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THE PREPARATION AND PROPERTIES OF SOME SPIROAMINOBARBITURIC ACIDS

A THESIS

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Doctor of Philosophy

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THE PREPARATION AND PROPERTIES OF SOME SPIROAMINOBARBITURIC ACIDS

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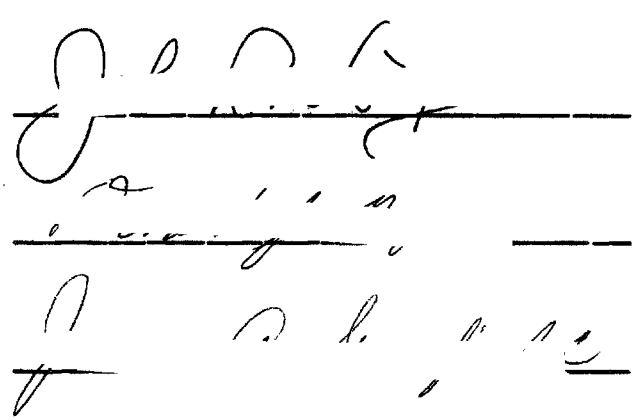

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SUMMARY

The primary purpose of this study was the preparation of compounds containing piperidine and barbituric acid ring systems fused to each other through a spiro carbon atom. The chemical properties as well as the preparation of such spiroaminobarbituric acids were of interest. In particular, information concerning the rates of basic hydrolysis of compounds of this class was desired. Interest in the basic hydrolysis reaction was prompted by an earlier report that a correlation existed between the physiological activities and hydrolysis rates of a number of common barbiturate drugs. Thus, a second purpose of this work was to study the basic hydrolysis reaction by making kinetic studies of the hydrolysis of some common barbiturates.

The first phase of the synthetic work involved the preparation of spirotetrahydropyran-4',5-(1-methylbarbituric acid) and its use as a synthetic intermediate. Although the preparation of this compound was studied in some detail, only low yields were obtained in its preparation. The ether linkage of spirotetrahydropyran-4',5-(1-methyl-barbituric acid) could be cleaved by potassium iodide in phosphoric acid to form 1-methyl-5,5-bis-(2-iodoethyl)-barbituric acid. However, reaction of the iodo compound with methylamine failed to yield the desired spiropiperidinebarbituric acid.

Due to a report of evidence that the reaction of 5,5-bis-(2-iodoethyl)-barbituric acid with primary amines led to products which did not have the desired spiro structures, an alternate route to the spiroaminobarbituric acids was sought. One such route involved reaction of 4,4-dicarbethoxypiperidine with urea to form the desired spiroamino compounds. In an effort to develop a method for preparing the required piperidine diesters, studies were made of methods for cleaving the sulfonamide linkage of the previously reported 1-benzenesulfonyl-4,4-dicarbethoxypiperidine to produce 4,4-dicarbethoxypiperidine. It was found that the desired cleavage could be effected by treatment of the sulfonamide with a solution of hydrogen bromide and phenol in acetic acid.

Studies were then undertaken to find a method for alkylating 4,4-dicarbethoxypiperidine. Piperidine was used as a model compound in these studies. Primary alkyl groups could be introduced in good yield by reaction of piperidine or its 4,4-dicarbethoxy derivative with an aldehyde and hydrogen in the presence of platinum oxide. This method could also be employed for the introduction of secondary alkyl groups by using ketones in place of aldehydes, but the yields were less satisfactory. Attempts to methylate piperidine and 4,4-dicarbethoxypiperidine by reaction with methyl iodide in the presence of potassium carbonate did not give satisfactory yields of the methyl-

ated derivatives. In contrast to this result, a reaction of piperidine with isopropyl bromide in the presence of potassium carbonate formed 1-isopropylpiperidine in slightly better yield than was obtained by reductive alkylation.

Several 1-substituted-4,4-dicarbethoxypiperidines were converted to the corresponding barbituric acid derivatives by reaction with urea in the presence of sodium ethoxide. The sodium salts of the spiroaminobarbituric acids were isolated before being acidified by treatment with exactly two equivalents of standard ethanolic hydrogen chloride solution. The use of standard ethanolic hydrogen chloride was superior to other methods which had been employed for acidifying the salts of spiroaminobarbituric acids. The acidification was rapid and the free acids could be readily removed from the sodium chloride formed as a by-product by extraction with organic solvents. Dimethylformamide was particularly effective for such extractions.

The preparation of some representative spiroaminobarbituric acids by the methods outlined made possible investigation of some of their physical and chemical properties. Physiological evaluation of some of these compounds has been undertaken by an independent laboratory. It is hoped that joining the piperidine and barbituric acid ring systems will result in compounds with pharmaceutical

usefulness.

One of the spiroaminobarbituric acids prepared, spiro-1'-(2-phenylethyl)-piperidine-4',5-barbituric acid, was shown to hydrolyze very readily under basic conditions. A sample of this compound was converted in good yield to 1-(2-phenylethyl)-4-carboxypiperidine-4-carbonylureide by treatment with two equivalents of aqueous base at room temperature for five minutes. In addition, approximate rate constants were determined for the hydrolysis of spiro-1'-(2-phenylethyl)-piperidine-4',5-barbituric acid and its 1'-methyl analog in excess base. These rate constants were considerably higher than similarly obtained constants for some 5,5-disubstituted-barbituric acids and were in good agreement with the hydrolysis rate constants for some other spirobarbituric acid derivatives.

In the concluding phase of this study, a spectrophotometric technique was used to measure hydrolysis rate constants for some common 5,5-disubstituted-barbituric acids at two temperatures. The rate constants obtained provided evidence supporting previous observations of an empirical relationship between hydrolytic stabilities and physiological activities of barbituric acids. Use of rate constants measured at different temperatures permitted calculation of activation energies and activation entropies for the hydrolyses investigated. The calculated activation energies and entropies were in agreement with a hydrolysis

mechanism involving attack of hydroxide ions on barbiturate mono- or dianions. It was found that barbituric acids containing phenyl substituents, which are interesting in that they have greater physiological potencies than would be predicted from their hydrolytic stabilities, showed lower activation energies and larger negative activation entropies than any of the other compounds studied.

CHAPTER I

INTRODUCTION

Barbituric acid was first reported by Baeyer (1) in 1864 and was studied by a number of other workers in the latter part of the nineteenth century. Interest in this class of compounds was greatly stimulated when Fischer and Mering (2) reported in 1903 that 5,5-diethylbarbituric acid had hypnotic properties. Since this initial report, more than 2,000 mono- and polysubstituted barbituric acids and salts have been reported, and most of these have been screened for physiological activity (3). The barbituric acid derivatives having the widest use as pharmaceuticals are the 5,5-disubstituted compounds, the general structure of which is shown in Figure 1. These and other barbituric acid derivatives, as well as their salts, are frequently referred to as barbiturates, and this practice will be followed in this thesis.

A variation of the structure shown in Figure 1 involves replacement of the two substituents at the 5-position of the barbituric acid ring by a spiro ring system. A number of

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(1)A. Baeyer, Ann., 130, 129 (1864).

(2)E. Fischer and v. Mering, Therap. der Gegenwart, 44, 97 (1903); Chem. Zentr, 1903, I, 1155.

(3)W. J. Doran, Medicinal Chemistry, Vol. IV., John Wiley and Sons, Inc., New York, N. Y., 1959, pp. 2, 48.

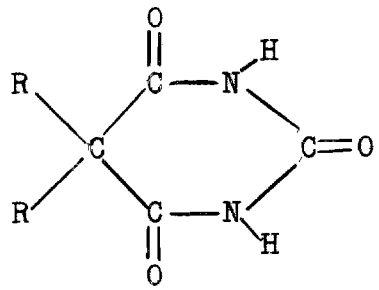

Figure 1. Structure of 5,5-Disubstituted-barbituric Acids

spirobarbituric acids containing carbocyclic spiro rings have been reported, and many of these compounds have physiological activities which compare favorably with the 5,5-disubstituted barbiturates (3).

The presence of piperidine rings in physiologically active natural products such as cocaine and in synthetic drugs such as Demerol (1-methyl-4-carbethoxy-4-phenylpiperidine) suggests that joining of the piperidine ring system to that of barbituric acid might produce compounds with useful physiological properties. Compounds containing a spiropiperidine-4',5-barbituric acid ring system would combine the 5,5-disubstituted-barbituric acid structure characteristic of many drugs and the 4,4-disubstituted-piperidine structure of Demerol in a relatively simple molecule. Figure 2 shows the structure of such a spiro compound.

Skinner and co-workers (4) have described a spiropiperidinebarbituric acid of the type shown in Figure 2 in which is

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(4)G. S. Skinner, H. R. Krysiak, and J. A. Perregrino, J. Am. Chem. Soc., 77, 2248 (1955).

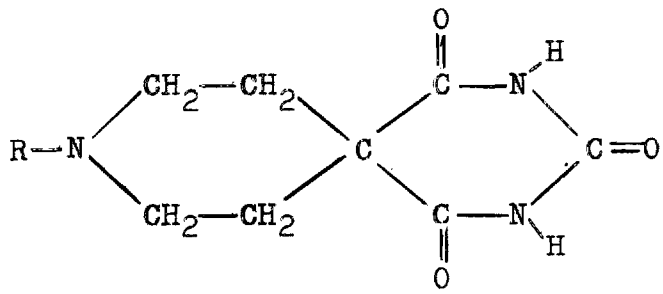

Figure 2. A Spiropiperidine-4',5-barbituric Acid

the R- group benzenesulfonyl. Büchi and co-workers (5) have reported synthesis of spiropiperidinebarbituric acids containing various substitutents on the piperidine nitrogen atom. Stanfield and Daugherty (6), working independently, developed a similar synthetic approach to these compounds and gave them the name "spiroaminobarbituric acids".[1] The syntheses developed by both of these groups involved preparation of 5,5-bis-(2-haloethyl)-barbituric acids and reaction of these dihalides with primary amines. In cases where the same compounds were reported by both groups, the physical constants were in good agreement. In addition, the structure assignments were supported by analytical and other data. However, Starnes (7) reported evidence that the spiro-1'-phenylpiperi-

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[1]This term will be used in this thesis to refer to compounds having the structure shown in Figure 2.

(5)J. Büchi, K. Leuenberger, and R. Lieberherr, Farm. Sci. e tec. (Pavia), 6, 429 (1951); C. A., 46, 8015 (1952).

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

(7)W. H. Starnes, Unpublished Ph. D. Thesis, Georgia Institute of Technology, 1960, p. 134.

dine-4',5-barbituric acid reported by Stanfield and Daugherty (6) did not actually have the structure assigned.[1] Starnes prepared spiro-1'-phenylpiperidine-4',5-barbituric acid from 1-phenyl-4,4-dicarbethoxypiperidine and found his product to be different from that previously reported. The evidence cited by Starnes (7) for the structure of his product included (a) the unambiguous formation of the barbituric acid ring from the diester; (b) elemental analyses in agreement with the structure assigned; (c) very rapid hydrolytic cleavage of the barbituric acid ring by excess base; (d) stepwise hydrolysis to normal barbiturate hydrolysis products which were isolated and characterized; and (e) exhaustive hydrolytic degradation to 1-phenyl-4-carboxypiperidine, a known compound.

In contrast to the large amount of research which has been reported on the synthesis of barbiturates, there has been little interest in their hydrolysis. In general, such interest has been confined to the stabilities of aqueous solutions of barbiturate salts (8), since such solutions have wide medicinal applications. However, Aspelund and co-workers have made semi-quantitative studies on the stabilities of

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[1]Nuclear magnetic resonance studies on the structure of Daugherty's compound and the precursor, 5,5-bis-(2-iodoethyl)-barbituric acid, are being made by Drs. Chamberlain and Stehling of the Humble Oil Company Laboratories, in Baytown, Texas. At present the proposed structure of the halo compound has been verified, but no conclusions have been reached concerning the spirobarbituric acid.

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

barbiturates to basic hydrolysis under various conditions. They have determined hydrolytic stabilities by isolation of the unreacted portion of barbiturate samples after treatment with base (9-11). This method has been used to obtain relative stability data for a number of barbiturates, most of which have medicinal uses, but it is subject to the inaccuracies associated with many attempts at quantitative isolation of organic compounds.

A convenient spectrophotometric method for measuring the rate of hydrolysis of barbiturates in excess base has been developed by Daugherty (12). This method was used by Starnes (13) to obtain hydrolysis rate constants for several common barbiturates. Starnes (14) showed that there was a good correlation between hydrolytic stability and physiological activity for the compounds studied. This correlation was not unexpected since structure changes which have been found to increase hypnotic activity, e. g. increased size and/or increased branching in 5-substituents (15), would be

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

(10)H. Aspelund and S. Stolt, ibid., No. 4.

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

(12)P. M. Daugherty, Unpublished Ph. D. Thesis, Georgia Institute of Technology, 1957, p. 88.

(13)Starnes, op. cit., p. 122.

(14)ibid., pp. 3-10, 145.

(15)Doran, op. cit., p. 32.

expected to decrease the rate of hydrolytic attack on the barbituric acid ring by hindering approach of hydroxide ions to the reactive 4- and 6-carbon atoms.

There were two purposes of this study. The first was the synthesis of some representative spiroaminobarbituric acids. It was originally intended that this synthetic work should be devoted mainly to the preparation of spiroaminobarbituric acids containing substituent groups on the barbituric acid nitrogen atoms. During the investigation, however, attention was shifted to developing a synthetic route to 1-alkyl-4,4-dicarbethoxypiperidines so that spiroaminobarbituric acids could be prepared from these intermediates and compared with those previously reported. In work done simultaneously with this investigation, Allen (16) developed a method for synthesizing esters of this type from isonicotinic acid, while this investigator used diethanolamine as a starting material.

The second purpose of this study was the continuation of kinetic studies on the hydrolysis of common barbiturates. Of particular interest was the determination of activation energies and entropies for these hydrolyses. Kinetic data were also desired for the hydrolysis of spiroaminobarbituric acids to determine the effect of the spiropiperidine ring on this reaction of the barbiturate ring.

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(16)G. C. Allen, Unpublished Ph. D. Thesis, Georgia Institute of Technology, 1961, p. 15.

CHAPTER II

METHODS OF ATTACK

The initial work of this investigation involved attempts to synthesize spiro-1'-substituted-piperidine-4', 5-(1-methylbarbituric acids). These attempts were based on the synthetic method reported by Stanfield and Daugherty (6) for preparation of spiroaminobarbituric acids having no substituent groups on the barbituric acid nitrogen atoms. An outline of this method is shown in Figure 3.

Difficulties in preparation of II by base catalyzed condensation as shown in Figure 3 led to a consideration of alternative paths to compounds of this type. Several preparations of barbituric acids under acidic conditions have been reported, including condensation of malonic acid with urea in the presence of phosphorous oxychloride (17) and reaction of malonyl chloride with 1,3-diethylurea (18). A procedure involving somewhat less vigorous conditions was that of Biltz and Wittek (19), who brought about condensation of malonic acid with ureas by dehydration with acetic anhydride. Since these workers prepared 1-methylbarbituric acid in good yield,

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(17)E. Grimaux, Compt. rend., 87, 752 (1878).

(18)H. Biltz and T. Hamburger, Ber., 49, 652 (1916).

(19)H. Biltz and H. Wittek, ibid., 54, 1037 (1921).

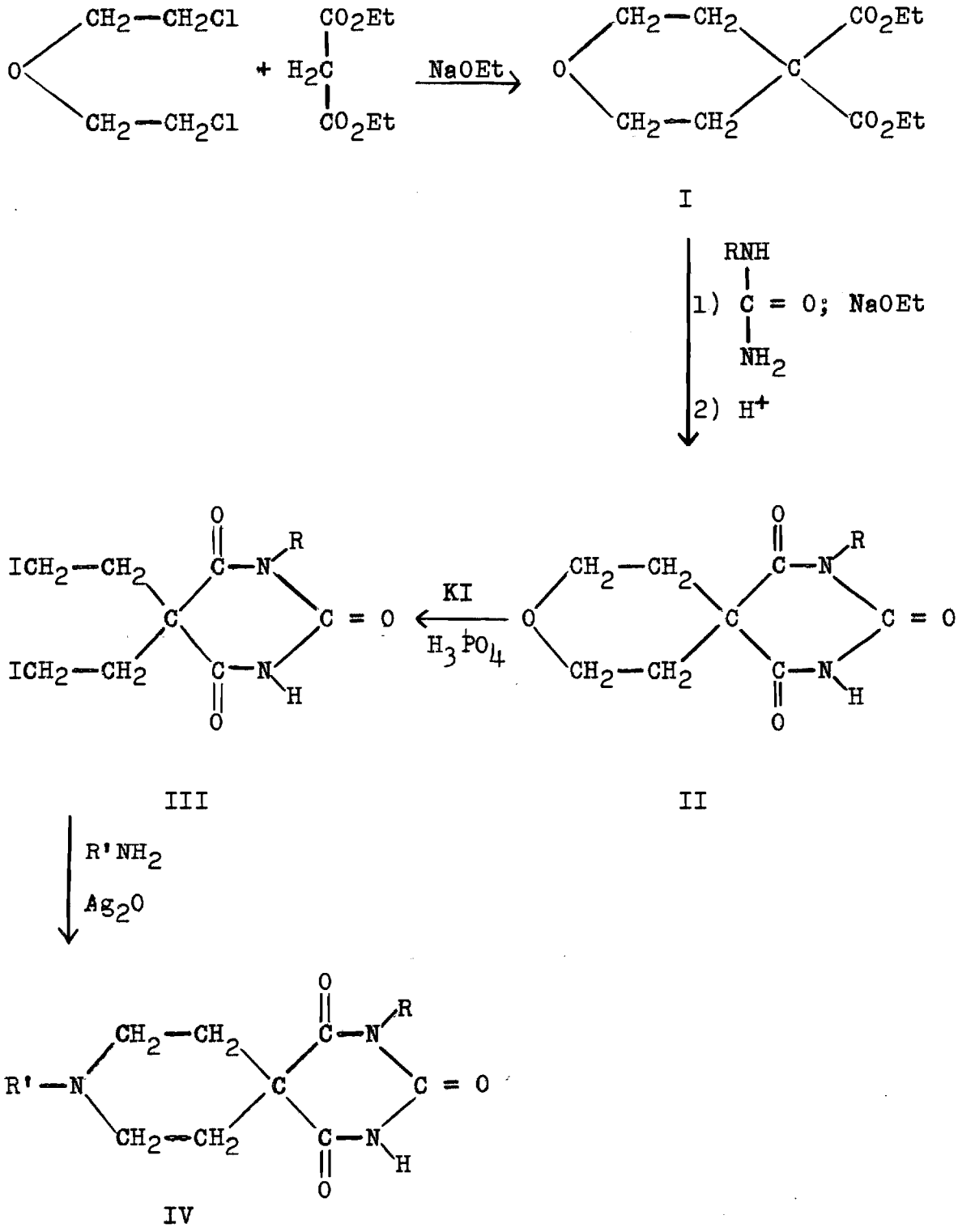

Figure 3. Proposed Synthetic Path to Spiroaminobarbituric Acids

attempts were made to apply this method to the synthesis of spirotetrahydropyran-4',5-(1-methylbarbituric acid). An outline of the procedure is shown in Figure 4.

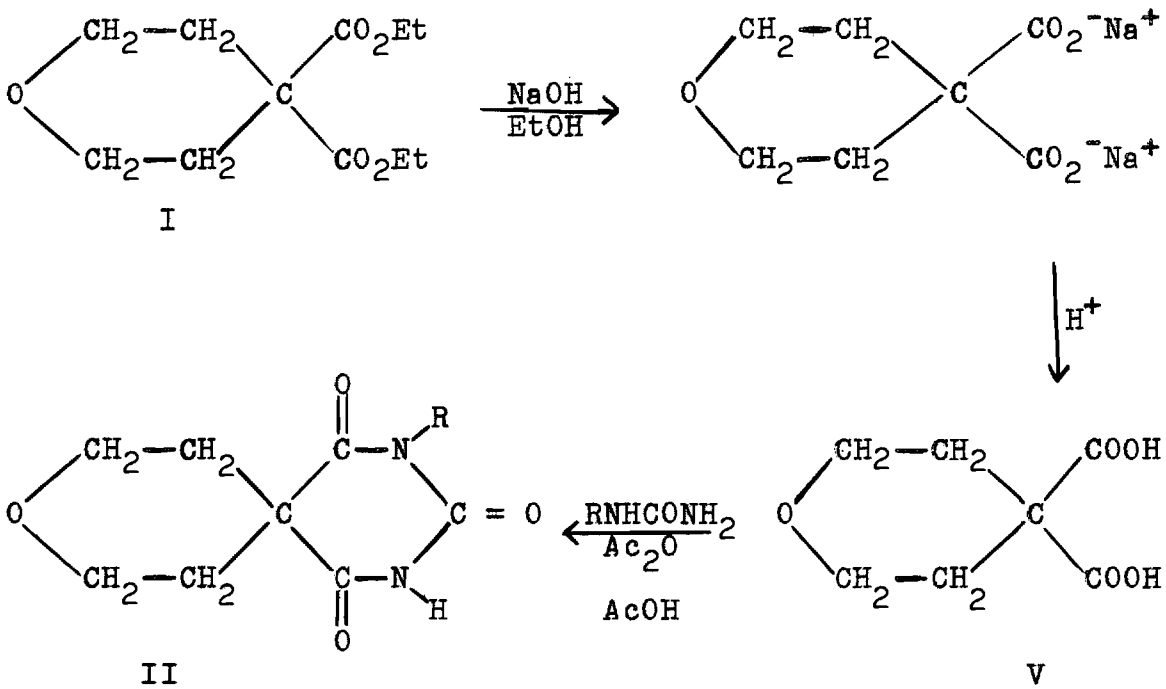

Figure 4. Alternative Synthesis of Spirotetrahydropyran-4',5-(1-alkylbarbituric Acids)

While synthetic experiments based on 4,4-dicarbethoxytetrahydropyran were in progress, evidence was reported that the product from reaction of the di-iodo compound, III, with aniline was not the desired spiro compound IV (R'= phenyl) (7). It seemed desirable to develop a method for synthesizing spiropiperidinebarbituric acids via the corresponding 1-alkyl-4,4-dicarbethoxypiperidines so that the spiro compounds prepared in this way could be compared with the compounds prepared by the method of Figure 3.

Schmutz and co-workers (20) had prepared 1-methyl-4,4-dicarbethoxypiperidine by a lengthy synthetic method which did not appear suited for use on a preparative scale, but they reported failure to obtain the desired ester in reactions of N,N-bis-(2-chloroethyl)-methylamine with diethyl sodiomalonate. Stanfield and Daugherty (6) and Starnes (21) also reported unsatisfactory results in attempts to use this condensation. The results reported by these different workers indicated that condensation of bis-(2-halo-ethyl)-amines with diethyl sodiomalonate could not be expected to proceed satisfactorily when the nucleophilicity of the nitrogen atom was high. Replacement of N-alkyl substituents by N-aryl groups apparently lowers the nucleophilicity sufficiently for piperidine formation to occur since N,N-bis-(2-chloroethyl)-aniline has been reported to yield 1-phenyl-4,4-dicarbethoxypiperidine by reaction with sodiomalonic ester (22). Starnes prepared this compound and its m-tolyl homolog from the bis-(2-p-toluenesulfonyloxyethyl)-arylamines and diethyl malonate.

Since removal of N-aryl substituents from a piperidine

---

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

(21)Starnes, op. cit., p. 104.

(22)R. M. Anker, A. H. Cook, and I. M. Heilbron, J. Am. Chem. Soc., 67, 917 (1945).

(23)Starnes, op. cit., pp. 66 ff.

derivative did not appear feasible, attention was turned to the reaction sequence shown in Figure 5. The first two steps

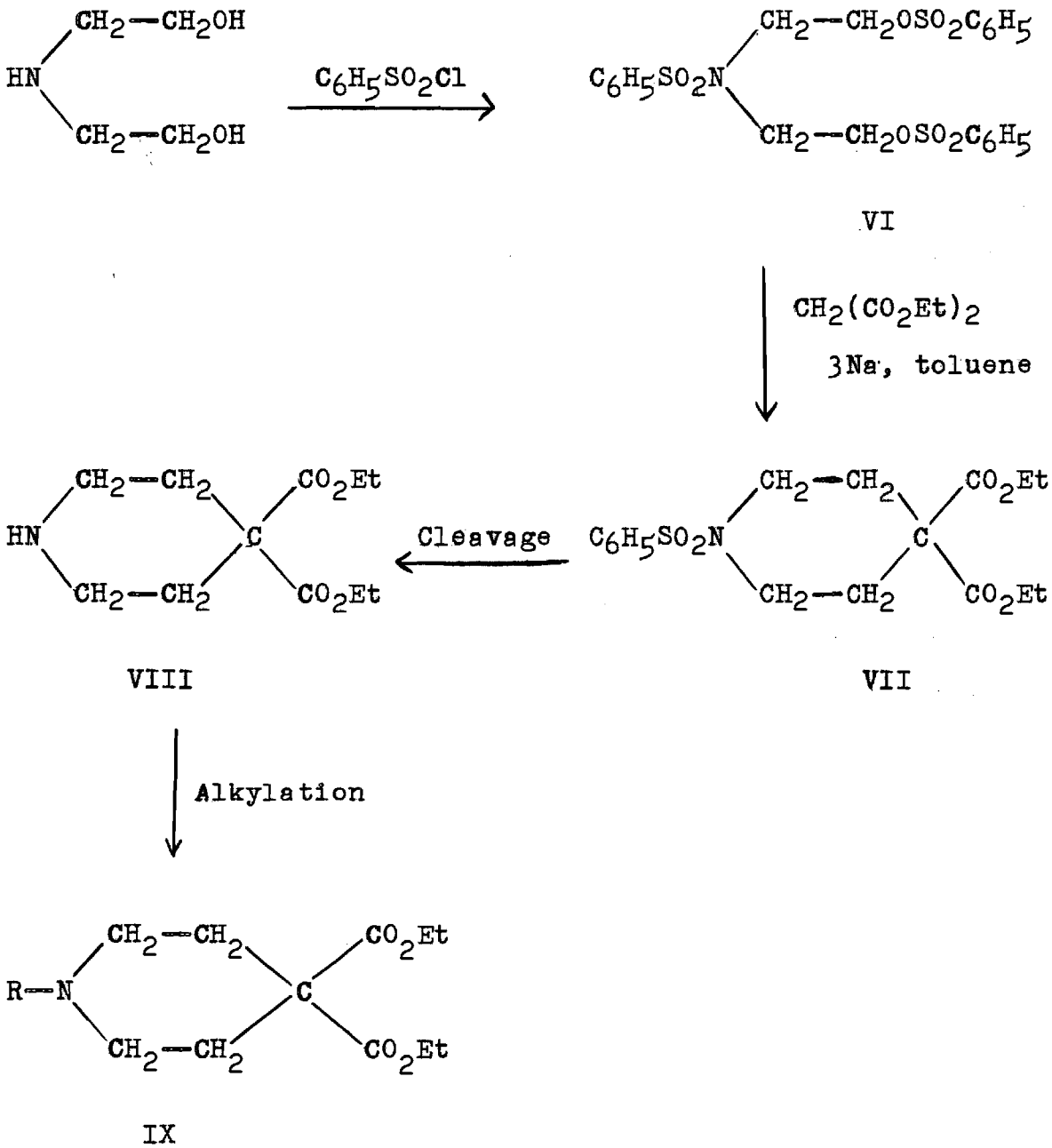

Figure 5. Proposed Synthesis of 1-Alkyl-4,4-dicarbethoxy-piperidines from Diethanolamine

of this synthesis had been reported by Skinner and co-workers (4). However, the most common procedures for sulfonamide cleavage involve prolonged treatment of the sulfonamide with hot concentrated hydrochloric or sulfuric acids (24). The probable destructive effect of such conditions on the diester group of VII made their use unacceptable and a more suitable method was sought. Klamann and Hofbauer (25) reported a good yield of piperidine from the reaction of 1-p-toluenesulfonylpiperidine with 51 per cent sodium isoamoxide in isoamyl alcohol, and an attempt to duplicate this result using n-amyl alcohol in place of isoamyl alcohol was made. A report by Takata (26) that some sulfonamides were cleaved by sodium ethoxide in toluene prompted an attempted alcoholysis of 1-p-toluenesulfonylpiperidine by prolonged treatment with sodium ethoxide in ethanol.

A method for cleaving sulfonamides which seemed particularly promising for use in the cleavage of the sulfonamide linkage of VII was treatment with an acetic acid solution of hydrogen bromide and phenol as described by Weisblat and co-workers (27). This procedure combined the advantages of

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(24)S. Searles and S. Neckina, Chem. Revs., 59, 1077 (1959).

(25)D. Klamann and G. Hofbauer, Ann., 581, 182 (1953).

(26)Y. Takata, J. Pharm. Soc. Japan, 71, 1474 (1951); C. A. 46, 8036 (1952).

(27)D. I. Weisblat, B. J. Magerlein, and O. R. Myers, J. Am. Chem. Soc., 75, 328 (1953).

the methods of Haeseler and co-workers (28, 29) who used hydrogen bromide in acetic acid to cleave sulfonamides containing ester groups without ester hydrolysis and of Snyder and co-workers (30, 31) who added phenol to aqueous hydrobromic acid in sulfonamide cleavages to prevent reaction of the free amine with bromine liberated in the reductive cleavage. The use of this cleavage method was studied by using 1-arylsulfonylpiperidines as model compounds and by applying it to the preparation of 4,4-dicarbethoxypiperidine.

Finding a method for the alkylation of 4,4-dicarbethoxypiperidine (VIII) was complicated by the necessity for avoiding conditions which would affect the diester grouping. Although not necessary, it was also highly desirable to use an alkylation procedure not involving the use of excess amine so that all the VIII in any reaction mixture could be alkylated. The first of these requirements immediately eliminated the Leuckart reaction (32) from consideration because of its use of hot aqueous solutions. The use of alkyl halides in alkylations of piperidine and its deriva-

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(28)H. Ohle, H. Friedeburg, and G. Haeseler, Ber., 69, 2311 (1936).

(29)O. Heinz and G. Haeseler, ibid., 2324.

(30)H. R. Snyder and R. E. Heckert, J. Am. Chem. Soc., 74, 2006 (1952).

(31)H. R. Snyder and H. C. Geller, ibid., 4864.

(32)M. L. Moore in Organic Reactions, Vol. V., John Wiley and Sons, Inc., New York, N. Y., 1949, p. 301.

tives has been reported by many workers, but such reactions have generally been carried out by using two moles of amine per mole of halide. The resulting inefficient use of the amine made such a procedure unattractive for alkylation of the difficultly available VIII.

A modification to the customary use of excess amine has been reported by McKay and Brownell (33). These workers alkylated diethanolamine in good yield by allowing equimolar amounts of amine and alkyl halide to react in the presence of excess potassium carbonate. This procedure appeared promising for alkylation of VIII. However, it seemed prudent to investigate its use in alkylations of piperidine before applying it to VIII.

Another procedure which met the general requirements for alkylation of VIII was reductive alkylation by a carbonyl compound and hydrogen in the presence of platinum oxide. Alkylations of piperidine and of many other secondary amines by this method have been reported (34), and Grob and Renk (35) have methylated 4-carboxamidopiperidine by treatment with formalin and hydrogen over Raney nickel at room temperature. Since water is a by-product of this reaction, it cannot be

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(33)A. F. McKay and H. H. Brownell, J. Org. Chem., 15, 648 (1950).

(34)W. S. Emerson in Organic Reactions, Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 174.

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

carried out under anhydrous conditions, but little hydrolytic attack on the diester grouping was expected under the mild conditions necessary for the reductive alkylation to proceed. As with the use of alkyl halides, the reductive alkylation was tested by applying it to piperidine before it was used for the preparation of IX (Figure 5).

In addition to 1-alkyl-4,4-dicarbethoxypiperidines, 1-phenyl-4,4-dicarbethoxypiperidine was desired for conversion to the corresponding spiroaminobarbituric acid. The procedure used by Starnes (23) for preparation of this compound from N,N-bis-(2-p-toluenesulfonyloxyethyl)-aniline and diethyl malonate was used with little variation.

The major objective of the synthetic work was the preparation of spiro-1'-substituted-piperidine-4',5-barbituric acids such as IV, Figure 3 (R'= hydrogen or alkyl). By analogy to the formation of barbituric acids by many alicyclic and heterocylic compounds containing gem-dicarbethoxy groupings (36), the condensation of piperidine-diesters with urea was expected to proceed smoothly to yield the disodium salt of IV. Acidification of the salt to the free acid, IV, presented two problems not encountered in most barbituric acid preparations. First, it was necessary to use strictly anhydrous conditions until the salts had been completely acidified since the salts hydrolyzed very rapidly under basic conditions. Second, it was necessary to avoid use of excess acid in order

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(36)Doran, op. cit., pp. 129-134.

to prevent loss of the free acid by piperidinium salt formation. Starnes (37) found that salts of the spiro-1'-aryl-piperidine-4',5-barbituric acids could be acidified by treatment of the salt with an excess of a weakly acidic ion exchange resin, and Allen (38) achieved similar results with the corresponding thiobarbiturates. However, in the 1'-alkyl series Allen obtained only low yields even when equivalent amounts of resin and salt were used. A more effective procedure for acidifying the salts of the amphoteric aminobarbituric acids was desirable. The use of standard solutions of hydrogen chloride in anhydrous ethanol for these acidifications was therefore investigated. The methods outlined were then used to prepare some representative spiroaminobarbituric acids.

The final phase of this investigation involved kinetic measurements of the rates of basic hydrolysis for two spiroaminobarbituric acids and of several 5,5-disubstituted-barbituric acids. Energies and entropies of activation were calculated for the hydrolysis of the 5,5-disubstituted acids.

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(37)Starnes, op. cit., p. 68.

(38)Allen, op. cit., p. 19.

CHAPTER III

EXPERIMENTAL

All melting points and boiling points are uncorrected. Melting points were determined in capillary tubes heated in an aluminum block at a rate of 1-2° per minute. To insure consistency, the same thermometer was used for all melting point determinations. Calibration against standard short-stem thermometers authenticated by the Bureau of Standards showed that the melting point thermometer indicated temperatures within less than one degree of those indicated by the standards over the range of 25-275°. Elemental microanalyses were performed by Drs. Weiler and Strauss, Oxford, England, or by Galbraith Laboratories, Knoxville, Tennessee.

Experiments Based on 4,4-Dicarbethoxytetrahydropyran

Attempted Preparation of Spiro-1'-m-tolylpiperidine-4',5-barbituric Acid

4,4-Dicarbethoxytetrahydropyran.--The method of Harnest and Burger (39) was followed in preparing this compound. A preparation on a four-molar scale resulted in a 55 per cent yield.

Spirotetrahydropyran-4',5-barbituric acid.--This compound was synthesized by the method described by Stanfield and

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

Daugherty (6). A yield of 39 per cent was obtained in a run on a 0.2 molar scale.

5,5-Bis-(2-iodoethyl)-barbituric acid.--Cleavage of the ether linkage of spirotetrahydropyran-4',5-barbituric acid with a mixture of 96 per cent phosphoric acid and potassium iodide yielded the desired product without difficulty. The procedure used was essentially that of Stanfield and Daugherty (6) except that the mixture was agitated by mechanical stirring instead of by shaking. By the use of a reaction time of two hours and one recrystallization from ethanol, a yield of 75 per cent was obtained.

"Spiro-1'-m-tolylpiperidine-4',5-barbituric acid".--Following the procedure outlined by Stanfield and Daugherty (6) for the preparation of spiropiperidinebarbituric acids, an attempt was made to prepare spiro-1'-m-tolylpiperidine-4',5-barbituric acid. The most significant variation from the literature procedure was the use of mechanical stirring in place of mechanical shaking. The reaction was carried out using 10.9 g. (0.025 mole) of 5,5-bis-(2-iodoethyl)-barbituric acid and 2.65 g. (0.025 mole) of redistilled m-toluidine. The total reaction time was 16 hr. From the reaction mixture there was obtained 1.6 g. of a white solid, m. p. 193-195°. This product was subsequently shown by melting point and infrared spectrum not to be identical with spiro-1'-m-tolylpiperidine-4',5-barbituric acid (m. p. 224-225°) prepared from 1-m-tolyl-4,4-dicarbethoxypiperidine and urea (40). Due to the small

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(40) Starnes, op. cit., p. 74.

amount of material produced in the reaction of the iodo-compound with m-toluidine, no additional work on its structure was undertaken.

Preparation of Spirotetrahydropyran-4',5-(1-methylbarbituric Acid)

Introduction.--Extension of the procedures described by Stanfield and Daugherty (6) to the preparation of spiroaminobarbituric acids containing substituents on the nitrogen atoms of the barbituric acid rings required preparation of spirotetrahydropyran-4',5-(1-substituted-barbituric acids) as key intermediates. Accordingly, the synthesis of spirotetrahydropyran-4',5-(1-methylbarbituric acid) was studied in some detail. The problem was complicated by the lack of stability of the desired product under any sort of hydrolytic conditions. This instability could be predicted from reports that spirotetrahydropyran-4',5-barbituric acid (41) and 1,5,5-trisubstituted-barbituric acids (42) are much less stable to conditions of basic hydrolysis than the more familiar 5,5-disubstituted-barbituric acids.

Two general synthetic methods were investigated in the course of attempts to prepare the desired product in good yield. The first method involved the base catalyzed condensation of 4,4-dicarbethoxytetrahydropyran with methylurea.

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(41)Daugherty, op. cit., p. 22.

(42)H. Aspelund and C. Skoglund, Acta Acad. Aboensis, Math. et Phys., 10, 22 (1937); C. A., 31, 6634 (1937).

The second was an adaptation of the acidic condensation and dehydration method of Biltz and Wittek (19). The experiments are described below with the most successful being described in detail and the others being summarized.

Catalysis by sodium isopropoxide in isopropyl alcohol.--In a 500 ml. three-necked flask equipped with a mechanical stirrer, a dropping funnel, and a reflux condenser containing a calcium chloride drying tube was placed 175 ml. of isopropyl alcohol (commercial 99+ per cent) and 4.8 g. (0.21 g.-atom) of freshly cut sodium. As soon as the sodium had all reacted, the dropping funnel was replaced temporarily by a powder funnel and 14.8 g. (0.20 mole) of methylurea was added. The dropping funnel was replaced and after the methylurea had dissolved, 46.0 g. (0.20 mole) of 4,4-dicarbethoxytetrahydropyran was added dropwise over a period of about 0.25 hr. During heating of the reaction mixture at reflux for four hours a white solid precipitated giving the mixture a milky appearance. To this milky mixture was added a sodium isopropoxide solution prepared from an additional 4.8 g. of sodium and 150 ml. of isopropyl alcohol. Heating at reflux was continued for four hours longer. Following the second reflux period, the mixture was cooled to 10° in an ice bath and then was poured with vigorous stirring into a mixture of 42.4 ml. (0.50 mole) of concentrated hydrochloric acid and 500 g. of ice. Filtration of the acid solution yielded 7.0 g. of white solid, m. p. 184-187°. After the filtrate had stood in the

refrigerator overnight without depositing any more solid, it was saturated with sodium chloride and extracted with three 150 ml. portions of ether. Evaporation of the ether extracts at aspirator pressure yielded 2.0 g. of solid, m. p. 187-189°. One recrystallization of the combined solids from ethanol yielded 7.4 g. (18 per cent yield) of spirotetrahydropyran-4',5-(1-methylbarbituric acid), m. p. 188-189°. An analytical sample, m. p. 187.8-188.6°, was prepared by recrystallizing a portion of the solid product once from water and once from ethanol.

Calculated for $C_9H_{12}N_2O_4$: N, 13.20.

Found: N, 13.55.

Catalysis by sodium ethoxide in ethanol.--Freshly cut sodium (2.3 g., 0.10 g.-atom) was added to 90 ml. of absolute ethanol in an apparatus similar to that described in the preceding section. When all the sodium had reacted, 7.4 g. (0.10 mole) of methylurea was added to the ethoxide solution, followed by addition of 23.0 g. (0.10 mole) of 4,4-dicarbethoxytetrahydropyran. The mixture was stirred at reflux for six hours. At the end of this period, only a small amount of solid had precipitated, so a sodium ethoxide solution prepared from 1.0 g. of sodium and 25 ml. of absolute ethanol was added. No additional precipitate was evident, however, even after refluxing for one more hour. The mixture was therefore cooled to 10° in an ice bath and maintained at this temperature while dry hydrogen chloride was passed in until

the pH (as indicated by pH paper) was 3-4. Filtration of the acidified mixture with suction yielded 22.2 g. of an alcohol-damp solid. Overnight refrigeration of the filtrate provided a small additional amount of solid. After being washed four times with ice water, the solid still left a residue on ignition. Treatment of the solid with a mixture of acetone and ether followed by filtration extracted the organic material from the inorganic impurities. Evaporation of the solvents followed by recrystallization of the residue from ethanol yielded 5.1 g. (24 per cent) of the desired product, m. p. 187-189°.

Other experiments involving base catalysis.--Three other synthetic runs were made using sodium isopropoxide catalyst in isopropyl alcohol solution, with reaction time and catalyst-reactant ratio being varied. In two of these runs, the reaction mixture was acidified by being poured into excess hydrochloric acid and ice, while in the third, the acidification was carried out by passing dry hydrogen chloride into the mixture. No more than a trace of crystalline product could be isolated in any of these experiments.

Preparation of 4,4-dicarboxytetrahydropyran.--Formation of the desired barbituric acids under acidic conditions required substituted malonic acids as the starting materials. An attempt to utilize the procedure of Harnest and Burger (39) for the preparation of 4,4-dicarboxytetrahydropyran on a 0.12-molar scale resulted in a yield of only 23 per cent of

the diacid. This procedure involved refluxing of 4,4-dicarbethoxytetrahydropyran in aqueous ethanolic potassium hydroxide for twenty hours followed by distillation of the ethanol and acidification of the residual solution. The low yield was due partly to losses encountered in attempting to purify the crude product.

In subsequent preparations of this compound, it was found that the use of aqueous ethanolic sodium hydroxide instead of potassium hydroxide resulted in the isolation of disodium tetrahydropyran-4,4-dicarboxylate in almost quantitative yield. Careful acidification of a solution of the salt produced the free acid in good yield. In a typical experiment, 12.0 g. (0.30 mole) of sodium hydroxide (technical grade) was dissolved in 36 ml. of water, and 23.0 g. (0.10 mole) of 4,4-dicarbethoxytetrahydropyran was added. Addition of 25 ml. of ethanol caused the mixture to become homogeneous. Almost immediately the temperature rose to the boiling point, and gentle refluxing continued for several minutes without external heating. After it had stood for 0.5 hr., the mixture had cooled somewhat, and a white solid had separated. This solid was removed by filtration. The filtrate was allowed to stand at room temperature overnight and was then diluted with 100 ml. of ethanol. Refrigeration of the diluted solution for several hours yielded more solid which was combined with the solid first obtained. Drying the combined solids to constant weight over calcium chloride

yielded 20.4 g. of the salt. All of the salt was dissolved in the minimum amount of water at 40°. The solution was next cooled in a ice bath after which it was made acidic to Congo red by the addition of concentrated hydrochloric acid. Continued cooling and vigorous stirring resulted in the precipitation of a white solid which weighed 16.5 g. (95 per cent) when dry. The product melted at 170-172° with decomposition and appeared pure enough for use in later syntheses. It could be recrystallized in reasonably good recovery from ethyl acetate-hexane mixture to yield pure product with m. p. 171-173° (lit. (39) m. p. 172-173°).

Attempted preparation of spirotetrahydropyran-4',5-(1-methylbarbituric acid) under acidic conditions.--In a procedure suggested by the work of Biltz and Wittek (19), a solution of 7.3 g. (0.042 mole) of 4,4-dicarboxytetrahydropyran in 50 ml. of glacial acetic acid was prepared by warming the mixture gently in a 200 ml. flask until all the solid acid dissolved. The flask was fitted with a pressure equalizing dropping funnel to permit dropwise addition of 12.9 g. (0.17 mole) of acetic anhydride followed by addition of a solution of 3.1 g. (0.042 mole) of methylurea in 10 ml. of glacial acetic acid. To protect the reaction mixture from atmospheric moisture while allowing free escape of any gases evolved during the reaction, the dropping funnel was replaced by a drying tube. After standing at room temperature for 92 hr., the reaction mixture was filtered to remove a small amount of white solid

which had separated. This solid was identified as the starting diacid by mixed melting point (170-172°) with authentic material. Evaporation of the filtrate to dryness at aspirator pressure by warming in a warm (40-50°) water bath yielded 4.0 g. of a solid (A), m. p. 177-179.5° with decomposition. Recrystallization of A from ethanol and from ethyl acetate raised the melting point only to 178-180°, although the decomposition at the melting point seemed to be considerably less vigorous. The infrared spectrum of A in Nujol mull showed definite similarities to that of pure spirotetrahydropyran-4',5-(1-methylbarbituric acid), but the differences between the two spectra indicated the presence of considerable amounts of other substances in A. In view of the small amount of material available, it was not considered worthwhile to attempt other purifications of A.

In an earlier attempt to use this same synthetic method, the ratio of reactants and the temperatures of 60-90° reported by Biltz and Wittek (19) were used, but extensive decarboxylation of the starting acid occurred, as evidenced by the evolution of carbon dioxide gas. This gas was identified by the formation of a precipitate when it was passed into lime water. None of the desired product could be isolated in this experiment.

Attempted Preparation of Spirotetrahydropyran-4',5-(1,3-dimethylbarbituric Acid

Preparation of 1,3-dimethylbarbituric acid.--An attempt was

made to prepare sodium 1,3-dimethylbarbiturate and to condense this salt directly with bis-(2-chloroethyl)ether, in analogy to the condensation of sodiomalonic ester with the chloroether. In a three-necked flask equipped with a mechanical stirrer, a reflux condenser, and a dropping funnel were placed 125 ml. of absolute ethanol and 5.75 g. (0.25 g.-atom) of sodium. When all the sodium had reacted, 22.0 g. (0.25 mole) of 1,3-dimethylurea was added to the hot ethoxide solution. The mixture was heated to reflux with a heating mantle, and 40.0 g. (0.25 mole) of diethyl malonate was added dropwise with stirring. A heavy white precipitate began to separate almost as soon as the addition of diethyl malonate was begun. After the mixture had been stirred at reflux for 9 hr., 29.3 g. (0.25 mole) of bis-(2-chloroethyl)ether was added from the dropping funnel and stirring at reflux was continued for 12 hr. A solution prepared by the reaction of 5.75 g. of sodium with 125 ml. of absolute ethanol was then added, and the stirring and heating were continued for 9 hr. longer. In order to remove the solids present, the mixture was cooled and filtered. The solids were washed with 50 ml. of ethanol, and the combined filtrates were acidified by passing in dry hydrogen chloride. Although the acidification caused only a faint cloudiness (due to the formation of sodium chloride), evaporation of the solution to a small volume yielded 3.0 g. of an acidic solid, m. p. 122-124°. Since no neutral product could be obtained from the filtrate, the

solid residue of the original reaction mixture was dissolved completely in 325 ml. of water to form a weakly basic solution. Extraction of this solution with ether failed to yield any product, but acidification with concentrated hydrochloric acid caused precipitation of 9.2 g. of white solid, m. p. 122-124°. Repeated concentrations of the filtrate provided an additional 8.2 g. of solid in several crops, all with melting points in the range of 121-124°. The reported melting point of 1,3-dimethylbarbituric acid is 123° (19), and the total of 21.4 g. of solid product obtained represents a yield of this compound of 60 per cent.

Attempted condensation of sodium 1,3-dimethylbarbiturate with bis-(2-chloroethyl)ether in methanol.--Experiments showed that sodium 1,3-dimethylbarbiturate was only very slightly soluble in ethanol. Thus, it seemed possible that the failure of the condensation described in the preceding paragraph was due to insolubility of the salt in ethanol. Since further experiments showed that sodium 1,3-dimethylbarbiturate was soluble in methanol to the extent of about one gram of the salt in 100 ml. of solvent, condensation of the salt with the chloroether was attempted in methanol. A sample of pure sodium 1,3-dimethylbarbiturate was prepared by adding a solution of 12.8 g. of 1,3-dimethylbarbituric acid in 100 ml. of hot ethanol to a solution formed by the reaction of 2.3 g. of sodium with 50 ml. of ethanol. The resulting precipitate was removed by filtration and was recrystallized from water. A

suspension of 7.75 g. (0.046 mole) of the dried sodium 1,3-dimethylbarbiturate in 250 ml. of absolute methanol was prepared in the same apparatus described in the preceding section. Bis-(2-chloroethyl) ether (6.7 g., 0.046 mole) was added, and the mixture was heated at reflux with stirring for 20 hr. After this period of heating, a solution prepared from 1.1 g. (0.048 g.-atom) of sodium and 50 ml. of methanol was added, and stirring at reflux was continued for 27 hr. Work-up of the reaction mixture by essentially the same procedure described in the preceding section yielded 4.4 g. (73 per cent recovery) of 1,3-dimethylbarbituric acid. The only other solid product isolable was sodium chloride. In addition to the solids, there was obtained 2.2 g. of an oil, b. p. 177-180°, which apparently was the starting ether (lit. (43) b. p. 178°).

Attempted Preparation of Spiro-1'-methylpiperidine-4',5-(1-methylbarbituric Acid)

1-Methyl-5,5-bis-(2-iodoethyl)-barbituric acid.--A 96 per cent solution of phosphoric acid was prepared by addition of 19 g. of phosphorous pentoxide to 81 g. of commercial 86 per cent phosphoric acid. In a three-necked flask equipped with a reflux condenser, a mechanical stirrer, and a thermometer, the 96 per cent phosphoric acid was mixed with 50 g. (0.30 mole) of potassium iodide and 10.5 g. (0.050 mole) of tetra-

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(43) O. Kamm and J. H. Waldo, J. Am. Chem. Soc., 43, 2225 (1921).

hydropyran-4',5-(1-methylbarbituric acid). Vigorous stirring was started, and the mixture was heated to 145° over a period of 1.0 hr. After the temperature was held at 145° for an additional 0.75 hr., the hot mixture was poured over 250 g. of crushed ice. The ice water mixture was filtered to remove the product as a brown solid which was ground with a mortar and pestle and washed with 400 ml. of ice water. When the resulting tan solid was dissolved in acetone and the acetone solution treated with 400 ml. of water, there resulted 18.4 g. (83 per cent) of white product of m. p. 114-116°. The 1-methyl-5,5-bis-(2-iodoethyl)-barbituric acid yellowed on prolonged standing, particularly in the light.

An analytical sample, m. p. 115-116° was prepared by recrystallizing from ethanol-water and from dioxane-water.

Calculated for $C_9H_{12}N_2O_3I_2$: C, 24.01; H, 2.69;
N, 6.22; I, 56.40.

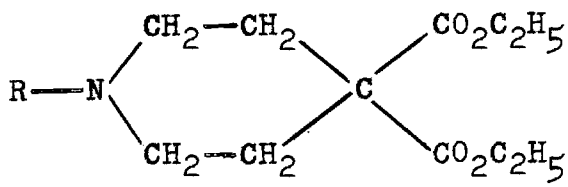
Found: C, 24.18; H, 2.77;
N, 6.65; I, 58.3.

One attempt was made to prepare spiro-1'-methylpiperidine-4',5-(1-methylbarbituric acid) by reaction of 1-methyl-5,5-bis-(2-iodoethyl)-barbituric acid with methylamine using the procedure of Stanfield and Daugherty (6). However, no identifiable product could be obtained from the reaction. Due to the reported evidence that the products obtained by reaction of 5,5-bis-(2-iodoethyl)-barbituric acid with primary amines were not the desired spiroaminobarbituric acids (7), the reaction was not repeated.

Experiments Based on 4,4-Dicarbethoxypiperidine

Experiments on the Cleavage of Sulfonamides

Introduction.--One possible route to 1-alkyl-4,4-dicarbethoxypiperidines involved intermediates of the type shown in Figure 6 (a). Continuation of the process required removal



(a) R = arylsulfonyl or acyl

(b) R = alkyl

Figure 6. Proposed 4,4-Dicarbethoxypiperidine Intermediates

of the protective group on the nitrogen atom. Since a compound of type (a) had been reported in which the protective group was benzenesulfonyl, experiments were conducted to develop a procedure for cleavage of sulfonamides on a synthetic scale. Efforts in this area were confined to reactions which were not expected to destroy the gem-diester group. With one exception, only non-aqueous systems were studied, since a similar diester had been shown to be very reactive under hydrolytic conditions.[1]

Preparation of model sulfonamides.--1-Benzenesulfonylpiperidine and 1-p-toluenesulfonylpiperidine were prepared by shaking redistilled piperidine and the appropriate sulfonyl

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[1]See above, p. 22.

chloride in excess 10 per cent sodium hydroxide. Removal of the solid products by filtration and recrystallization from 95 per cent ethanol produced 1-benzenesulfonylpiperidine, m. p. 94-96°, and 1-p-toluenesulfonylpiperidine, m. p. 97-98°, in yields of 73 per cent and 68 per cent, respectively.

Anhydrous ethanol.--Commercial absolute ethanol was found to contain small amounts of water. In order to provide anhydrous ethanol of consistent purity, commercial absolute ethanol was re-dried by treatment with sodium and diethyl phthalate according to the method of Smith (44). Ethanol dried by this procedure is referred to as "re-dried" in this chapter. The term "absolute" ethanol is used to designate the commercial product.

Treatment of 1-p-toluenesulfonylpiperidine with sodium ethoxide.--A solution of sodium ethoxide was prepared by adding 2.3 g. (0.10 g.-atom) of clean sodium to 50 ml. of re-dried ethanol. When the reaction was complete, 12.0 g. (0.050 mole) of 1-p-toluenesulfonylpiperidine was added. Refluxing of the mixture for 20 hr. followed by cooling yielded 9.1 g. (76 per cent recovery) of starting material. The fate of the unrecovered sulfonamide was not determined. A strong indication that simple cleavage of the sulfur-nitrogen bond had not occurred was the fact that no piperidine could be isolated from the reaction mixture. The characteristic odor of piperidine could be detected in very dilute

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

ethanol solutions, and absence of this odor in the reaction mixture provided additional evidence that very little piperidine was present.

Treatment of 1-p-toluenesulfonylpiperidine with sodium hydroxide in ethanol.--To a solution of 8.0 g. (0.034 mole) of 1-p-toluenesulfonylpiperidine in 35 ml. of absolute ethanol was added 1.54 g. of sodium. After the mixture had been refluxed for 0.5 hr. and all the sodium had reacted, it was treated with 0.61 g. (0.034 mole) of water. The solution which resulted was refluxed for 18 hr. At the end of this reflux period, there was still no precipitate of sodium p-toluenesulfonate although this salt was shown by separate experiments to be virtually insoluble in hot ethanol. Cooling the reaction mixture yielded 4.3 g. (54 per cent) of the starting sulfonamide which was removed by filtration and washed with cold water. The filtrate of the reaction mixture and the washings were made strongly acidic with concentrated hydrochloric acid and extracted with ether. Evaporation of the ether extracts yielded about one gram of yellow oil which was converted to a gummy solid by drying several days in a calcium chloride desiccator. Efforts to purify and identify this material were unsuccessful. Treatment of the aqueous acid solution with sodium hydroxide and benzenesulfonyl chloride failed to produce any 1-benzenesulfonylpiperidine.

Treatment of 1-p-toluenesulfonylpiperidine with sodium n-amoxide in n-amyl alcohol.--In a procedure suggested by work

of Klamann and Hofbauer (45) commercial n-amyl alcohol was purified by distillation after drying over anhydrous calcium sulfate. Sodium (18 g., 0.78 g.-atom) was added to 200 ml. of the redistilled n-amyl alcohol. Refluxing of the alcohol-sodium mixture for two hours was necessary to bring about complete reaction of all the sodium. When the solution was allowed to cool slightly below the boiling point a considerable amount of the sodium n-amoxide precipitated. It was necessary to add 85 ml. more of the alcohol to redissolve all the precipitate. After the mixture had once again become homogeneous, 8.0 g. (0.034 mole) of 1-p-toluenesulfonylpiperidine was added. The reaction mixture was refluxed for 20 hr. and was then allowed to cool to room temperature. The amyl alcohol solution was extracted with 200 ml. of water in four portions. The strongly basic water solution was extracted twice with 25 ml. portions of ether and the ether was combined with the amyl alcohol. Making the water solution strongly acidic with sulfuric acid and extracting it with ether yielded only a small amount of a yellow oil which could not be induced to crystallize. The combined amyl alcohol-ether solution was extracted with five 10 ml. portions of 10 per cent hydrochloric acid. The combined acid extracts were made basic by the addition of 50 per cent sodium hydroxide and were then treated with p-toluenesulfonyl chloride in

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(45) D. Klamann and G. Hofbauer, Chem. Ber., 86, 1246 (1953).

an effort to isolate any piperidine present as the p-toluenesulfonamide. However, hydrolysis of the excess sulfonyl chloride by warming and shaking the mixture yielded none of the expected sulfonamide. Removal of the solvent from the remaining amyl alcohol solution by steam distillation and recrystallization of the residue from 95 per cent ethanol yielded 5.8 g. (72 per cent) of the starting material.

Preparation of hydrogen bromide in acetic acid.--In an adaptation of the method described by Duncan (46), hydrogen bromide was prepared by slowly adding bromine to xylene (Eastman Kodak practical grade) in a flask which was placed so that it could be illuminated by one or two 40 watt incandescent lights. The rate of the reaction could be controlled fairly easily by adjusting the rate of addition of the bromine and by turning the lights on or off as required. The hydrogen bromide produced in the reaction was passed through additional xylene to remove bromine which had been carried over. After passing through a trap to prevent backing up of liquid into the wash and reaction flasks, the gas was passed into a gas absorption tower containing 250 g. of glacial acetic acid. The outlet of the absorption tower was protected from moisture by a calcium chloride drying tube. The solution produced in this way was analyzed by adding 0.5-1.0 g. samples of the acid to accurately weighed beakers containing 10 ml. of distilled

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(46)D. R. Duncan, in Inorganic Syntheses, Vol. I, McGraw-Hill Book Company, Inc., New York, N. Y., 1939, p. 151.

water. The sample weights were determined by reweighing the beakers of solution. The bromide ion concentration was determined by addition of excess standard silver nitrate and back-titration of the excess silver nitrate with standard potassium thiocyanate using ferric alum indicator (47). The hydrogen bromide concentration determined by this method was 31 per cent. The hydrogen bromide-acetic acid solution prepared as described above was used for several preliminary experiments involving its use in sulfonamide cleavage. However, the later synthetic work was carried out using Eastman 30-32 per cent hydrobromic acid in acetic acid.

Reaction of model sulfonamides with anhydrous hydrogen bromide in acetic acid and phenol.--Several experiments were conducted on the cleavage of 1-benzenesulfonylpiperidine and 1-p-toluenesulfonylpiperidine by hydrogen bromide-acetic acid solution containing phenol. The procedures used were based on the sulfonamide cleavage method of Weisblat and co-workers (27). In each case, 2.0 g. of phenol was added to 23.5 g. of the hydrogen bromide solution contained in a ground glass stoppered Erlenmeyer flask. When the phenol had all dissolved, 0.010 mole of the sulfonamide was added, the flask was tightly stoppered, and the mixture was allowed to stand at room temperature or in a constant temperature bath for the times indicated in Table 1. At the end of the reaction period, the

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(47)I. M. Kolthoff and E. B. Sandell, Textbook of Quantitative Inorganic Analysis, The McMillan Company, New York, N. Y., 1936, p. 454.

Table 1. Results of Cleavages of Arylsulfonylpiperidines by Hydrogen Bromide in Acetic Acid

Aryl Group	Temperature[a]	Reaction Time (hr.)	Yield of Piperidine Hydrobromide (per cent)
phenyl	room	15	44
p-tolyl	room	22	10
p-tolyl	room	72	53
p-tolyl	50°	16	87

[a]Room temperature during these experiments was 25-29°.

mixture was poured into 150 ml. of dry ether. Filtration of the ether solution separated the piperidine hydrobromide formed in the reaction. The reaction conditions and yields are summarized in Table 1. The piperidine hydrobromide obtained in these reactions melted over ranges of three degrees or less and all melting points were between 236° and 240°. The reported (48) melting point of piperidine hydrobromide is 235°. Use of this method for cleaving sulfonamides on a preparative scale is described in a subsequent paragraph.[1]

Preparation of 4,4-Dicarbethoxypiperidine

N,N-Bis-(2-benzenesulfonyloxyethyl)-benzenesulfonamide.--The preparation of this compound was based on the procedure

[1]See below, p. 40.

(48)C. A. Bischoff, Ber., 31, 2839 (1898).

described by Skinner and co-workers (4). In a typical experiment, a solution of 140 g. (1.33 mole) of diethanolamine in 1280 ml. of anhydrous pyridine was prepared in a three-necked flask equipped with an efficient mechanical stirrer, a thermometer, and a pressure equalizing dropping funnel protected from atmospheric moisture by a calcium chloride drying tube. After the reaction flask was immersed in an ice-salt bath, the diethanolamine solution was stirred until its temperature reached 5°. Benzenesulfonyl chloride (776 g., 4.4 mole of Eastman white label) was added dropwise with the rate of addition being controlled so that the temperature of the reaction mixture remained below 10°. Almost as soon as the addition of benzenesulfonyl chloride was complete, the mixture became too thick for stirring to be effective. After the stirrer was stopped, the mixture was allowed to stand in the ice-bath for 4 hr. During the first hour, the temperature at the thermometer bulb rose to 15° but thereafter dropped very slowly. The dark, greenish-brown reaction mixture was added with vigorous manual stirring to an excess of concentrated hydrochloric acid and ice. A short period of stirring with the cold acid caused the viscous oil which first separated to solidify sufficiently for it to be separated by suction filtration. After being washed three times with ice water, the product was obtained as a slightly gummy green solid which retained a large amount of water. For purification, the solid was divided into four approximately

equal portions. Two of these portions were treated with sufficient boiling acetone to dissolve all the solid. The acetone solutions were boiled five minutes with decolorizing charcoal and filtered while hot. Cooling the filtrates yielded a light yellow, crystalline solid which was removed by filtration and air dried. The remaining portions of crude product were recrystallized from the filtrates of the first recrystallizations by the same procedure. The combined solids weighed 565 g. (81 per cent yield) and had a m. p. 126-127.5° (lit. (4) m. p. 127-128°).

1-Benzenesulfonyl-4,4-dicarbethoxypiperidine.--The procedure used for preparing this ester was a modification of the procedure of Skinner and co-workers (4). The chief modifications were based on the method described by Starnes (23) for the preparation of the structurally similar 1-phenyl-4,4-dicarbethoxypiperidine. Commercial toluene was purified by distillation from sodium. To 1800 ml. of purified toluene in a three-necked flask provided with a mechanical stirrer, a dropping funnel, and a reflux condenser containing a Drierite drying tube was added 19.2 g. (0.80 g.-atom) of freshly cut sodium. Heat was applied by a heating mantle until the sodium melted at which point addition of diethylmalonate (Eastman white label) from the dropping funnel was begun. A total of 256 g. (1.60 mole) of diethyl malonate was added over a period of 0.5 hr. during which the mixture refluxed gently without external heating. When the addition

was complete, heating was resumed until all the sodium had reacted. With heating again stopped, the dropping funnel was replaced by a powder funnel whereupon 210 g. (0.40 mole) of N,N-bis-(2-benzenesulfonyloxyethyl)-benzenesulfonamide was added as rapidly as possible. Heating was resumed, but after 2-3 minutes the reaction became very vigorous. Removal of the heating mantle and cooling with a water bath were necessary to prevent loss of material through the reflux condenser. When this initial reaction had subsided, the mixture was heated at reflux with stirring for 20 hr. After cooling and filtering to remove precipitated sodium benzenesulfonate, the solution was distilled at aspirator pressure to remove toluene and at 1-2 mm. to remove diethyl malonate. When the pot temperature reached 95°, the distillation was stopped and the hot residue was treated with 150 ml. of 95 per cent ethanol. Overnight refrigeration of the ethanol solution brought about separation of white solid, m. p. 64-66°, which was removed by filtration. Evaporation of the filtrate from the recrystallization provided additional solid product in several crops with melting points in the range of 62-66°. The total crude product amounted to 92 g. (62 per cent) but was contaminated with the solid starting material. It was possible to obtain pure 1-benzenesulfonyl-4,4-dicarbethoxypiperidine, m. p. 69-70°, from the crude product by fractional crystallization from ethanol, but this procedure resulted in considerable loss of material. Two simple

recrystallizations of the crude product from 95 per cent ethanol provided material with a m. p. 66-67.5°. The purity of such samples was sufficient to permit their use in subsequent reactions.

4,4-Dicarbethoxypiperidine.--In a 500 ml. Erlenmeyer flask with a ground glass stopper was placed 450 g. of freshly opened 30-32 per cent hydrogen bromide-acetic acid solution (1.67 mole of hydrogen bromide). To this solution were added 92.3 g. (0.25 mole) of 1-benzenesulfonyl-4,4-dicarbethoxypiperidine and 50 g. (0.53 mole) of phenol. The stopper of the flask was fastened tightly in place with rubber bands, and the mixture was swirled gently until all the solids had dissolved. After standing at room temperature for 10 hr., the mixture, which had turned from light yellow to brown, was poured into a mixture of 200 g. of potassium carbonate and 300 g. of crushed ice. The resulting weakly acidic mixture was shaken in a separatory funnel with one liter of ether. Following separation of the aqueous phase, the ether was extracted with two 50 ml. portions of 10 per cent hydrochloric acid. An additional 50 g. of potassium carbonate was added to the combined aqueous solutions, and the resulting solution was cooled in an ice bath while it was made strongly basic (pH above 10) to pH paper by the addition of 50 per cent sodium hydroxide solution. After an additional 50 ml. of sodium hydroxide was added, the basic solution was extracted with three 100 ml. portions of ether. The ether

extracts were dried over anhydrous sodium sulfate for 3 hr. and then dried with Drierite overnight. Removal of ether from the filtered solution by evaporation at aspirator pressure left a light yellow liquid which was distilled under vacuum to yield 31.2 g. (55 per cent) of 4,4-dicarbethoxypiperidine as a colorless liquid, b. p. 112-114° at 0.2-0.3 mm. pressure. Treatment of 5 drops of this liquid with 10 drops of benzenesulfonyl chloride in excess sodium hydroxide yielded a solid product which, after recrystallization from ethanol, was shown to be identical with the starting material by its melting point (67-69°), a mixed melting point (67-68.5), and its infrared spectrum.

In other preparations of this ester using the same ratio of reactants, attempts to isolate 4,4-dicarbethoxypiperidine hydrobromide by pouring the reaction mixture into a large excess of ether yielded only a water soluble red oil. Extraction of the acidic ether solutions with water and making the water extracts strongly basic with sodium hydroxide yielded the desired product. The yields (35-42 per cent) was obtained with this method of isolation were lower than that obtained with the procedure described above and this procedure was more time consuming. The low yields obtained in some of these preparations of 4,4-dicarbethoxypiperidine suggested that insufficient time was being allowed for completion of the reaction. To study this possibility, an investigation was made of the neutral material present in

one of the cleavage mixtures. The mixture studied had been run on a 0.07-molar scale and had been worked up by pouring into ether to give a 38 per cent yield of 4,4-dicarbethoxypiperidine. After removal of the salts of the basic material by washing the strongly acidic ether solution with water, the ether solution was extracted with small portions of saturated sodium carbonate until the extracts remained basic. Additional washing with 10 per cent sodium hydroxide removed any remaining acidic material. The neutral ether solution which resulted was evaporated to a dark brown oil, the infrared spectrum of which had no absorption in the ester carbonyl region (5.5-6.0 microns). The oil, therefore, was assumed not to contain any appreciable amount of the starting ester. When the brown oil was taken up in an equal volume of alcohol and the resulting solution was refrigerated, there was obtained 3.2 g. of a light tan solid, m. p. 53-55°. This was believed to be diphenyl disulfide (lit. (49) m. p. 60°). Systematic concentration of the filtrate yielded an additional 2.0 g. of this solid, m. p. 56-57.5°. The 5.2 g. of disulfide recovered represented a yield of 68 per cent of this compound based on the starting sulfonamide. In addition to the disulfide formed in the cleavage, the presence of thiophenol in the cleavage mixture was indicated by its characteristic odor. The yield of the disulfide and the

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(49)H. Lecher, Ber., 48, 525 (1915).

absence of starting material in the reaction mixture definitely indicated that the low yields were not due to insufficient reaction time.

1-Benzenesulfonyl-4,4-dicarboxypiperidine.--An impure[1] sample of 1-benzenesulfonyl-4,4-dicarboxypiperidine (32 g., 0.088 mole) was suspended in 50 ml. of 25 per cent sodium hydroxide solution and the mixture was heated at reflux for 6 hr. After the hydrolysis mixture had been cooled to room temperature, it was extracted with two 10 ml. portions of ether to remove a small amount of a light yellow oil which had failed to react with the strong base. The identity of the oil was not determined. It apparently was not the starting ester since it did not solidify at room temperature. The aqueous solution was heated to drive off ether and was then cooled to 5° in an ice-salt bath. Acidification by dropwise addition of concentrated hydrochloric acid caused separation of a grey precepitate which was removed by filtration and washed twice with ice water. After drying to constant weight over calcium chloride in a desiccator, the solid acid (A) weighed 17.4 g. and melted sharply at 159° with decomposition. Skinner and co-workers (4) reported the m. p. of 1-benzenesulfonyl-4,4-dicarboxypiperidine as 124°.

It was noted that these workers reported the melting point of 1-benzenesulfonyl-4-carboxypiperidine as 159-160°. These reported values were somewhat unexpected since 4,4-di-

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[1]The major impurity was bis-(2-benzenesulfonyloxyethyl)-benzenesulfonamide.

carboxytetrahydropyran (39) and 1-phenyl-4,4-dicarboxypiperidine (50) melt considerably higher than the corresponding monoacids. Although the melting point reported for 1-benzenesulfonyl-4-carboxypiperidine is the same as that found for A, this product was believed to be the diacid. The evidence for the diacid structure included a neutral equivalent in agreement with that calculated for the diacid and conversion of the product by sulfonamide cleavage to a compound which was indicated by analysis to be 4,4-dicarboxypiperidine hydrobromide.[1] It seemed possible that Skinner and co-workers may have reported their melting points incorrectly.

The neutral equivalent of the product of this experiment was determined by stirring weighed samples of the acid with measured amounts of standard sodium hydroxide until all the solid dissolved. The resulting solutions were then titrated to phenolphthalein end points with additional standard sodium hydroxide.

Calculated for $C_{13}H_{15}NO_6S$: neutral equivalent 157.
Found: neutral equivalent 156, 157, 158.

4,4-Dicarboxypiperidine hydrobromide.--A mixture of 37.3 g. of 30 per cent solution of hydrogen bromide in acetic acid, 3.0 g. (0.033 mole) of phenol, and 4.70 g. (0.015 mole) of 1-benzenesulfonyl-4,4-dicarboxypiperidine was placed in a

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[1]See below, p. 46.

(50)Starnes, op. cit., p. 79.

ground glass stoppered Erlenmeyer flask, and the stopper was fastened firmly in place with rubber bands. Even after the mixture had stood for about 0.5 hr. with occasional swirling of the contents, a part of the starting acid had not dissolved. The powdery starting material gradually disappeared during the next several hours and in its place there was deposited a white crystalline solid of distinctly different appearance. After a reaction time of 36 hr. the reaction mixture was filtered through a sintered glass funnel to remove 3.0 g. of white solid. This solid, following a wash with several portions of dry ether, decomposed without melting at 250-270°. Addition of the liquid portion of the reaction mixture to 250 ml. of cold, dry ether yielded an additional 0.6 g. of a light pink solid, making the total yield of 4,4-dicarboxypiperidine hydrobromide 94 per cent.

The neutral equivalent of the product was determined by titration with standard sodium hydroxide solution to a phenolphthalein end point. The calculated value of the neutral equivalent was based on an assumption of two acidic hydrogen atoms per molecule. Calculations using the approximate acidity constant of piperidine hydrobromide (1×10^{-11})[1] as a maximum value for the third ionization of 4,4-dicarboxypiperidine hydrobromide show that the extent of reaction of the third acidic hydrogen would be less than

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[1]This constant was calculated from the basicity constant of piperidine and the ionization constant of water.

5 per cent at the phenolphthalein end point. The values found indicated that the third acidic hydrogen atom probably was reacting in some molecules. Ionic bromide was determined by treatment of aqueous solutions of the solid samples with one equivalent of standard base and titration of the resulting solutions with standard silver nitrate solution using eosin as indicator.

Calculated for $C_7H_{12}BrNO_4$: neutral equivalent, 127; Br, 31.4.

Found: neutral equivalent, 121, 122, 123; Br, 31.6, 31.6.

Attempted esterification of 4,4-dicarboxypiperidine hydrobromide.--This esterification procedure is based on that described by Rubtsov (51). A solution of 11.2 g. (0.044 mole) of 4,4-dicarboxypiperidine hydrobromide and 2.0 g. of concentrated sulfuric acid in 50 ml. of absolute ethanol was placed in a 100 ml. flask connected to a Sohxlet extraction apparatus. In the extraction thimble was placed 30 g. of anhydrous magnesium sulfate. The Sohxlet apparatus was filled by adding a mixture of 60 ml. of benzene and 15 ml. of absolute ethanol, a part of which was allowed to pass down into the reaction flask. Although the mixture was refluxed for 48 hr., its reflux temperature remained almost constant at 70-72°. At the end of the reflux period, the acidic

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

mixture was cooled and poured onto a mixture of 3.0 g. of potassium carbonate and 25 g. of crushed ice. The mixture was treated with 2.0 ml. of 50 per cent sodium hydroxide solution and then with excess solid potassium carbonate. The organic phase was removed and the aqueous solution was extracted three times with 20 ml. portions of benzene. Drying of the combined organic solutions first over potassium carbonate and then over Drierite was effected after which the solvent was removed at room temperature under aspirator vacuum. Distillation of the small amount of residue through a six-inch Vigreux column yielded 1.4 g. of a liquid b. p. 70-80°/0.2-0.3 mm., which had an infrared spectrum distinctly different from that of authentic 4,4-dicarbethoxypiperidine.[1] Because of the small amount of material obtained, no attempt was made to determine its composition.

Experiments on the Alkylation of Piperidine

Introduction.--Although many procedures have been described for the alkylation of piperidine and substituted-piperidines,[2] most are not suitable for use in alkylation of 4,4-dicarbethoxypiperidine due to the employment of aqueous acid or to the low conversion of the piperidine to its alkylated derivative. Attempts were therefore made to determine conditions for alkylating piperidine in good yield under conditions

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[1]The preparation of this compound is described on p. 40.

[2]See the discussion of Chapter II, pp. 13-15.

which would not be destructive to the gem-diester grouping in 4,4-dicarbethoxypiperidine. The experiments were devoted to the introduction of either methyl or isopropyl groups as representative examples of primary and secondary alkyl groups.

Reaction of piperidine with methyl iodide.--Attempted reactions of piperidine with methyl iodide by adding either compound to the other without solvent led to very vigorous reactions which were difficult to keep under control. It was found that the reaction was more moderate when carried out in ethanol, and a preparative methylation was attempted in this solvent. A solution of 8.5 g. (0.10 mole) of freshly distilled piperidine in 25 ml. of absolute ethanol was placed in a three-necked flask fitted with a stirrer, a reflux condenser, and a dropping funnel. Anhydrous potassium carbonate (20.7 g., 0.15 mole) was added and stirring was commenced. While the flask was cooled in a water bath, 13.6 g. (0.097 mole) of methyl iodide was added dropwise over a period of 0.5 hr. When addition of the methyl iodide was complete, the cooling bath was removed, and the mixture was stirred for 0.3 hr. at room temperature and for 0.3 hr. at reflux. After the reaction mixture had cooled somewhat, it was filtered with suction to remove potassium carbonate and potassium iodide. The residue from this filtration was washed with 15 ml. of hot ethanol, and the washings were allowed to mix with the original filtrate. Addition of 175 ml. of dry ether to the ethanol solution produced a white precipitate

which was removed by filtration and discarded. Distillation of the filtrate through a six-inch Vigreux column yielded 4.5 g. of an amine fraction boiling at 95-115°. This amine fraction was shaken with 100 ml. of 10 per cent sodium hydroxide solution while 16.8 g. of benzenesulfonyl chloride was added in small portions. After the resulting mixture had been warmed and shaken for several minutes, a pink solid formed. Acidification of the mixture had no effect on the solid so the solid was removed by filtration. The acidic filtrate was made strongly basic by the addition of solid sodium hydroxide and was extracted with five 25 ml. portions of ether. After the combined ether solutions had been dried over Drierite, addition of excess dry hydrogen chloride caused precipitation of 1-methylpiperidine hydrochloride. Drying overnight in a vacuum desiccator yielded a product having a m. p. 205-210°, (lit. (52) m. p. 209-210°) and weighing 1.5 g. (11 per cent yield).

Reaction of piperidine with isopropyl bromide.--In a ground glass stoppered Erlenmeyer flask were placed a solution of 8.5 g. (0.10 mole) of redistilled piperidine in 25 ml. of re-dried ethanol, 20.7 g. (0.15 mole) of anhydrous potassium carbonate, 12.3 g. (0.10 mole) of isopropyl bromide, and a Teflon-coated magnetic bar. The flask was stoppered, and the mixture was stirred magnetically for 26 hr. at room

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(52)H. W. Magnusson and E. R. Schierz, Univ. Wyoming Pub., 7, 1 (1940); C. A., 34, 6867 (1940).

temperature. When this period of stirring had ended, the mixture was filtered to remove the solid residue which was washed with several small portions of warm ethanol. The combined filtrate and washings were made strongly acidic by the addition of concentrated hydrochloric acid and the resulting solution was evaporated to dryness at aspirator pressure by warming on a steam bath. There was obtained 15.7 g. of a light green solid. This solid was added to 100 ml. of 15 per cent sodium hydroxide, and the resulting mixture was shaken with 26.6 g. (0.15 mole) of benzenesulfonyl chloride. When it appeared that all the benzenesulfonyl chloride had reacted with the amine or with the warm base, the mixture was made acidic by the addition of concentrated hydrochloric acid. The acidic mixture, after being cooled to 20°, was shaken with 100 ml. of ether, and the aqueous layer was removed. The ether solution was extracted with 25 ml. of 10 per cent hydrochloric acid, after which it was evaporated to dryness to yield 5.2 g. (23 per cent yield) of 1-benzenesulfonylpiperidine, m. p. 92-96°. Treatment of the combined acidic solutions with an excess of 50 per cent sodium hydroxide caused separation of a light brown oil which was removed by extraction with three 25 ml. portions of ether. Distillation of the ether solution provided 3.5 g. (27 per cent of the theoretical) of 1-isopropylpiperidine, b. p. 147-150° (lit. (53) b. p. 149-150°).

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(53)A. Ladenburg, Ber., 14, 1348 (1881).

The reason for such a large amount of starting material remaining unaccounted for were not determined. Since no evolution of propylene gas was observed during the reaction period, it was assumed that little or no dehydrohalogenation of the isopropyl bromide had occurred. In a separate experiment 1.0 g. of 1-isopropylpiperidine and 1.0 g. of isopropyl bromide were dissolved in 10 ml. of re-dried ethanol, and the mixture was allowed to stand at room temperature for 48 hr. Adding 100 ml. of dry ether caused only a faint turbidity, which was not increased by addition of more ether. This result seemed to be good evidence that neither quaternization nor dehydrohalogenation had taken place to any appreciable extent under the conditions used, which corresponded to the conditions of the alkylation reaction.

Reductive alkylations of piperidines.--The reductive alkylation of piperidine by formaldehyde and acetone was studied to determine the usefulness of this reaction for introducing N-methyl and N-isopropyl groups into piperidine compounds. In a single reaction of methanolic piperidine with an equimolar amount of 38 per cent formalin in the presence of hydrogen and platinum oxide, 87 per cent of the theoretical amount of hydrogen was absorbed in 1.0 hr. Under the same conditions, formalin alone did not absorb an appreciable amount of hydrogen in 1.5 hr. The hydrogenation data were regarded as sufficient evidence that the reductive alkylation had taken place, although the product was not isolated.

Three attempts were made to bring about reductive alkylation of piperidine by acetone. In the first experiment 8.5 g. (0.10 mole) of piperidine and 8.7 g. (0.15 mole) of acetone were hydrogenated in ethanol. The second experiment was the same as the first except that 10 ml. of glacial acetic acid was added to catalyze the condensation step (54). No 1-isopropylpiperidine was isolated in either of these experiments. The third experiment, which was the most successful, is described in detail below.

Piperidine (8.5 g., 0.10 mole), 8.7 g. (0.15 mole) of acetone, and 10 ml. of acetic acid were dissolved in 50 ml. of absolute ethanol. While this mixture was warmed on a steam bath for 0.25 hr., a suspension of 0.25 g. of platinum oxide in 25 ml. of absolute ethanol was shaken under 50 p. s. i. of hydrogen in the Parr hydrogenation apparatus. Addition of the warm reaction solution to the pre-reduced catalyst and hydrogenation of this mixture resulted in a more rapid absorption of hydrogen than was obtained in either of the previous experiments. After 4 hr., 75 per cent of the theoretical amount of hydrogen had been absorbed and the reaction was still proceeding slowly. The catalyst was removed by filtration, and after treating the filtrate with an excess of concentrated hydrochloric acid, the acidic solution was evaporated to dryness under aspirator pressure by warming on a steam bath. The resulting greenish-yellow solid was taken up

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(54) Emerson, op. cit., p. 198.

in an excess of 15 per cent sodium hydroxide, and benzenesulfonyl chloride was added to remove the secondary amine present. This reaction mixture was acidified and extracted with 500 ml. of ether, which on evaporation yielded 7.2 g. (41 per cent) of 1-benzenesulfonylpiperidine, m. p. 91-94°. The aqueous solution was made basic by addition of solid sodium hydroxide and was extracted three times with 25 ml. portions of ether. Treatment of the dried ether solution with anhydrous hydrogen chloride yielded 3.5 g. of a hygroscopic solid, m. p. 215-220°. No report of the melting point of 1-isopropylpiperidine hydrochloride could be found. Reference (52) reports the melting point of 1-n-propylpiperidine hydrochloride as 225°; the reported melting point of piperidine hydrochloride is 246-247° (52). It appeared from these data that the solid obtained was mostly 1-isopropylpiperidine hydrochloride. The yield of this compound was 22 per cent.

Preparation of 1-Substituted-4,4-dicarbethoxypiperidines

1-Methyl-4,4-dicarbethoxypiperidine.--A solution was prepared by dissolving 8.6 g. (0.035 mole) of 4,4-dicarbethoxypiperidine in 50 ml. of absolute ethanol and adding 3.2 g. (0.41 mole) of 38 per cent formalin. There seemed to be slight warming when the formalin was added, but the solution was too dilute for this effect to be very pronounced. After the reactants had stood together at room temperature for 1 hr., 0.25 g. of platinum oxide was added and the mixture was

shaken in the Parr hydrogenation apparatus under hydrogen pressure of 50.0 p. s. i. In contrast to the facile hydrogenation of piperidine-formalin mixture[1], the mixture of formalin with 4,4-dicarbethoxypiperidine reacted very slowly with hydrogen, probably because of the presence of sulfur-containing impurities in the starting ester. Even after two additional 0.25 g. amounts of platinum oxide had been added at different times, the reaction mixture absorbed only 75 per cent of the theoretical amount of hydrogen. When the hydrogen absorption which followed the last addition of catalyst had stopped, the mixture was filtered to remove the catalyst and was evaporated at aspirator pressure to yield a yellow oil. Distillation of this oil through a six-inch Vigreux column yielded 5.8 g. (64 per cent) of 1-methyl-4,4-dicarbethoxypiperidine, b. p. 93.5-94.5°/1 mm. This product had an infrared spectrum identical with that of an authentic sample of this material, b. p. 85°/1 mm., prepared by a different method (55).

An earlier attempt to prepare this compound had been made by adding a solution of 3.2 g. of methyl iodide in 10 ml. of absolute ethanol in small portions to a refluxing mixture of 5.1 g. (0.022 mole) of 4,4-dicarbethoxypiperidine, 6.1 g. (0.44 mole) of powdered anhydrous potassium carbonate,

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[1]See above, p. 51.

(55)Allen, op. cit., p. 43.

and 10 ml. of absolute ethanol. After a total reaction time of 1.7 hr., the mixture was cooled and filtered, and the residue was washed with small amounts of hot ethanol. Evaporation of the ethanol left a red gum which was extracted exhaustively with ether, leaving a red, semi-solid material undissolved. The ether solution was shaken with 2.5 g. of benzenesulfonyl chloride and was then extracted with 36 ml. of 7 per cent hydrochloric acid. Treatment of the acidic extracts with excess 50 per cent sodium hydroxide caused separation of an oil which was removed by four extractions with 10 ml. portions of ether. When the ether insoluble red solid was dissolved in water and the solution was made basic, an oil separated. Therefore, this basic solution was extracted with ether and the process described above was repeated to isolate any tertiary amine present. After being dried over Drierite, the combined ether solutions were evaporated under aspirator pressure. Distillation of the residue in a semi-micro apparatus yielded 0.5 g. (9 per cent yield) of product, b. p. 85-89°/0.7 mm.

1-(2-Phenylethyl)-4,4-dicarbethoxypiperidine.--To a solution of 6.4 g. (0.028 mole) of 4,4-dicarbethoxypiperidine in 25 ml. of absolute ethanol were added a solution of 3.4 g. of freshly redistilled phenylacetaldehyde in 25 ml. of absolute ethanol and 0.50 g. of platinum oxide. When the resulting mixture was shaken under hydrogen pressure of 50 p. s. i., it absorbed slightly more than the theoretical amount of hydrogen in

0.4 hr. After removal of the catalyst by filtration and drying of the filtrate over Drierite for 6 hr., the solvent was removed by distillation at aspirator pressure. Fractionation of the residue through a six-inch heated Vigreux column yielded 0.6 g. of 4,4-dicarbethoxypiperidine identified by infrared spectrum, b. p. 100-115°/0.2 mm., and 7.8 g. (84 per cent yield) of liquid, b. p. 166-173°/0.2 mm. The infrared spectrum of the higher boiling fraction showed the ester carbonyl and mono-substituted benzene absorptions expected for the desired product. In an attempt to redistill this liquid in a semi-micro apparatus, the rather high viscosity of the condensing liquid caused the column to flood badly, so that no effective separation could be made. From a second redistillation at 0.2 mm. pressure using the heated Vigreux column, there was obtained 0.60 g. of forerun, b. p. 163-165°, 4.47 g. of pure product, b. p. 165-165.5°, and 0.82 g. of distillate obtained by super-heating the column. The infrared spectra of these three fractions were essentially identical.

An analytical sample was taken from the fraction, b. p. 165-165.5°/0.2 mm.

Calculated for $C_{19}H_{27}NO_4$: C, 68.45; H, 8.16; N, 4.20.

Found: C, 68.36; H, 8.09; N, 4.29.

1-Phenyl-4,4-dicarbethoxypiperidine.--This compound was prepared using the procedure described by Starnes (23). The N,N-bis-(2-p-toluenesulfonyloxyethyl)-aniline required as a

starting material was furnished by G. C. Allen, who has described its preparation (56). The yield of crystalline product, m. p. 51-53.5°, was 62 per cent.

Preparation of Spiroaminobarbituric Acids

Spiro-1'-phenylpiperidine-4',5-barbituric acid.--The procedure used in the preparation of this compound was essentially that of Starnes (57) with certain variations. Sodium (3.45 g., 0.15 g.-atom) was added to 100 ml. of re-dried ethanol in a three-necked flask equipped with a mechanical stirrer, a ground glass stopper, and a reflux condenser protected from atmospheric moisture by a drying tube. Moderate stirring was maintained while the sodium and alcohol reacted. When the reaction was complete, the stopper was replaced by a powder funnel, 6.00 g. (0.10 mole) of urea (Matheson, Coleman and Bell U. S. P. grade) was added and the funnel was rinsed with 15 ml. of re-dried ethanol. Since the urea dissolved quite rapidly in the warm ethanol, the powder funnel was left in place for the addition of 15.3 g. (0.050 mole) of 1-phenyl-4,4-dicarbethoxypiperidine which dissolved immediately. The funnel was again rinsed with 15 ml. of the solvent and was then replaced by the stopper. Heating of the reaction mixture was commenced by placing a pre-heated heating mantle under the flask. During the approximately 0.3 hr.

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(56)ibid., p. 32.

(57)Starnes, op. cit., p. 68.

required for the solution to heat to reflux, a heavy white precipitate began to form. The reaction mixture was stirred at reflux for 11 hr. and was then filtered with suction after it had cooled to approximately 50°. The white solid obtained was washed several times with hot, re-dried ethanol. After drying to constant weight in a vacuum desiccator, this sodium salt weighed 13.1 g. (82 per cent). The free acid was formed by stirring 12.1 g. of the salt with 60 g. of Amberlite IRC-50 acidic ion exchange resin (Rohm and Haas) in 150 ml. of re-dried ethanol for 45 hr. This mixture was heated to boiling and filtered to remove the resin. Chilling of the filtrate yielded 3.5 g. of solid as pale yellow plates. The resin was stirred with 150 ml. more re-dried ethanol for 27 hr. Heating and filtering this mixture followed by chilling of the filtrate provided 3.1 g. of solid similar in appearance to that obtained first. Extraction of the resin with boiling acetone and evaporation of the filtered acetone solution yielded an additional 1.8 g. of powdery white solid. Attempts to extract additional product from the ion-exchange resin were unsuccessful. The total of 8.4 g. of product represented a yield of 81 per cent based on the sodium salt and 66 per cent based on the starting ester. The combined solids were recrystallized in good recovery from 95 per cent ethanol and from 60 per cent aqueous acetone to yield the pure product, m. p. 230-231° (lit. (57) m. p. 231-232°).

Acidification of barbiturate salts with ethanolic hydrogen chloride.--Although the acidification of barbituric salts by the use of ion exchange resins as described above is effective, it is also tedious and time-consuming. It seemed desirable to seek a simpler method for acidification of the salts of the amphoteric spiroaminobarbituric acids under anhydrous conditions and with avoidance of any excess of strong acid. Accordingly, a solution of hydrogen chloride in ethanol was prepared by passing the anhydrous gas into re-dried ethanol while the absorption flask was cooled in ice water. The resulting solution was standardized by titrating aliquots with standard sodium hydroxide solution and was found to be 0.142 molar in acid.

The use of the ethanolic hydrogen chloride reagent was tested by treating a sample of 0.98 g. (0.0031 mole) of disodium spiro-1'-phenylpiperidine-4',5-barbiturate in a ground glass stoppered Erlenmeyer flask with 43.5 ml. of 0.142 molar ethanolic hydrogen chloride (0.0062 mole) added from a burette. The flask was stoppered and the mixture was stirred magnetically for 0.3 hr. at room temperature. The mixture was heated to boiling with continued magnetic stirring before being filtered, and the filtration residue was washed twice with 25 ml. portions of boiling absolute ethanol. When the combined ethanol solutions were refrigerated overnight, 0.50 g. of white solid, m. p. 228-231°, was obtained by filtration. Concentration and refrigeration of the filtrate

yielded an additional 0.19 g. of solid, m. p. 225-228°. Both of these crops of solid were shown to be spiro-1'-phenylpiperidine-4',5-barbituric acid by mixed melting points with pure material obtained by the ion-exchange method.

It was found that ethanolic hydrogen chloride solutions as strong as 3.56 molar could be prepared without difficulty. These stronger solutions showed a slow but steady decrease in acidity on standing, even in tightly stoppered containers. Since it seemed likely that this decrease in acidity was due to reaction of the hydrogen chloride with ethanol to form ethyl chloride and water, only freshly prepared ethanolic hydrogen chloride was used in acidification of spiroaminobarbiturates.

Spiro-1'-benzylpiperidine-4',5-barbituric acid.--Freshly cut sodium (2.07 g., 0.090 g.-atom) was added in small pieces to 25 ml. of re-dried ethanol in the apparatus described above for preparation of the phenyl derivative. When the sodium had all reacted, 3.60 g. (0.060 mole) of U. S. P. urea was added through a powder funnel which was then rinsed with 10 ml. of re-dried ethanol. After the mixture was stirred for several minutes to dissolve the urea, 9.57 g. (0.030 mole) of 1-benzyl-4,4-dicarbethoxypiperidine[1] was added. The flask in which the ester was weighed and the funnel used in its addition to the reaction flask were washed with 15 ml. of

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[1]This compound was furnished by G. C. Allen. For its preparation, see reference (16).

re-dried ethanol. The mixture was heated to reflux and was refluxed for 7 hr., after which it was allowed to stand at room temperature for 10 hr. The heavy white precipitate which was formed in the reaction flask was removed by filtration and washed well with re-dried ethanol. After drying to constant weight in a vacuum desiccator, the solid weighed 8.0 g. (80 per cent). All of this dried solid (0.024 mole) was suspended in 50 ml. of re-dried ethanol, and to the suspension was added 13.6 ml. of 3.56 molar ethanolic hydrogen chloride (0.048 mole). Magnetic stirring was employed during addition of the acidic solution, but shortly after all the acid had been added, the mixture became too thick to be stirred effectively, even after it was diluted with an additional 150 ml. of re-dried ethanol. The acidified solution was allowed to stand 16 hr. at room temperature, diluted with 200 ml. of absolute ethanol, and then heated to boiling. Filtration of the hot mixture followed by cooling of the filtrate produced a gelatinous precipitate of the desired product. After this cooled mixture had been filtered to remove the gelatinous precipitate, the residue of the first filtration was extracted with the mother liquor. Filtration and cooling produced a second crop of gelatinous solid product similar to the first. The combined solids weighed 3.2 g. and had a m. p. 251-253°. Additional extractions and systematic concentration of the mother liquors yielded 1.2 g. more solid in several crops with melting points ranging from

248-250° to 250-251°. The total of 4.4 g. represented a yield of 63 per cent from the salt and 50 per cent over-all. The spiro-1'-benzylpiperidine-4',5-barbituric acid was readily soluble in dilute sodium hydroxide but not in sodium bicarbonate. It also dissolved slowly in 10 per cent hydrochloric acid.

An analytical sample, m. p. 254-255°, was prepared by recrystallizing a portion of the purest product twice from acetone-water mixtures and once from dimethylformamide-water.

Calculated for $C_{15}H_{17}N_3O_3$: C, 62.70; H, 5.97; N, 14.63.

Found: C, 62.55; H, 6.26; N, 14.53.

Spiro-1'-(2-phenylethyl)-piperidine-4',5-barbituric acid.--Re-dried ethanol (50 ml.) was placed in the usual apparatus for barbituric acid condensations, and 1.04 g. (0.045 g.-atom) of sodium was added in small pieces. When all the sodium had reacted, 1.80 g. (0.030 mole) of U. S. P. urea was added, and the mixture was stirred until it dissolved. Addition of 5.00 g. of 1-(2-phenylethyl)-4,4-dicarbethoxypiperidine and warming of the solution thus formed brought about almost immediate formation of a white solid. After 15 hr. of stirring at reflux, the mixture was filtered to remove the solid product. This product was washed thoroughly with hot re-dried ethanol. After it had dried to a constant weight of 5.1 g. (quantitative yield) in a vacuum desiccator, the salt was suspended in 100 ml. of re-dried ethanol and was treated with 8.40 ml. of 3.47 molar ethanolic hydrogen chloride.

After being stirred magnetically for 1 hr., the mixture was heated to boiling and filtered. No product could be isolated from the filtrate, but it was found that the residue weighed 5.4 g. (theoretical weight of product and sodium chloride is 6.2 g.). Treatment of the solid with hot water did not dissolve it or remove much of the sodium chloride. Attempts to remove the product from the sodium chloride by extraction with organic solvents revealed that it was not appreciably soluble in ethanol, acetone, methanol, ether, or ethyl acetate. Continuous extraction of the mixture with ethanol in a Sohxlet apparatus resulted in little separation of the two components. The solubilities of the spiroaminobarbituric acid and of sodium chloride in ethanol apparently were nearly the same. When the mixture was treated with warm dimethylformamide, the product dissolved readily, whereas the sodium chloride did not dissolve; thus, the sodium chloride could be separated by filtration. Refrigeration of the dimethylformamide solution did not yield any solid, but treatment with an equal volume of water caused the product to precipitate as a finely divided solid, which was washed with cold water and cold ethanol. The solid melted at 273-274°.

A second preparation was run using the same quantities of reactants and the same procedure up to the acidification step. In this preparation the acidification mixture was filtered while cold, and the solid residue was treated with 25 ml. of warm (40°) dimethylformamide. After removal of the

sodium chloride by filtration 25 ml. of water was added to the solution. Following a 1 hr. period of refrigeration, the crystallization mixture was filtered and the solid product was washed with cold water and cold ethanol. When it was dry the spiro-1'-(2-phenylethyl)-piperidine-4',5-barbituric acid weighed 3.7 g. (82 per cent) and melted at 273-274.5°. It dissolved readily in 5 per cent sodium hydroxide but not in saturated sodium bicarbonate. It seemed to dissolve to some extent when heated with 5 per cent hydrochloric acid but was almost insoluble in this acid when cold.

An analytical sample, m. p. 274-275°, was prepared by dissolving 1.0 g. of the product in 10 ml. of dimethylformamide and adding 10 ml. of 95 per cent ethanol to the resulting solution. Refrigeration of the solution formed by this procedure resulted in almost quantitative recovery of the pure product.

Calculated for $C_{16}H_{19}N_3O_3$: C, 63.77; H, 6.35; N, 13.95.

Found: C, 63.95; H, 6.33; N, 13.85.

As a test of the stability of this spirobarbituric acid in aqueous base, a 0.301 g. (0.00100 mole) sample weighed on an analytical balance was dissolved in 1.97 ml. of 1.014 molar sodium hydroxide solution (0.00200 mole) and 5.00 ml. of distilled water. The solution was allowed to stand at room temperature for exactly five minutes and was then neutralized by addition of 3.73 ml. of 0.536 molar hydrochloric acid (0.00200 mole). Vigorous stirring of the neutralized solution

while it was cooled in an ice bath brought about precipitation of 0.240 g. of a white solid, m. p. 228-230°, which was insoluble in water and in all organic solvents with which it was tested. On the basis of its physical properties and method of formation, this compound was identified as 1-(2-phenylethyl)-4-carboxypiperidine-4-carbonylureide. If this structure is assumed to be correct, the yield of the hydrolysis was 75 per cent.

No solvent for recrystallizing this compound could be found. An analytical sample, m. p. 228-250°, was prepared by dissolving a carefully weighed sample in exactly two equivalents of standard sodium hydroxide and reprecipitating the compound by adding two equivalents of standard hydrochloric acid.

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

Found: C, 60.37; H, 6.08; N, 13.21.

Attempted preparation of spiropiperidine-4',5-barbituric acid.--Freshly cut sodium (0.69 g., 0.030 g.-atom) was added to 20 ml. of re-dried ethanol in the apparatus previously described for condensation reactions. After the reaction of the sodium was complete, 1.20 g. (0.020 mole) of U. S. P. urea and 2.29 g. (0.010 mole) of 4,4-dicarbethoxypiperidine were added, and the mixture was stirred in a bath at 45° for 0.5 hr. Since no reaction was apparent, the bath temperature was raised to 70° over a period of 1.3 hr. and was maintained at this temperature for 1.0 hr. more. Only a faint

cloudiness had developed so the mixture was allowed to stand overnight at room temperature and was then refluxed for 2 hr. During the reflux period a small amount of white solid separated from the reaction solution. This solid was so finely divided that attempts to remove it by filtration after the mixture was cooled were only partially successful. The failure of the expected amount of barbiturate salt to precipitate indicated that this salt might be appreciably soluble in ethanol. To test this possibility, ether was added to the ethanol solution. As a result, a gelatinous precipitate formed which appeared to consist largely of sodium ethoxide. All of the solid obtained from the reaction (0.90 g.) was stirred magnetically in 25 ml. of re-dried ethanol with 2.0 g. (0.00600 mole of acid) of IRC-50 ion exchange resin. Only a trace of solid could be recovered from this mixture after removal of the resin. Extractions of the resin with various solvents did not result in any recovery of the desired product.

Attempted preparation of spiro-1'-methylpiperidine-4',5-(1-methylbarbituric acid) from 1-methyl-4,4-dicarbethoxy-piperidine.--In an Erlenmeyer flask fitted with a reflux condenser containing a calcium chloride drying tube, 50 ml. of re-dried ethanol was stirred by a magnetic stirring bar while 1.04 g. (0.045 g.-atom) of sodium cut into small pieces was added through the condenser. When no sodium remained unreacted, the condenser was removed briefly to permit the

addition of 2.22 g. (0.030 mole) of methylurea (Eastman white label) and 3.95 g. (0.015 mole) of 1-methyl-4,4-dicarbethoxypiperidine. The funnel used for these additions was rinsed with 10 ml. of re-dried ethanol before the condenser was replaced. Heating the reaction mixture to reflux with continued magnetic stirring caused a slight cloudiness to develop, but after 18 hr. at reflux the amount of solid had not noticeably increased. Cooling the reaction mixture to room temperature produced no further changes, so the reaction flask was tightly stoppered and allowed to stand in a refrigerator at 0° for 24 hr. There was no evidence of any solid product so the solution was evaporated to approximately one-third of its original volume and was refrigerated for five days. When this treatment failed to produce any product, it was concluded that the attempted condensation had failed, and the mixture was not examined further.

Experiments on the Physical and Chemical Properties of Some Barbituric Acids

Infrared Spectra

All infrared spectra were obtained using a Perkin-Elmer Model 137 Infracord double-beam spectrophotometer with sodium chloride optics. The spectra of liquid samples were recorded using thin films of the liquids between sodium chloride plates. Nujol mulls of solid samples were examined in the same manner as liquids. The sharp 6.24 micron absorption band of polystyrene was recorded on all spectra to serve

as a reference point for calibration of wavelengths. It was assumed that the correction determined at this wavelength applied over the entire 2.5-15.0 micron range of the spectra. The infrared spectra of new compounds prepared in this investigation are reproduced in Appendix A.

Ultraviolet Spectra

A Beckman Model DK-1 double-beam recording spectrophotometer was used in recording ultraviolet spectra and in making other ultraviolet measurements. The use of this instrument in measuring hydrolysis rates for barbituric acid derivatives is discussed in the following section. Descriptions of the ultraviolet spectra of some spiroaminobarbituric acids are included in the section concerning kinetic studies on these compounds.[1]

Kinetic Studies

The procedure for measuring the hydrolysis rates of barbituric acid derivatives was patterned after that developed by Daugherty (12). The modifications of Daugherty's procedure which were used by Starnes (58) were followed as closely as possible, since it was desired to use Starnes' data with those obtained in this investigation to calculate activation energies[2] for the hydrolysis of the common

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[1]See below, p. 75.

[2]See below, p. 74.

(58)Starnes, op. cit., p. 122.

barbiturates studied. In addition, a method was developed for obtaining approximate rate constants for the very rapid hydrolysis of some spiroaminobarbituric acids. This method and the results obtained are discussed at the end of this section.

Materials and apparatus.--All distilled water used in the kinetic studies was boiled for approximately 30 minutes before use. A stream of nitrogen was bubbled through the water while it cooled to prevent absorption of carbon dioxide. The boiled water was stored in a large bottle connected by polyethylene tubing to a 25 ml. burette with a two-way stopcock so that the burette could be refilled by siphoning. The air vent of the water bottle and the burette were protected from atmospheric carbon dioxide by soda lime tubes.

Standard sodium hydroxide was prepared by dissolving Baker reagent grade pellets in enough water to form a 50 per cent solution. After filtration to remove sodium carbonate, the concentrated solution was diluted with boiled distilled water to give a carbonate-free solution which was approximately 1.1 molar. The basic solution was stored in a one gallon polyethylene bottle which was connected to a 50 ml. burette by an arrangement similar to that used for the distilled water. The base was standardized by titration against accurately weighed samples of potassium acid phthalate (primary standard grade) which had been dried in an oven at 115°

for three days. Phenolphthalein was used as the indicator in these titrations.

The stock solutions of barbituric acids, which were 1.00×10^{-3} in barbituric acid, were prepared by dissolving samples of purified commercial materials, weighed to an accuracy of $\pm 2 \times 10^{-4}$g., in the proper amounts of boiled distilled water in volumetric flasks. Extrapolation of the kinetic plots to zero time gave values for initial optical density of mixtures of these solutions with strong base in good agreement with the values found by Starnes (59).

The optical densities of the various hydrolysis solutions were measured on the Beckman DK-1 spectrophotometer using a thermostatted cell compartment set at the temperature of the hydrolysis being studied. The temperature of the cell compartment, as measured by a thermometer in the thermometer well, fluctuated from the mean temperature. The observed variations were plus and minus approximately 1.4° at mean temperatures of 34.7° and 50.4°. The fluctuation followed cyclic patterns, with periods at 34.7° and 50.4° of approximately 18 and 10 minutes, respectively. It appeared likely that the temperature changes of samples in the cell compartment were not nearly as large as those measured in the thermometer well, due to the high heat capacity of water and the relatively small temperature difference between the cell and its surroundings. This assumption was substantiated by the

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(59)Starnes, op. cit., p. 123.

fact that no cyclic deviations were noted in the kinetic plots for reactions run in the thermostatted cell compartment.

Water baths maintained at the reaction temperature of 34.7° and 50.4° showed temperature fluctuations of less than 0.1°. The 50.4° bath was equipped with a device for maintaining automatically a constant water level. Evaporation from the 34.7° bath was sufficiently slow for its level to be maintained satisfactorily by periodic additions of tap water while no kinetic runs were in progress.

Procedures.--For each of the kinetic runs at 50.4° and for the 34.7° runs on 5-methyl-5-phenylbarbituric and 5,5-diallylbarbituric acids, 10.00 ml. of barbituric acid stock solution was pipetted into a screw cap polyethylene bottle. At the same time 90.00 ml. of 1.082 molar sodium hydroxide was prepared from appropriate amounts of the standard base and distilled water and was placed in a separate screw-cap polyethylene bottle.[1] The tightly capped bottles were placed in a bath at the reaction temperature for at least one hour while the spectrophotometer was allowed to warm up, and the thermostatted cell compartment was allowed to equilibrate at the reaction temperature. Just before a run was to start, the zero and one hundred per cent controls of the spectrophotometer were reset at the wavelength to be used in the run using distilled water in both the sample and reference cells.

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[1]For a few runs, equivalent smaller quantities of stock solution and sodium hydroxide, e. g. 3.00 ml. of stock solution and 27.00 ml. of base, were used.

After this adjustment the sample cell was dried by allowing nitrogen to blow into it. The solutions in the bath were then rapidly mixed, and the time of mixing was recorded as zero time. For the fastest reactions, a stopwatch was started at the time of mixing and was used to measure elapsed time throughout the run. An aliquot of the reaction mixture was placed in the sample cell immediately after mixing and the cell was replaced in the cell compartment, while the reaction mixture was tightly capped and returned to the bath. The reaction mixture was allowed to stand in the cell compartment for 10-15 minutes to reach thermal equilibrium before any kinetic data were taken. Following the period of standing, periodic measurements of the optical density were made without disturbing the sample.

Many of the reactions run at 34.7° were too slow to be followed by the technique described above. In these cases, the reactants were mixed as already described and the mixtures were returned to the constant temperature bath. Aliquots were taken periodically and their optical densities determined using distilled water in the reference cell. The zero and one hundred per cent controls were reset before each reading, using distilled water in both cells. When a number of points were taken in succession, there was little or no drift of the controls. However, it was found that very thorough rinsing of the sample cell was necessary to remove all traces of the samples. Checking the one hundred per cent

reading was a convenient method for determining whether or not the sample cell was completely clean.

It was found that the optical densities of the reaction mixtures reached constant values which varied somewhat for the different mixtures. Therefore, the measurements of optical density were continued for all reactions until constant values were obtained. These constant values for each reaction were then subtracted from all optical densities measured for that particular reaction mixture to give corrected optical densities.

Calculations.--Plotting the logarithms of the corrected optical densities against time gave good straight line plots for the reactions studied. There was some scattering of points for runs in which aliquots were taken from reaction mixtures in the constant temperature bath, so the method of least squares was used to determine the slopes of the lines in these cases. The points for reactions run in the cell compartment scattered only slightly. When the plots for these reactions were spot checked by the method of least squares, it was found that the slopes determined graphically agreed with those calculated by least squares within one per cent. Since the reaction mixtures contained a large excess of base, the rate constants calculated from the kinetic plots were actually pseudo-first-order (60).

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(60)A. A. Frost and R. G. Pearson, Kinetics and Mechanism, John Wiley and Sons, New York, N. Y., 1958, p. 11.

The kinetic methods outlined above were used to determine rate constants for the hydrolysis of eight 5,5-disubstituted-barbituric acids at 34.7° and 50.4°. In addition Starnes (61) measured hydrolysis rate constants for the same compounds at 65.0°. The available rate constants for the hydrolyses of these compounds were used to calculate activation energies and entropies for the hydrolysis reactions. For these calculations, plots of log k *vs.* 1/T were used with the equation (62):

$$2.303 \log k = -E_a/Rt + 2.303 \log (kT/h) + Sa/R$$

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 °K;
R is the gas constant in cal deg^{-1} $mole^{-1}$;
h is Planck's constant in erg sec $molecule^{-1}$;
k is the Boltzmann constant in erg deg^{-1} $molecule^{-1}$.

In the calculation of E_a, the term log (kT/h) was assumed to be constant, and the values obtained are thus Arrhenius activation energies. In the calculation of S_a, a value of 323°K was used for T, and k was the rate constant at this temperature.

Measurements on spiroaminobarbituric acids.--Efforts were made to extend the kinetic method described above to the hydrolysis of some spiroaminobarbituric acids. As a part of

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(61)Starnes, *op. cit.*, p. 139.

(62)F. Daniels and R. A. Alberty, *Physical Chemistry*, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 352.

these efforts, a 1.00 x 10^{-3} molar solution of spiro-1'-methylpiperidine-4',5-barbituric acid[1] was prepared by placing an accurately weighed sample of the acid in a volumetric flask and adding distilled water up to the mark. Similar solutions of spiro-1'-(2-phenylethyl)-piperidine-4',5-barbituric acid in distilled water or in 95 per cent ethanol could not be prepared because of the low solubility of the acid in these solvents.

The ultraviolet spectrum of the stock solution of spiro-1'-methylpiperidine-4',5-barbituric acid was determined 48 hr. after its preparation. The spectrum was identical with that of a distilled water blank in the 300-225 millimicron region. However, when a few small crystals of the solid acid were added to the sample cell the spectrum showed a strong maximum at 240 millimicrons. The optical density of this absorption decreased noticeably during examination of the solution. The spectrum of a freshly prepared saturated solution of spiro-1'-(2-phenylethyl)-piperidine-4',5-barbituric acid in ethanol showed no maximum from 300 millimicrons to a cut-off at 228-225 millimicrons.

Ultraviolet spectra of the two spirobarbituric acids just discussed were obtained in strong base by a technique similar to that used with the methyl compound in neutral solution. Both the sample and reference cells were filled with

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[1]An analytically pure sample of this compound was furnished by G. C. Allen.

1.0 molar sodium hydroxide, and the controls of the spectrophotometer were adjusted. Very small samples of the desired spiroaminobarbituric acid were then added to the sample cell, and the mixtures were stirred well. Rapid scanning of the 300-225 millimicron region showed no maxima, but slower scanning of the 230-220 millimicron region showed maxima at approximately 223 millimicrons for both compounds. In order to study wavelengths below 225 millimicrons, it was necessary to operate the spectrophotometer at very high sensitivity with a correspondingly high noise level. The cutoff for the sodium hydroxide solution was approximately 221 millimicrons at the highest sensitivity used. The positions of the absorption maxima shown by these spiroaminobarbituric acids coincided with a rapid drop in the reference energy of the spectrophotometer. It could not be determined with certainty whether the observed maxima were due to sample absorption or to a peculiarity of the instrument. Since the sodium hydroxide solutions gave a normal cut-off it seemed likely that the observed maxima were valid.

The technique used for obtaining spectra of the spiroaminobarbituric acids could be used to estimate their hydrolysis rates in strong base. In such experiments the sample and reference cells were filled with 0.9738 molar sodium hydroxide solution and were placed in the thermostatted cell compartment at 34.7°. The zero and one hundred per cent controls were set at a wavelength of 230 millimicrons, selected

because of the very high noise level at the absorption maximum. Approximately 0.1 mg. of the sample was then added to the sample cell and the mixture was stirred well. It was noted that samples of the methyl compound dissolved instantly after being added to the cell, while samples of the 2-phenylethyl derivative were slower in dissolving. The sample solution was allowed to stand for one minute, after which the recorder was started and allowed to run for 15 minutes. The chart speed was checked by use of a stopwatch so that values of optical density and time could be read directly from the chart. Plotting the logarithm of the optical density vs. time gave reasonably good kinetic plots in all runs. Rate constants of 1420×10^{-4} min.$^{-1}$ and 1410×10^{-4} min.$^{-1}$ were obtained for the hydrolysis of spiro-1'-methylpiperidine-4',5-barbituric acid. In three hydrolysis runs on spiro-1'-(2-phenylethyl)-piperidine-4',5-barbituric acid, rate constants of 940×10^{-4} min.$^{-1}$, 1120×10^{-4} min.$^{-1}$ and 1260×10^{-4} min.$^{-1}$ were obtained.

CHAPTER IV

DISCUSSION OF RESULTS

Attempted syntheses of spiroaminobarbituric acids *via* the corresponding spirotetrahydropyran derivatives were unproductive. An attempt to synthesize spiro-1'-*m*-tolylpiperidine by this method yielded a product which was not identical with the product from a base catalyzed condensation of 1-*m*-tolyl-4,4-dicarbethoxypiperidine with urea. This result was in agreement with a report that "spiro-1'-phenylpiperidine-4',5-barbituric acids" prepared by the two methods were also different (7).

The preparation of spirotetrahydropyran-4',5-(1-methylbarbituric acid) was considerably more difficult than that of the unsubstituted acid. Although the synthesis of this compound was studied in some detail, it was obtained only in low yield. The difficulty of preparing spirobarbituric acids containing substituents on the pyrimidine nitrogen was further demonstrated by the failure of 1-methyl-4,4-dicarbethoxypiperidine to form a product with methylurea. In other recent work in these laboratories, it was found that no spiroaminobarbituric acids were isolable in reactions of some 1-substituted-4,4-dicarbethoxypiperidines with substituted thioureas when sodium ethoxide or potassium *tert*-butoxide

were used as condensing agents (63).

It seems likely that the inability of 1-substituted barbituric acids to "protect" themselves against nucleophilic attack by forming a dianion may account for the low yields obtained in attempts to prepare them. A similarity may be seen between the base-catalyzed reaction of a diester with a substituted urea and base-catalyzed self-condensation of esters. The low yields in some condensations of esters containing only one alpha-hydrogen have been attributed to inability of the product to form an enolate ion (64). It should be pointed out that although such esters usually do not undergo condensation in the presence of sodium ethoxide, many of them undergo self-condensation in good yield when a very strong base such as triphenylmethyl sodium is employed as the condensing agent. It may be that triphenylmethyl sodium could be employed advantageously in barbiturate condensations involving substituted ureas.

The yields obtained in the cleavage of sulfonamides by hydrogen bromide and phenol in acetic acid were, in many cases, superior to those which had been reported (27, 65) for the cleavage of sulfonamides of non-aromatic amines. It was

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

(64)C. R. Hauser and B. E. Hudson, Jr., in Organic Reactions, Vol. I, John Wiley and Sons, New York, N. Y., 1942, p. 269.

(65)D. I. Weisblat, B. J. Magerlein, and D. R. Myers, U. S. Patent 2,562,222 (July 31, 1951); C. A., 46, 3093 (1952)

found that the yields of piperidine hydrobromide in cleavages of 1-arylsulfonylpiperidines invariably increased with increased reaction time or with increased temperature. However, the best yield of 4,4-dicarbethoxypiperidine from the benzenesulfonamide was obtained in a reaction which was allowed to proceed for 10 hr. at room temperature. Preparations involving longer reaction times or higher temperatures resulted in lower yields. Hydrolytic attack on the ester groups by water formed in the reductive cleavage may be one cause of this reversal. However, in a cleavage of 1-benzenesulfonyl-4,4-dicarboxypiperidine it was found that 4,4-dicarboxypiperidine hydrobromide had a low solubility in the acetic acid-hydrogen bromide reagent. Since none of this hydrobromide precipitated from the ester cleavage mixtures, it seemed likely that simple ester hydrolysis was not occurring to any great extent.

It was shown that piperidine and some of its derivatives can be alkylated in good yield by treatment with aliphatic aldehydes followed by hydrogenation over Adams platinum catalyst. No alkylations by aromatic aldehydes were studied during this investigation, but a number of amine preparations involving reductive alkylations by benzaldehyde have been reported (66), and the preparation of 1-benzylpiperidine derivatives by reductive alkylation seems feasible. The introduction of a secondary alkyl group onto the piperi-

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(66)Emerson, op. cit., pp. 175 ff.

dine ring was achieved in similar yield through reductive alkylation by a ketone and through reaction of piperidine with a secondary alkyl halide in the presence of potassium carbonate. Although the experimental results did not indicate a definite choice between the two methods of alkylation studied, the use of secondary alkyl halides seems somewhat more promising. The yield obtained in a single reaction of piperidine with isopropyl bromide was slightly higher than the best yield obtained in three reductive alkylations of piperidine by acetone.

The use of standard solutions of hydrogen chloride for acidification of salts of spiroaminobarbituric acids was a significant improvement over acidification by ion-exchange resins. The hydrogen chloride acidification is rapid and eliminates any possibility of loss of product by absorption on or reaction with a resin. The discovery that some spiroaminobarbituric acids which are virtually insoluble in most common solvents dissolve readily in dimethylformamide provided a convenient method for purification of such acids.

The preparation of some spiroaminobarbituric acids by methods developed during this work was the culmination of the synthetic portion of the investigation. Although it is not known whether these compounds will have useful physiological properties, development of a method for their preparation will make it possible for them to be studied in some detail. In addition, the synthesis of the previously

unreported 4,4-dicarbethoxypiperidine makes available a compound which can be used as an intermediate in producing a wide variety of piperidine derivatives.

The very rapid hydrolysis of spiroaminobarbituric acids suggested that they should have little hypnotic activity. However, a sample of spiro-1'-(2-phenylethyl)-piperidine-4',5-barbituric acid was submitted for physiological screening by an independent laboratory to determine whether it might have use as a drug.

The insolubility of spiro-1'-benzyl- and spiro-1'-(2-phenylethyl)-piperidine-4',5-barbiturate acids in water and their low solubilities in ethanol suggest that these compounds are not zwitterionic. This is confirmed by the ultraviolet spectrum of the phenylethyl compound in saturated ethanol solution. This spectrum did not exhibit an absorption maximum near 240 millimicrons where the monoanions of spirobarbituric acids usually absorb. In contrast, the ultraviolet spectrum of spiro-1'-methylpiperidine-4',5-barbituric acid showed a strong maximum at 240 millimicrons. The ultraviolet spectrum and the water solubility of the methyl compound provide good evidence that it exists largely in the zwitterionic form.

The difference between the zwitterionic structure of spiro-1'-methylpiperidine-4',5-barbituric acid and the apparently non-ionic structure of the analogous 2-phenylethyl compound would have to be due to a fairly large difference in

basicities of the piperidine nitrogen atoms in the two compounds. It seems very unlikely that the change from one substituent to the other should affect the acidities of the barbituric acid hydrogen atoms appreciably. No data on the basicity of 1-(2-phenylethyl)-piperidine were available. However, basicity data were available for 1-methylpiperidine (pK_b= 4.0) (67); for methylamine (pK= 3.4), dimethylamine (pK_b= 3.4), and trimethylamine (pK_b= 4.2) (68); and for 2-phenylethylamine (pK_b= 4.2) and N-methyl-2-phenylethylamine (pK_b= 3.9) (69). The differences in basicity between analogous methyl- and 2-phenylethyl amines and between 1-methylpiperidine and trimethylamine were used to estimate a value of 4.4 for the pK_b of 1-(2-phenylethyl)-piperidine. All these data on amine basicities led to a prediction that spiro-1'-(2-phenylethyl)-piperidine-4',5-barbituric acid should exist in the inner salt form to nearly the same extent as its 1'-methyl analog. It may be that the phenylethyl compound exists in the ionic form but is insoluble in water because of its high molecular weight. If this is the case, the failure of this compound to show barbiturate monoanion absportion would have to be ascribed to its very low solubility in ethanol.

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(67)W. F. K. Wynne-Jones and G. Salomon, Trans. Faraday Soc., 34, 1321 (1938).

(68)H. C. Brown, H. Bartholomay, Jr. and M. P. Taylor, J. Am. Chem. Soc., 66, 435 (1944).

(69)W. H. Carothers, C. F. Bickford, and G. J. Hurwutz, J. Am. Chem. Soc., 49, 2908 (1927).

The kinetic data obtained in the hydrolyses of several common 5,5-disubstituted-barbituric acids are presented in Table 2. For purposes of comparison, rate constants obtained by Starnes (61) for the hydrolysis of these compounds at 65° are included in the table. There was one significant difference between the method used by Starnes in calculating rate constants and the method used in the present study. Starnes corrected observed optical densities by subtracting the optical density of sodium hydroxide solution having the same strength as that used for the hydrolysis experiments. It was found in this study that the optical densities of the hydrolysis mixtures reached constant values which will be referred to as infinity optical densities. These infinity optical densities were significantly higher in many cases than the optical density of the base used. The correction factor for each hydrolysis run was the infinity optical density of that particular mixture. The use of these individual factors resulted in somewhat larger values for the rate constants than would have been obtained using a constant correction factor. The differences in infinity optical densities may have been due to differences in the amount of carbon dioxide absorbed by the various mixtures during exposure to the atmosphere, although longer runs did not necessarily have larger infinity optical densities.

In many cases, the rate constants calculated using infinity optical densities and constants calculated using a

Table 2. Pseudo-first-order Rate Constants for the Hydrolysis of Barbituric Acids in 0.9738 Molar Sodium Hydroxide

Barbituric Acid[a]	$k(min^{-1}) \times 10^4$		
	34.7°C.	50.4°C.	65.0°C.[b]
5-allyl-5-isobutyl-	3.3 3.4	11.9 12.9	37.6 39.2
5-ethyl-5-isoamyl-	3.5 3.9	14.0 14.7	40.3 41.1
5-ethyl-5-n-butyl-	3.5 3.5	14.4 14.6	45.4 46.4
5-ethyl-5-phenyl-	8.9 8.9	32.3 35.5	87.9 88.3
5-allyl-5-n-butyl-	10.6 10.9	43.6 44.7	131 138
5-allyl-5-phenyl-	21.6 22.1	77.0 79.3	194 195
5,5-diallyl-	34.0 36.5	125 130	377 384
5-methyl-5-phenyl-	343 350	1024 1040	2310 2410
spiro-1'-methyl-piperidine-4',5-	1410[c] 1420		
spiro-1'-(2-phenyl-ethyl)-piperidine-4',5-	940[c] 1121 1260		

[a]Acid concentration 1.00×10^{-4} molar in every case except the last two in which the concentrations were not known with certainty.

[b]Values obtained by Starnes (61).

[c]Values obtained by the method described on p. 79.

constant correction factor did not differ by more than the differences between constants obtained in duplicate runs. In other cases the differences between the two methods were more significant. Although there was no strong experimental reason for a choice between the two methods in the reactions studied, the use of infinity optical densities seems preferable on theoretical grounds. It provides for the fact that the amounts of absorbing impurities such as carbonate ion are not necessarily constant. It also can be used in cases in which there is a second, non-reacting chromophore in the barbituric acid molecule.

The rate constants obtained at 34.7° and 50.4° are in reasonable agreement with the 65.0° values. There is an inversion of the order of stabilities for 5-ethyl-5-isoamyl and 5-ethyl-5-n-butylbarbituric acids in going from 65.0° to 34.7°, but the difference in stability of the two acids is quite small at each temperature. The observed order of stabilities for the 5,5-disubstituted-barbituric acids studied has been discussed by Starnes (70) in terms of the steric and electronic effects of the various substituents.

The rate constants observed for the hydrolysis of spiro-1'-methyl- and spiro-1'-(2-phenylethyl)-piperidine-4',5-barbituric acids correspond quite well with the values obtained by Daugherty (12) for the hydrolysis of spirotetrahydropyran-4',5- and spirocyclohexane-1',5-barbituric acids.

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(70)Starnes, op. cit., p. 144.

In all cases the spiro acids hydrolyzed 300-500 times faster than barbital. The observed difference between the average hydrolysis rates of the two spiroaminobarbituric acids is about the same as the difference between the high and low values for the hydrolysis rate constant of the phenylethyl compound. The wide spread of values obtained for this latter rate constant apparently was due to variations in the rate of solution of the acid in strong base. Since the solutions were quite dilute, the presence of even a very small amount of slowly dissolving solid acid during the rate measurements would have a large effect on the observed value of the rate constant. In comparison, the methyl compound dissolved instantly in strong base and the two rate constants measured for it were in excellent agreement with each other. While the rate constants for the hydrolysis of the spiroaminobarbituric acids were not precise, their agreement with the hydrolysis rate constants of other spirobarbiturates provides evidence that the spiro structures are correct.

The reactivity of spirobarbituric acids in basic hydrolysis is probably due in large part to low steric hindrance around the two reactive carbonyl groups. However, the ultraviolet spectra suggest that a second factor may be involved. In all the 5,5-disubstituted-barbituric acids studied, the dianions showed ultraviolet absorption maxima around 255 millimicrons. In contrast, the spirobarbituric acids absorb

at considerably shorter wavelengths.[1] Such a shift to shorter wavelength is often associated with a decrease in the conjugation of the chromophore (71). In the particular case under discussion, it seems likely that the presence of the spiro ring fixes the bond angles of the spiro carbon atom in such a way as to prevent the atoms of the barbituric acid ring from being completely co-planar and that there is a resulting loss in resonance stabilization of the barbiturate dianion. Such a loss in resonance stabilization would result in a low energy of activation for the hydrolysis reaction and would account for both the very rapid hydrolysis and unusual ultraviolet spectra of the spirobarbiturates.

The limitations of the method used in measuring the hydrolysis rates of the spiroaminobarbituric acids are obvious. However, this method is convenient for determining approximate rate constants in very fast hydrolyses. A possible variation of the method for increased accuracy would involve introducing accurately measured small amounts of stock solutions directly into the cell by use of a micropipette or a syringe.

The hydrolysis rate constants for the barbiturates

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[1]See above p. 75 for ultraviolet data of two spiroaminobarbituric acids and reference (12) for data on other spirobarbiturates.

(71)R. L. Shriner, R. C. Fuson, and D. Y. Curtin, The Systematic Identification of Organic Compounds, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 180.

listed in Table 2 were used as described earlier[1] to calculate activation energies and activation entropies for the hydrolysis reactions. The results are presented in Table 3.

Table 3. Activation Energies and Entropies for the Hydrolysis of Barbituric Acids in 0.9738 Molar Sodium Hydroxide

Barbituric Acid	Ea (Kcal $mole^{-1}$)	Sa (cal $mole^{-1}$ $degree^{-1}$)
5-ethyl-5-n-butyl-	17.7	-25.3
5-allyl-5-n-butyl-	17.4	-23.9
5-allyl-5-isobutyl-	16.7	-28.7
5-ethyl-5-isoamyl-	16.4	-29.3
5,5-diallyl-	16.2	-25.5
5-ethyl-5-phenyl-	15.7	-29.8
5-allyl-5-phenyl-	15.0	-30.2
5-methyl-5-phenyl-	13.2	-30.8

The values obtained for the activation energies are rather closely grouped except for that of the very rapid hydrolysis of 5-methyl-5-phenylbarbituric acid. It may be seen that in general the activation energies are lower for the more reactive compounds, although this agreement is not at all exact. The activation energy for 5-allyl-5-n-butylbarbituric acid is surprisingly high in view of its fairly rapid hydrolysis while the value for 5-ethyl-5-isoamylbarbituric acid is unexpectedly low. These variations are not sufficiently

[1]See above, p. 74.

significant, however, to permit any generalizations as to their cause. The values obtained provide evidence that all of the hydrolyses studied probably proceed by the same mechanism.

The activation entropies all have large negative values characteristic of reactions between similarly charged ions (72). The entropy data definitely indicate that the hydrolysis of the barbituric acids studied proceeds by an attack of hydroxide ion on the barbiturate dianion or monoanion. Attack of hydroxide ion on the monoanion would be expected to occur at the carbonyl group not adjacent to the point of ionization. Thus there would actually be a spreading of negative charge in the transition state, and the activation entropy should have a positive or small negative value. This argument supports a mechanism of reaction involving reaction of hydroxide with barbiturate dianion. However, if there is a very rapid equilibrium between the two possible monoanions, the negative charge would be effectively spread over the entire ring, and the entropy effect would probably be similar to that for the dianion.

Although the rates of hydrolysis of the three acids containing phenyl groups vary considerably, these three acids have the lowest activation energies and the largest negative activation entropies of all the compounds studied. Aspelund and co-workers (10) have noted that phenylbarbituric acids

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(72)Frost and Pearson, op. cit., pp. 132 ff.

are less stable to hydrolysis than barbituric acids containing saturated groups of similar size. The activation energy and entropy data suggest that the phenyl group increases the hydrolysis rate by lowering the energy of the transition state through some direct interaction of the aromatic ring with the portion of the molecule undergoing reaction. The high negative entropy of activation for the phenyl compounds supports this possibility since a particular spatial arrangement of atoms would be required for such an interaction.

CHAPTER V

RECOMMENDATIONS

Application of the synthetic methods described in this thesis to dialkanolamines other than diethanolamine should produce spiropiperidinebarbituric acids with substituents on the carbon atoms of the piperidine ring. It would also be of interest to develop a satisfactory method for the condensation of substituted ureas with 4,4-dicarbethoxypiperidines. Combination of these two approaches would provide a wide variety of spiroaminobarbituric acids.

It is recommended that additional kinetic experiments on the hydrolysis of barbituric acids be carried out. In particular the dependence of the reaction rate on base concentration should be studied to clarify the nature of the barbiturate species undergoing reaction. Kinetic data at two other base concentrations with constant ionic strength should provide sufficient information to permit definite conclusions regarding the mechanism of basic hydrolysis.

Since an empirical correlation between the rates of basic hydrolysis and physiological activity has been noted, it would be of interest to obtain kinetic data for the hydrolysis of barbituric acids in buffer solutions having pH values near those of human body fluids. Under such conditions,

the mechanism of hydrolysis would undoubtedly be different from the mechanism for strongly basic solutions, and the effects of structure on the hydrolysis rate might also be different. In any case, such experiments would provide additional information on the chemistry of barbituric acids and might also assist in understanding the physiological action of these compounds.

APPENDIX

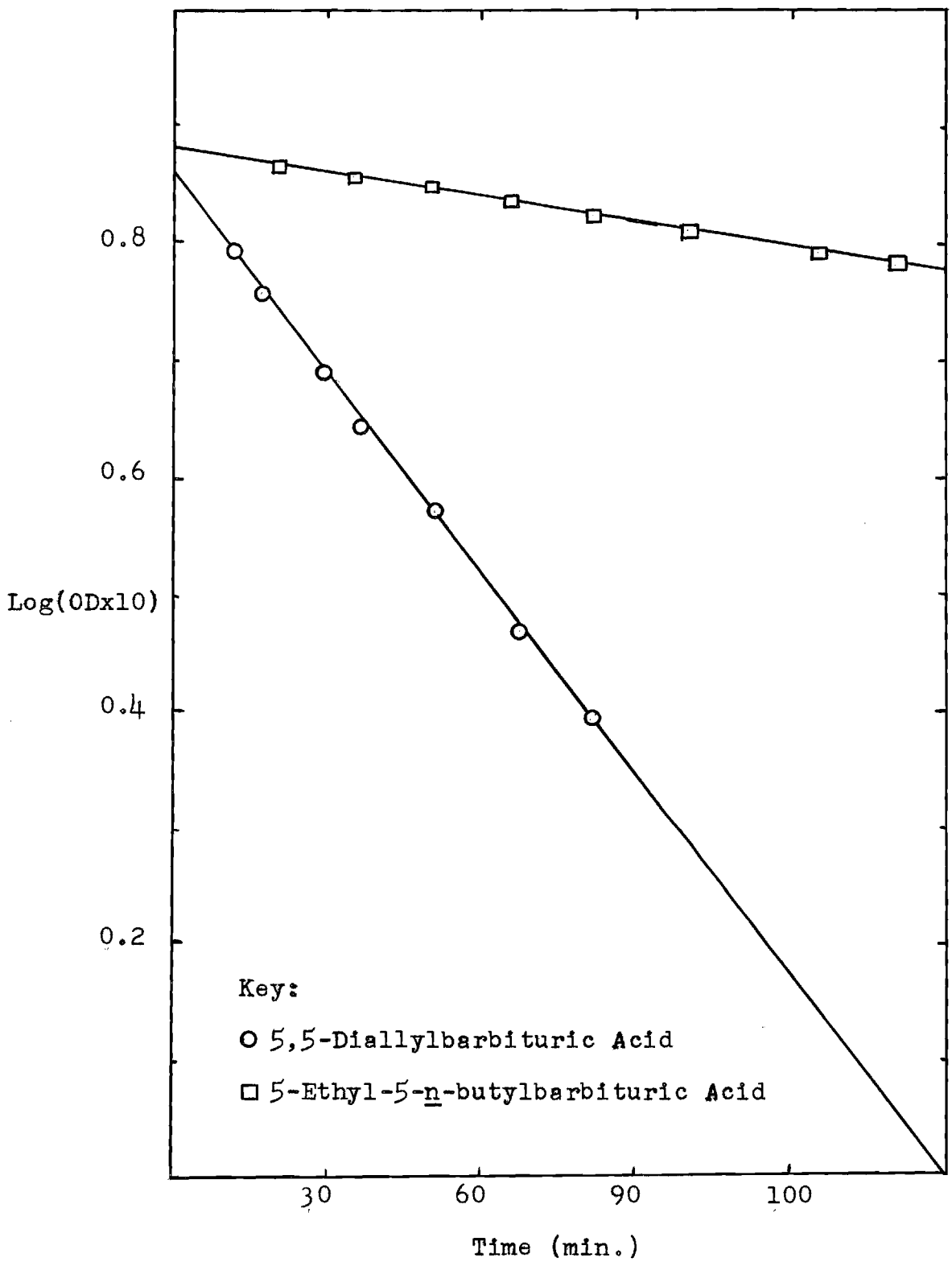

Figure 7. Sample Kinetic Plots for the Hydrolysis of Barbituric Acids at 50.4°.

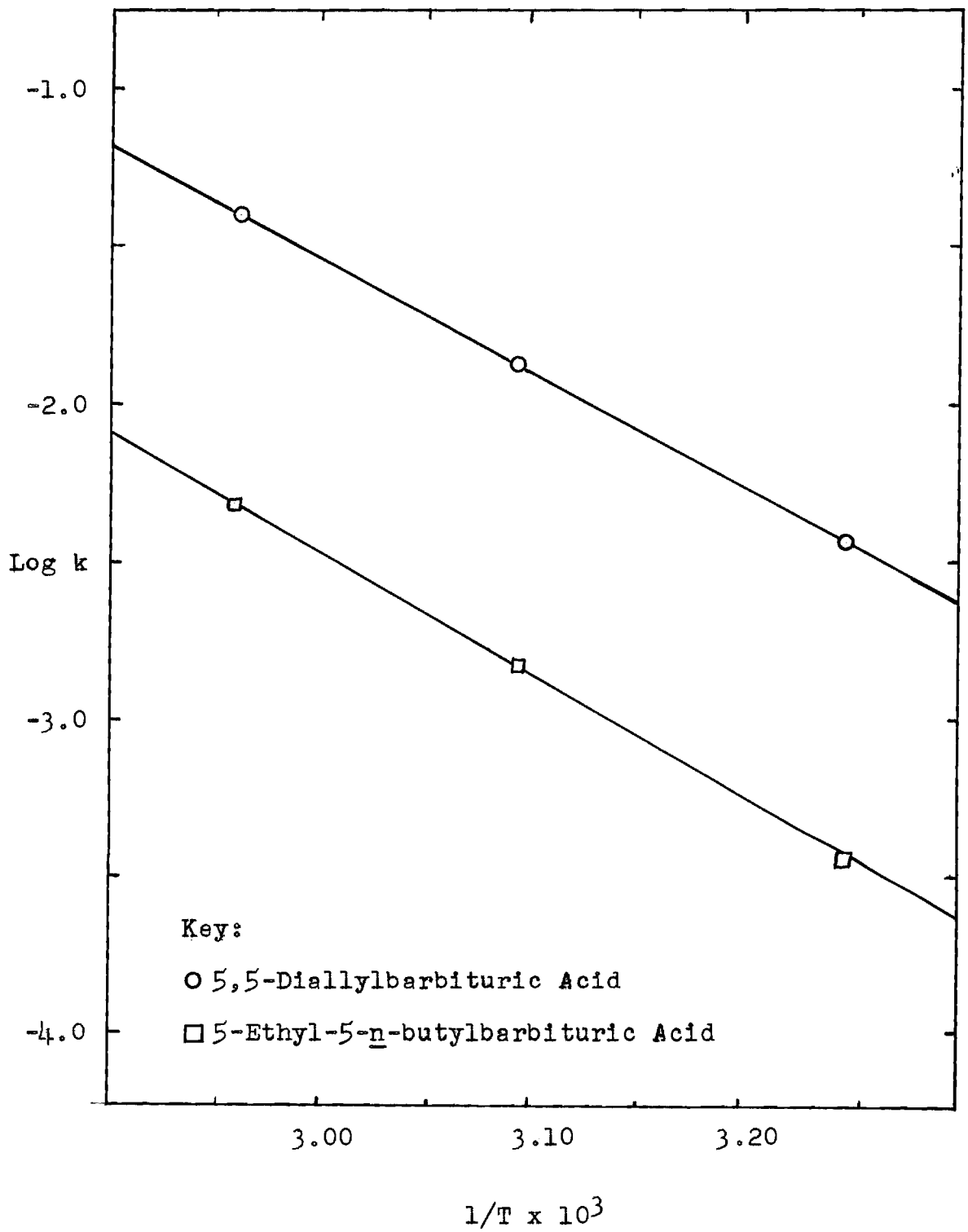

Figure 8. Sample Plots of Log k vs. 1/T for the Hydrolysis of Barbituric Acids.

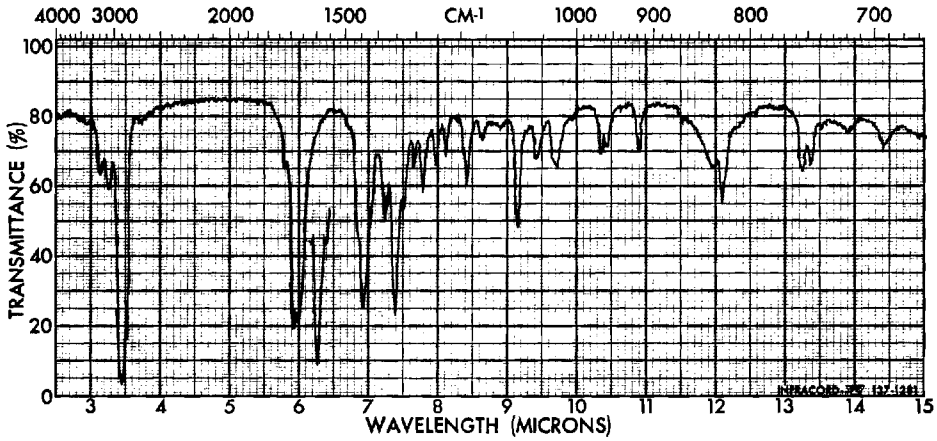

Figure 9. Infrared Spectrum of Spirotetrahydropyran-4,5-(1-methyl-barbituric Acid) (Nujol Mull).

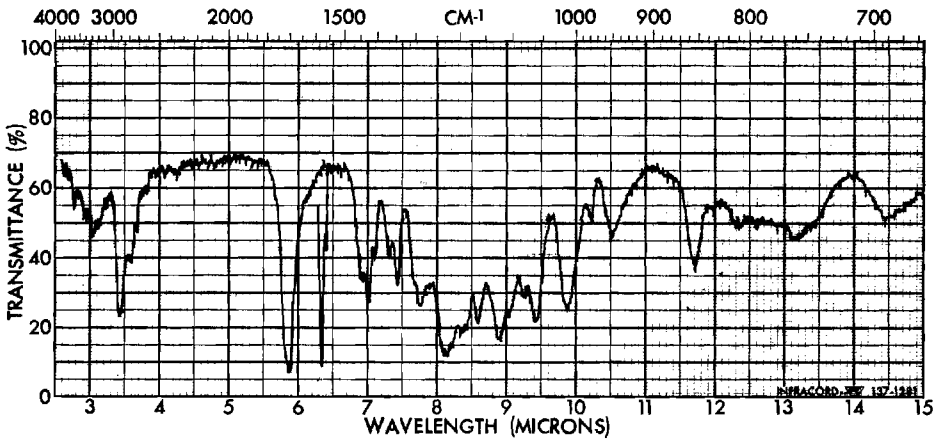

Figure 10. Infrared Spectrum of 4,4-Dicarbethoxypiperidine (Liquid Film).

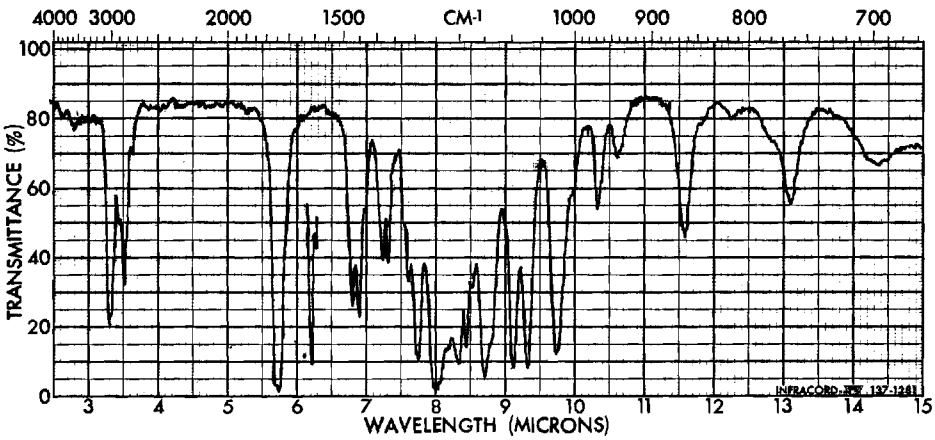

Figure 11. Infrared Spectrum of 1-Methyl-4,4-dicarbethoxypiperidine (Liquid Film).

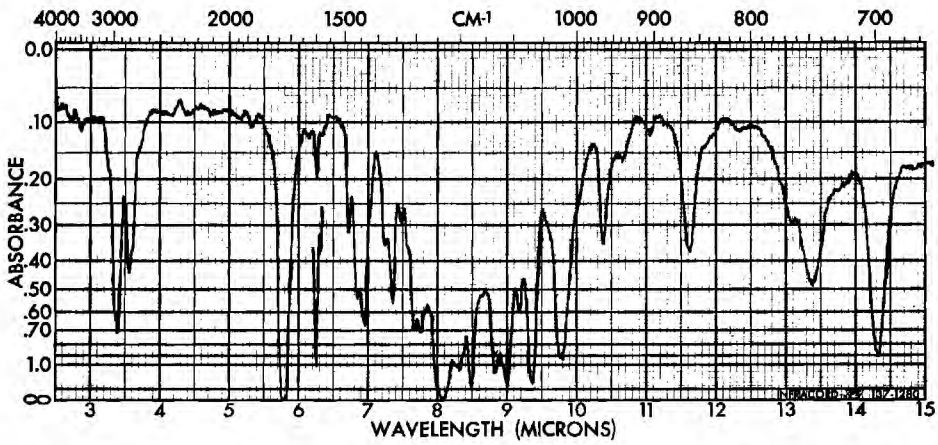

Figure 12. Infrared Spectrum of 1-(2-phenylethyl)-4,4-dicarbethoxy-piperidine (Liquid Film).

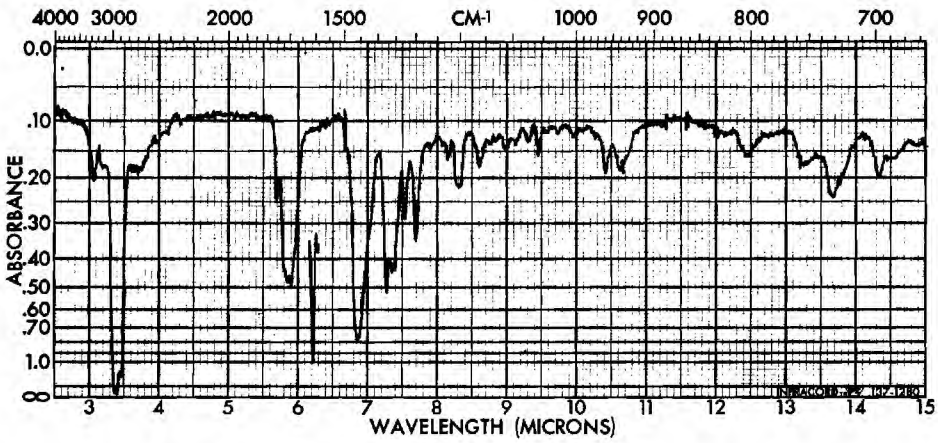

Figure 13. Infrared Spectrum of Spiro-1'-benzylpiperidine-4', 5-barbituric Acid (Nujol Mull).

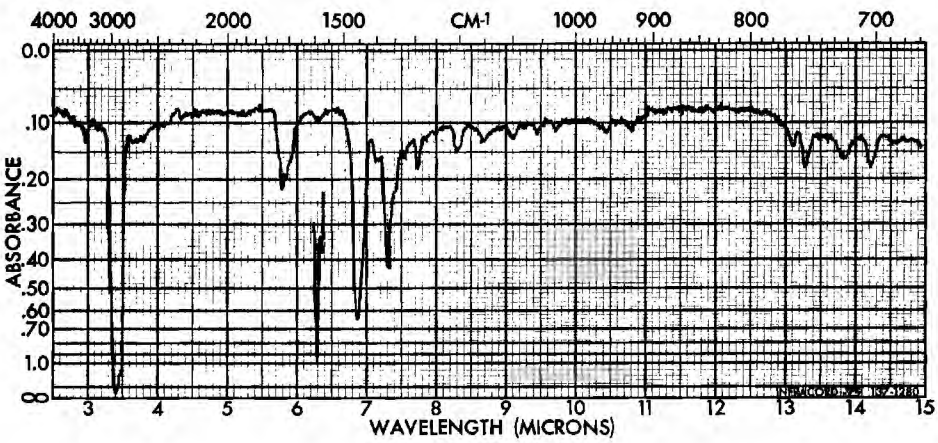

Figure 14. Infrared Spectrum of Spiro-1'-(2-phenylethyl)-piperidine-4', 5-barbituric Acid (Nujol Mull).

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VITA

VITA

John G. Thweatt was born November 21, 1932, in Norton, Virginia to Gladys McGee Thweatt and the late John Griffin Thweatt. He attended public schools in Forsyth, Georgia and was graduated with honor from Mary Persons High School in Forsyth in 1949. He attended Georgia Institute of Technology, Atlanta, Georgia, where he received the B. S. degree in Chemistry with honor in 1953. While in college he was a member of the Naval ROTC and upon graduation accepted a commission in the U. S. Navy. While serving on active duty in the Navy he was married to the former Charlotte Goss of Rome, Georgia, and they are now the parents of a daughter, Sandra Lynn, born in December, 1959.

After a period of four years of active duty he enrolled in the Graduate Division, School of Chemistry, at Georgia Institute of Technology. During a portion of his enrollment at Georgia Tech he held a teaching assistantship in the Chemistry Department and was Training Officer of a Naval Reserve Ships Supply Officer Division. He was awarded an Eastman Kodak Fellowship for research during the year 1959-1960.

He is a member of Sigma Xi, Phi Eta Sigma, Phi Lambda Upsilon, and the American Chemical Society, Northeast Tennessee Section. He is presently employed as a research chemist with the Tennessee Eastman Company, Kingsport, Tennessee.