	0.000020	1 M aqueous NaOH	220-223	>2.0
diethylmalonamic acid	0.0010	1 M aqueous NaOH	220-223	>2.0
1-phenyl-4-carboxy-piperidine-4-carbonylureide	0.000050	aqueous NaOH, pH = 11.8	239	0.5
1-phenylpiperidine-4-carbonylureide	0.000058	95% aq. EtOH 0.0055 M in NaOH	251	0.7[c]
1-phenyl-4,4-dicarboxypiperidine	0.000060	0.0055 M aqueous NaOH	241.5	0.6
5,5-bis(2-iodoethyl)-barbituric acid	(sat.)[d] x 0.1	water	none	--
"	(sat.) x 0.1	1 M aqueous NaOH	220-223	>2.0
"	(sat.) x 0.9	0.11 M aqueous NaOH	220-242	>2.0
"	(sat.) x 0.18	0.0002 M aqueous NaOH	227.5	0.8

[a]The region scanned was 220-300 mμ.

[b]Optical density (defined according to reference (69) compared to distilled water blanks.

[c]Compared to a 95% EtOH blank.

[d]"(sat.)" is the concentration of a saturated solution of the compound in water at room temperature. This concentration is less than 10^{-3} molar.

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(9) Doran, op. cit., p. 130.

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VITA

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William H. Starnes, Jr. was born Dec. 2, 1934, in Knoxville, Tennessee, to William H. and Edna O. Starnes. He attended the public schools in Ewing, Virginia, and was graduated from Thomas Walker High School in Ewing in 1950. After attending Union College in Barbourville, Kentucky, for two years, he transferred to the Virginia Polytechnic Institute in Blacksburg, Virginia, where he received the B. S. degree in chemistry with honors in 1955. He attended Duke University in Durham, North Carolina, during 1955-1956 and matriculated at the Georgia Institute of Technology in September, 1956.

During a portion of his enrollment at Union College and the Virginia Polytechnic Institute he held part-time employment as a chemistry laboratory instructor, and he held a chemistry teaching assistantship while at Duke University. His research at Georgia Tech was supported by National Institutes of Health fellowships in 1956-1958 and by National Science Foundation pre-doctoral fellowships in 1958-1960.

He was employed by the Eastman Kodak Co. in Rochester, New York, during the summer of 1954 and by E. I. du Pont de Nemours, Inc., at Belle, West Virginia, during the summers of 1955 and 1956. At the present time he has accepted employment with the research and development division of the Humble Oil and Refining Co. in Baytown, Texas.

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