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A STUDY OF METHYLENEDISULFONIC ACID AND ITS DERIVATIVES.*

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Chemotherapeutic studies of the barbital and sulfonal groups of hypnotics have established definitely a relationship between their chemical structure and their therapeutic action.

The two drugs, barbital and sulfonal, may be considered the precursors of two important series of hypnotics, the methylenedisulfonic acid group and the malonylureide group. The chemotherapeutic concepts of these compounds undoubtedly link their physiological activities with their characteristic molecular structures, and it would seem rational to conceive of a compound having a structure which included the hypnophore groups of both of these series. The basic structure of such a barbituric acid sulfonal hybrid would be $\text{C}-\text{SO}_2\text{NH}\cdot\text{CO}\cdot\text{NH}\cdot\text{SO}_2$, and the

relation of methylenedisulfonic acid to it would be analogous to the relation of malonic acid to the barbiturates.

A survey of the literature revealed only one attempt to prepare such a hybrid compound, and this was unsuccessful and offered little encouragement to future investigators. However, the synthesis and pharmacological study of such a series of compounds would add much information to our present knowledge of the chemotherapy of hypnotics, and might result in the production of some valuable therapeutic agents. The work reported here has as its object the study of the problems involved in the preparation of derivatives of methylenedisulfonic acid and as its hope the preparation of the hybrid methylenedisulfonureide structure shown above.

EXPERIMENTAL.

The basic compound methylenedisulfonic acid has been prepared by Schroeter (1) who obtained it as its barium salt in yields of 15 per cent and by Backer (2) who obtained it as the potassium salt in yields of 85 per cent.

* Scientific Section, A. P. H. A., Dallas meeting, 1936.

¹ Abstracted, in part, from a thesis submitted by John C. Bauer to the Faculty of the Graduate School of the University of Maryland in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Preparation of Potassium Methylenedisulfonate (2).—One mol. (85 Gm.) of methylenechloride was bombed for two hours with 400 Gm. of potassium sulfite dissolved in 350 cc. of water at a temperature of 150° to 160° C. and a pressure of about 20 atmospheres. Constant stirring is essential. The reaction product, which was completely free of methylenechloride, consisted of a large quantity of crystalline material and an aqueous solution. The crystals were dissolved in the aqueous solution by boiling and filtered while hot. The potassium methylenedisulfonate, which is soluble 4 parts in 100 of cold water, immediately began to crystallize out in the filtering flask, and when cold the filtrate yielded a large quantity of the compound. The product was recrystallized from hot water, and 75 per cent of the theoretical yield of the potassium salt was obtained as large prismatic crystals. The compound was dried and identified by converting it into the barium salt.

| | Wt. of Sample. | Wt. of $\text{H}_2\text{C}(\text{SO}_3)_2\text{Ba}\cdot 2\text{H}_2\text{O}$. |
|--|----------------|--|
| Calculated for $\text{H}_2\text{C}(\text{SO}_3)_2\text{K}$ | 4.6 Gm. | 6.4 Gm. |
| Observed | 4.6 Gm. | 6.3 Gm. |

The barium salt was dried *in vacuo* at 105° C. to eliminate all of its water of hydration and identified by analyzing for barium.

| | Wt. of Sample. | Wt. of Barium. | Per Cent of Barium. |
|---|----------------|----------------|---------------------|
| Calculated for $\text{H}_2\text{C}(\text{SO}_3)_2\text{Ba}$ | 0.3873 Gm. | 0.1709 Gm. | 44.13 |
| Observed | 0.3873 Gm. | 0.1721 Gm. | 44.43 |

Preparation of Barium Methylenedisulfonate.—A hot concentrated solution of barium chloride was added to a hot solution of potassium methylenedisulfonate which had been acidified with hydrochloric acid. Barium methylenedisulfonate separated from the cooled reaction mixture as small white crystalline plates, having a silvery luster; 363 Gm. of potassium methylenedisulfonate yielded 489 Gm. of barium methylenedisulfonate. A portion of this barium salt was purified by recrystallization from hot water. The resulting product was insoluble in chloroform, alcohol and cold water, and only sparingly soluble in hot water. Thus it is apparent that the water solubility of this compound parallels barium sulfate more closely than it does the barium alkylmonosulfonates. When heated strongly the crystals fused, charred with the evolution of sulfur dioxide, and left a white residue of barium sulfate.

A sample of the purified barium methylenedisulfonate was dried at 105° C. and placed in a desiccator over sulfuric acid to determine the loss of water of hydration. Drying was continued for thirty days and weighings were made at five-day intervals.

| | Wt. of Sample. | Loss in Wt. | Per Cent Loss in Wt. |
|--|----------------|-------------|----------------------|
| Calculated for $\text{H}_2\text{C}(\text{SO}_3)_2\text{Ba}\cdot 2\text{H}_2\text{O}$ giving $\text{H}_2\text{C}(\text{SO}_3)_2\text{Ba}\cdot \text{H}_2\text{O}$ | 0.7159 Gm. | 0.0371 Gm. | 5.18 |
| Observed | 0.7159 Gm. | 0.0365 Gm. | 5.10 |

This dried material was analyzed for barium.

| | Wt. of Sample. | Wt. of Barium. | Per Cent of Barium. |
|---|----------------|----------------|---------------------|
| Calculated for $\text{H}_2\text{C}(\text{SO}_3)_2\text{Ba}\cdot \text{H}_2\text{O}$ | 0.0493 Gm. | 0.0206 Gm. | 41.78 |
| Observed | 0.0493 Gm. | 0.0206 Gm. | 41.78 |

Drying at 120° C. also removes one molecule of water of hydration and, as shown by a preceding analysis, at 105° C. *in vacuo* the unhydrated salt is formed.

Preparation of Methylenedisulfonic Acid.—While boiling and stirring, 500 Gm. of barium methylenedisulfonate were added in 5- to 10-Gm. portions to 141 Gm. of concentrated sulfuric acid dissolved in 2 liters of water. After adding all of the barium salt, boiling and stirring were continued until 2 drops of the filtered reaction mixture when diluted to 10 cc. and treated with barium chloride gave no precipitate of barium sulfate. The barium sulfate was removed from the reaction mixture by suction filtration and the filtrate, which contained the methylenedisul-

onic acid, was concentrated until the temperature of the boiling solution reached 132° C. Drying was completed by heating in an oven for fourteen hours at 153° C. under reduced pressure. Upon cooling, 253 Gm. of a white crystalline product were obtained. Based on the assumption that it was 95 per cent pure (1), the yield was 94.6 per cent.

This is essentially the method described by Schroeter (1) with certain modifications which in our hands permitted us to obtain greater yields of a cleaner product.

Methylenedisulfonic acid is extremely hygroscopic and if the crystalline substance is exposed to air it rapidly absorbs water and dissolves.

Preparation of Methylenedisulfonylchloride.—Phosphorus pentachloride was added in small portions to 250 Gm. of the crystalline methylenedisulfonic acid during a period of 50 hours. The stratified solid reaction mixture was warmed sufficiently to start the reaction. After the initial heating required to start the reaction, no heat was applied and the phosphorus pentachloride was added in small portions to prevent overheating. When no more solid methylenedisulfonic acid remained, the excess phosphorus pentachloride was removed by filtering the reaction mixture through glass wool. Further purification was effected by fractional distillation. The phosphorus oxychloride was removed by distilling on a steam-bath under 150-mm. pressure. The residual heavy oil was distilled under 15-mm. pressure and the methylenedisulfonylchloride was collected in the fraction which distilled between 120° C. and 140° C.; 256 Gm. of the product were collected which corresponds to a yield of 89 per cent. When purified by repeated fractionations a clear, colorless, heavy oil was obtained, b. p. 135° to 138° C. at 15-mm. pressure, sp. gr. 1.824 at 19° C. The oil is not decomposed by cold water or alcohol, but rapidly forms methylenedisulfonic acid when warmed with these substances.

The procedure, which is also a modification of the method described by Schroeter (3), permitted us to obtain larger yields.

An effort was made to prepare this compound using sulfonylchloride in place of phosphorus pentachloride, but no methylenedisulfonylchloride could be isolated from the reaction mixture.

Alkylesters of methylenedisulfonic acid could not be prepared from methylenedisulfonylchloride and an aliphatic alcohol, but were obtained by refluxing the dry silver salt of methylenedisulfonic acid with an anhydrous benzene solution of an alkyl iodide (4).

Preparation of Silver Methylenedisulfonate (3).—A solution of methylenedisulfonic acid was prepared by decomposing 237 Gm. of barium methylenedisulfonate with 36 cc. of concentrated sulfuric acid dissolved in 360 cc. of water. The reaction mixture was filtered and the filtrate, which contained the methylenedisulfonic acid, was added to a slight excess of freshly precipitated silver carbonate. When there was no further evolution of carbon dioxide the reaction mixture was filtered, concentrated to a small volume, cooled and diluted with an equal volume of alcohol. The silver methylenedisulfonate precipitated out as a white crystalline product which was dried in a vacuum desiccator and finally in an oven at 104° C. A yield of 227 Gm. (91 per cent) was obtained.

Preparation of the Dimethylester of Methylenedisulfonic Acid (4).—19.5 Gm. of the finely powdered silver salt which had been dried at 104° C. for 20 hours was treated with 10 cc. of methyl iodide which had been dried over calcium chloride and freed of iodine by shaking with mercury. Ten cc. of anhydrous benzene were added and the mixture refluxed for 3 days. Additional benzene and small volumes of methyl iodide were added occasionally. The reaction mixture was filtered hot and the residue extracted with several portions of hot benzene. The filtrate and extractions were united and concentrated. When cool 7.8 Gm. (76.5 per cent) of the dimethylester were obtained, m. p. 47.5° C.

The procedure for preparing the dimethylester as described here varies considerably from that described by Schroeter (3), however, we obtained excellent results using the above method.

As reported by Schroeter (3), the compound was found to be unstable when warmed with water or alcohol. Water decomposes it into the free acid and alcohol, and warm alcohol produces the free acid and ether. When boiled in alcoholic solution, good yields of ether are obtained. This property of the compound to form ether when boiled with alcohol is not in accord with the usual behavior of the esters of alkylcarboxylic acids, but is quite analogous to the behavior of sulfuric acid in the preparation of diethylether, and probably explains why the alkylesters of methylenedisulfonic acid cannot be prepared from methylenedisulfonylchloride. In confirmation of an observation made by Schroeter (4), we noted that the free acid was efficient in the synthesis of the higher molecular weight ethers and succeeded in obtaining a large yield of di-isoamylether by distilling a mixture of the acid and isoamyl alcohol.

The methylene hydrogen atoms of the alkylesters can be replaced by sodium or potassium but not as readily as in the case of the aryler. Contrary to the findings of others (5), we were unable to alkylate the methylene carbon atom.

Arylesters of Methylenedisulfonic Acid.—The diphenylester was prepared by Schroeter (5) by refluxing a toluene solution of methylenedisulfonylchloride and phenol for 20 hours. Recently Raschig and Prahl (6) described a more efficient method of preparing this compound.

Preparation of the Diphenylester of Methylenedisulfonic Acid (6).—21.3 Gm. of methylenedisulfonylchloride were dissolved in 100 cc. of benzene and cooled to 0° C. While shaking and cooling this solution was added to a solution containing 17.8 Gm. of phenol and 30 cc. of pyridine in 100 cc. of benzene which had also been cooled to 0° C. The reaction mixture was decomposed with ice and shaken out with dilute hydrochloric acid and water. When all of the pyridine had been removed, the diphenylester was shaken out into a warm 2*N* sodium hydroxide solution. The diphenylester can be isolated from this alkaline solution in a number of ways. We diluted the alkaline extract, acidified with hydrochloric acid and obtained 21 Gm. of the diphenylester of methylenedisulfonic acid which, after recrystallization from alcohol, melted at 82° to 83° C. (uncorrected) (5).

This compound is soluble in ether, benzene, chloroform, hot alcohol and hot carbontetrachloride. The methylene hydrogen atoms can be replaced by sodium or potassium by adding the alkali metal to an anhydrous toluene or alcoholic solution of the ester, or by treating it with aqueous sodium or potassium hydroxide. These metal derivatives are insoluble in benzene and alcohol and they undergo reactions analogous to the alkali metal derivatives of the malonic acid esters.

Amides of Methylenedisulfonic Acid.—Similarly to the esters, the aryl and alkyl amides must be prepared by different methods.

Preparation of the Dianilide of Methylenedisulfonic Acid (3).—0.1 mol of methylenedisulfonylchloride was dissolved in 100 cc. of benzene and cooled in an ice-water mixture. While stirring, a cold benzene solution containing 0.4 mol of aniline was added slowly, and when the reaction had subsided, the mixture was refluxed for 30 minutes. The methylenedisulfonanilide was shaken out into warm 2*N* sodium hydroxide as the *N*-sodium derivative. After washing with several portions of benzene, the aqueous solution was acidified with concentrated hydrochloric acid and the precipitated anilide was collected on a suction filter. By crystallization from hot alcohol 25 Gm. (77% of the theoretical yield) of anilide, m. p. 192° to 193° C., were obtained. The compound was analyzed for sulfur.

| | Wt. of Sample. | Wt. of BaSO ₄ . | Per Cent of Sulfur. |
|--|----------------|----------------------------|---------------------|
| Calculated for H ₂ C- (SO ₂ NH.C ₆ H ₅) ₂ | 0.1372 Gm. | 0.1963 Gm. | 19.65 |
| Observed | 0.1372 Gm. | 0.1963 Gm. | 19.65 |

As previously reported by others (3) amides of secondary amines containing at least one aryl group were prepared by the same method in good yields.

The amide hydrogen atoms of the secondary amides of methylenedisulfonic acid impart acidic properties to the compounds so that they react with aqueous sodium and potassium hydroxide to form soluble products. These hydrogen atoms can also be replaced by metallic sodium or potassium in alcoholic or benzene medium. The tertiary amides of methylenedisulfonic acid contain no amide hydrogen, but the hydrogen atoms attached to the methylene carbon atom can be replaced by metallic sodium or potassium when the reaction is carried out in anhydrous alcohol or benzene. The reactions with the alkali metals are of importance in the synthesis of derivatives of these compounds.

Preparation of Methylenedisulfonamide (3).—A cold benzene solution containing 33 Gm. of the diphenylester of methylenedisulfonic acid was saturated with dry ammonia gas. Toward the end of the reaction two immiscible liquid layers formed. This mixture was transferred to a bomb and heated for four hours between 140° and 145° C. A benzene insoluble crystalline material was obtained which, when recrystallized from hot water, yielded 12.7 Gm. (73 per cent of the theoretical yield) of the diamide, m. p. 232° to 233° C. (uncorrected).

The compound is insoluble in alcohol, benzene, glacial acetic acid and water, but forms water-soluble *N*-sodium and potassium compounds analogous to the secondary aryl- and alkyl-amides of methylenedisulfonic acid.

Other efforts to prepare this amide include the following methods: The passing of dry ammonia into an anhydrous benzene solution of methylenedisulfonylchloride, the passing of dry ammonia into an anhydrous benzene solution of methylenedisulfonylchloride and pyridine, the slow distillation of a solution of ammonium methylenedisulfonate in glacial acetic acid, and the passing of dry ammonia into an anhydrous solution of methylenedisulfonic acid dimethylester in benzene. Reactions occurred in all of these experiments and the products were isolated and identified by analysis but in no case was any amide obtained. The method in which ammonia was permitted to react with the dimethylester of the acid was interesting, since it yielded the ammonium salt of methylenedisulfonic acid and methylamine. This result is quite contrary to the reaction which occurs when the methylesters of carboxylic acids are treated in this manner but directly analogous to the reaction which occurs when dimethylsulfate is treated with ammonia under the above conditions.

Alkyl substitution of the methylene hydrogen atoms: Schroeter was the first to effect this synthesis using a method similar to the malonic acid synthesis (3). He reported that when the monosodium derivative of methylenedisulfonic acid diphenylester, $\text{Na.HC(SO}_2\text{OC}_6\text{H}_5)_2$, made by treating a solution of methylenedisulfonic acid diphenylester in anhydrous benzene with sodium, was treated with an alkyl iodide or sulfate, the monoalkyl derivative was formed $\text{R.HC(SO}_2\text{OC}_6\text{H}_5)_2$. The second hydrogen atom of this monoalkylated compound likewise can be replaced by sodium, but the subsequent addition of alkyl iodide or alkyl sulfate may or may not yield the dialkyl derivative. If the first radical introduced is a methyl group, the second radical readily attached itself to the methylene carbon atom, but if the first radical introduced is not a methyl group, then disubstitution cannot be effected except when the resulting compound would be methylalkylmethylenedisulfonic acid diphenylester. Thus the dialkyl derivatives which have been syn-

thesized are limited to methyl ethyl, methyl propyl, etc., and the only symmetrical dialkyl derivative which has been made is dimethyl.

We prepared the alkyl substituted derivatives by a modification of the Schroeter method and succeeded in obtaining the dimethylmethylenedisulfonic acid diphenylester by a single treatment with sodium followed by complete alkylation.

Preparation of Dimethylmethylenedisulfonic Acid Diphenylester.—Five Gm. of powdered sodium were prepared in 50 cc. of anhydrous toluene, and when the mixture had cooled, 0.1 mol. (33 Gm.) of the diphenylester of methylenedisulfonic acid dissolved in 250 cc. of anhydrous toluene was added. When the evolution of hydrogen became sluggish, the temperature of the reaction mixture was raised to boiling and refluxing was continued until practically all of the sodium had disappeared. The disodium derivative separated as a white voluminous precipitate. After cooling, 0.3 mol. (14.5 cc.) of freshly distilled dimethylsulfate was added and the temperature of the mixture was raised gradually to boiling. After refluxing for ninety minutes the voluminous precipitate was replaced by a heavy precipitate of sodium methylsulfate which was filtered off. The toluene was removed from the filtrate by distillation under reduced pressure and the residual impure diphenylester of dimethylmethylenedisulfonic acid was purified by crystallization from hot carbontetrachloride. The method yielded 26 Gm. (73%) of the dimethyl derivative, m. p. 95° to 97° C. (uncorrected). The compound was analyzed for sulfur.

| | Wt. of Sample. | Wt. of BaSO ₄ . | Per Cent of Sulfur. |
|---|----------------|----------------------------|---------------------|
| Calculated for (CH ₃) ₂ C-(SO ₂ OC ₆ H ₅) ₂ | 0.2761 Gm. | 0.3614 Gm. | 17.98 |
| Observed | 0.2761 Gm. | 0.3622 Gm. | 18.02 |

The tertiary arylamides of methylenedisulfonic acid, such as the diethyl-anilide, may also be used for alkylation of the methylene carbon atom, but the primary and secondary anilides form *N*-alkyl derivatives as the result of the greater activity of the amido hydrogen atoms. Schroeter attempted to overcome this difficulty by acetylating the amide groups but found that the resulting compounds were not acted upon by metallic sodium. Schroeter (3) prepared the dialkyl derivatives of these anilides using anhydrous benzene as the solvent and reported that the intermediate sodium derivatives were readily decomposed by alcohol. However, we had greater success in the preparation of these compounds when anhydrous alcohol was added to the reaction mixture, but in no case did we obtain yields as great as those reported by Schroeter.

Preparation of Monomethylmethylenedisulfonethylanilide.—Two and five hundredths Gm. of sodium were permitted to react with 50 cc. of anhydrous alcohol which had been freshly distilled from sodium. Thirty-four Gm. of methylenedisulfonethylanilide dissolved in 150 cc. of anhydrous benzene were added and the reaction mixture was refluxed for one hour. Upon the addition of 10 cc. of methyl iodide a reaction took place immediately as evidenced by the precipitation of sodium iodide. After refluxing for thirty minutes the sodium iodide was removed by filtration and by shaking out the filtrate with water. The benzene and alcohol were distilled off and the residue when cooled yielded 28.5 Gm. of crude product which when purified by crystallization from alcohol yielded 25.5 Gm. (72 per cent) of pure monomethylmethylenedisulfonethylanilide, m. p. 150° to 152° C. (uncorrected) (3).

Preparation of Dimethylmethylenedisulfonethylanilide.—One and one-tenth Gm. of sodium were permitted to react with 5 to 7 cc. of anhydrous alcohol which had been freshly distilled from sodium. Heat was required to complete this reaction. 12.5 Gm. of monomethylmethylenedisulfonethylanilide dissolved in 150 cc. to 200 cc. of anhydrous benzene were added and the reaction mixture was refluxed for one hour during which time a flocculent precipitate was formed; 8 cc. of methyl iodide were added and refluxing continued for three hours. The solvent was removed by distillation and evaporation and the thick sirupy residue cooled. When this was stirred with cold alcohol it set to a crystalline mass which, after washing on a suction filter with

hot water followed by cold alcohol, yielded 12.5 Gm. of crude product, m. p. 114° to 118° C. When purified by fractional crystallization from hot alcohol a yield of 4.5 Gm. (35 per cent) of dimethylmethylenedisulfonethylanilide was obtained, m. p. 132° C. (uncorrected) (3) and 4.2 Gm. of the unchanged monomethyl derivative, m. p. 150° to 152° C. (uncorrected) were recovered.

The use of the alkylesters of methylenedisulfonic acid in the synthesis of these alkyl substituted derivatives is of questionable value. Schroeter (3) reported that the methylene hydrogen atoms of the alkylesters could be replaced by sodium but that the reaction was sluggish, and he succeeded in preparing the monoethyl derivative in poor yields by this means. All attempts in our laboratory to prepare either the mono- or dialkyl substituted derivatives produced either no yields of the expected product or quantities too small to be used for synthetic studies.

Hydrolysis of the Arylestere or Anilides of Methylenedisulfonic Acid and Its Alkyl Derivatives.—These compounds are characterized by their stability in boiling acids and alkalis. To saponify methylenedisulfonic acid diphenylester or its monoalkyl derivative it is necessary to boil them for four hours with 50 per cent potassium hydroxide solution (5) or to heat them four hours at 140° to 145° C. with a 4 per cent alcoholic solution of ammonia. Prolonged boiling with either sodium ethoxide or nitric acid is ineffective (5). The diethylanilides of these compounds are likewise very stable to alkalis but are hydrolyzed by heating for two hours with 15 per cent hydrochloric acid at 150° to 200° C. (5). The dialkyl derivatives are even more resistant to hydrolysis and cannot be split by acids, but when heated for seven hours with an alcoholic solution of sodium methylate at 150° to 160° C. one of the sulfonic acid groups is split off leaving the salts of the corresponding dialkyl- α hydroxy-methylmonosulfonic acids (5).

If our hope of preparing a hybrid sulfonal barbital compound was to be realized, it was essential to find a method of hydrolyzing these dialkylated arylestere or anilides and a number of experiments were directed toward hydrolyzing the diphenylester of dimethylmethylenedisulfonic acid.

Method 1—3.0 Gm. of the compound when bombed with dry ammonia in anhydrous ether for three hours at 150° C. under a pressure of 21 atmospheres yielded none of the desired ammonium salt, and 2.8 Gm. of the original ester were recovered and identified.

Method 2—1 Gm. of the compound when fused for four hours with 10 Gm. of urea yielded none of the desired ammonium salt or ureide, and 0.81 Gm. of the original ester was recovered and identified.

Method 3—1.5 Gm. of the compound when refluxed for three hours with 2 Gm. of aluminum chloride in carbondisulfide yielded none of the desired aluminum salt, and 1.3 Gm. of the original ester were recovered and identified.

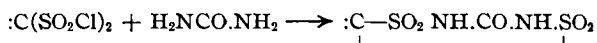
Method 4—Experiment 3 was repeated substituting 30 cc. of concentrated hydrochloric acid for the carbondisulfide but again the original ester was recovered quantitatively and identified.

Method 5—3.5 Gm. of the compound, when bombed for four hours under 10 atmospheres of pressure with 38.8 Gm. of potassium sulfite and 10 Gm. of potassium hydroxide in 200 cc. of water, yielded none of the desired potassium salt, however, the original ester could not be identified in the reaction product.

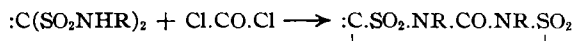
Recently Schroeter reported (7) that when 3.56 Gm. of the dialkylated diphenylester was bombed for fourteen hours at 210° C. with an equimolar quantity of barium hydroxide in alcoholic solution it yielded 0.2 Gm. of the desired barium salt $(\text{CH}_3)_2\text{C}(\text{SO}_3)_2\text{Ba}$, and 4.1 Gm. of the dialkylated diethylanilide under similar

conditions yielded 2.3 Gm. of the desired barium salt. We were unable to hydrolyze the diethylanilide to the corresponding barium salt by this procedure.

Cyclic Ureides of Methylene-disulfonic Acid and Its Derivatives.—Two series of experiments were carried out in an effort to prepare these cyclic ureides, one in which attempts were made to condense urea with the disulfonylchloride,



and the other in which attempts were made to close the ring by treating the primary and secondary amides with phosgene,



Method 1—Twelve Gm. of anhydrous aluminum chloride, 2 Gm. of dried urea and 7.1 Gm. of methylenedisulfonylchloride in 25 cc. of anhydrous carbontetrachloride were refluxed until the calculated amount of hydrogen chloride has been given off. None of the desired ureide could be obtained from the reaction mixture and the original methylenedisulfonylchloride was recovered quantitatively as the barium salt $\text{CH}_2(\text{SO}_2)_2\text{Ba.H}_2\text{O}$, and identified by analysis.

Method 2—Method 1 was repeated substituting carbondisulfide for the carbontetrachloride but again none of the desired ureide was obtained and the methylenedisulfonylchloride was recovered quantitatively as the barium salt and identified by analysis.

Method 3—When the disulfonylchloride was heated with urea in the absence of a solvent or a condensing agent it formed a thick homogeneous mixture with the evolution of a gas and heat, but none of the desired ureide could be isolated and the original methylenedisulfonylchloride was recovered and identified as the barium salt.

Methods 4, 5, 6—Similar experiments were carried out using no condensing agent and using sodium ethoxide and sodium bicarbonate as condensing agents, but in each case none of the desired ureide was obtained and the original methylenedisulfonylchloride was recovered quantitatively as the barium salt and identified by analysis.

Method 7—0.01 mol. (3.3 Gm.) of methylenedisulfonanilide were bombed for seven hours at 100° C. with 7 cc. of a benzene solution containing 0.01 mol. of phosgene. None of the expected ureide was obtained and 3 Gm. of the original anilide were recovered and identified by the mixed melting point method.

Method 8—0.01 mol. of phosgene was permitted to react with 0.01 mol. of methylenedisulfonanilide in the presence of 0.02 mol. of pyridine in benzene solution, and although all of the original anilide could not be recovered, none of the expected ureide was obtained.

Method 9—0.01 mol. of *N,N'*-dipotassium methylenedisulfonanilide was bombed for six hours at 120° to 130° C. with 0.01 mol. of phosgene in benzene solution. Much decomposition occurred and only about one-half of the original anilide could be recovered from the reaction mixture. A few crystals of a sulfur containing organic compound were also obtained which, after washing with alcohol, melted with decomposition between 277° and 281° C. These crystals could not be identified as the cyclic ureide.

Preparation of N,N'-Dipotassium Methylene-disulfonanilide.—Four hundredths mol. (12.8 Gm.) of the anilide were refluxed for three hours with an excess of alcoholic potassium hydroxide. The cooled reaction mixture was filtered and 13.5 Gm. of the white crystalline dipotassium derivative were obtained. The product was purified by crystallization from hot dilute alcohol and identified by analysis.

| | Wt. of Sample. | Wt. of BaSO ₄ . | Per Cent of Sulfur. |
|---|----------------|----------------------------|---------------------|
| Calculated for H ₂ C- (SO ₂ NKC ₆ H ₅) ₂ | 0.1507 Gm. | 0.1748 Gm. | 15.94 |
| Observed | 0.1507 Gm. | 0.1762 Gm. | 16.05 |

DISCUSSION.

Methylene-disulfonic acid and malonic acid are not only similar in structure but they also have many properties in common. The analogy between the activity

of the methylene hydrogen atoms of these two compounds is extremely interesting and suggests the possibility of the synthesis of a series of derivatives exactly analogous to the barbiturates. Unfortunately this is not entirely possible. Alkylation of the arylestere and arylamides can be effected in a manner similar to the malonic acid synthesis, but certain differences in the properties of these two compounds defeat efforts to prepare methylenedisulfonic acid derivatives simulating the barbiturates. The alkylesters of methylenedisulfonic acid do not permit efficient alkylation and when treated with alcohol or ammonia they exhibit properties characteristic of the alkylesters of sulfuric acid. It might be stated that this similarity to sulfuric acid should be expected since the alkylmonosulfonic acids possess some of these properties. However, the insolubility of barium methylenedisulfonate and the inability to form alkylesters and amides from methylenedisulfonylchloride are certainly exceptions to the recognized properties of the alkylmonosulfonic acids.

In spite of our many unsuccessful attempts to prepare cyclic ureides of methylenedisulfonic acid we still are not convinced that these compounds cannot be made. It is our opinion that the properties of the dialkyl derivatives of the free acid might approach those of the more characteristic organic compound malonic acid, and permit the preparation of the cyclic ureide. It was this opinion that encouraged us to endeavor to prepare the free dialkylmethylenedisulfonic acids.

SUMMARY.

1. Methylenedisulfonic acid and a number of its derivatives have been prepared and studied.
2. Methods of hydrolyzing dialkylmethylenedisulfonic acid arylestere and amides have been studied.
3. A number of attempts to prepare the cyclic ureide of methylenedisulfonic acid have been made under varying conditions.

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ACORNS OF QUERCUS RUBRA.*

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Remarkably little attention has been paid to the chemical composition of the common acorn, although it can be obtained in almost unlimited quantity. Attempts have been made repeatedly to utilize the kernels as fodder for cattle, swine and poultry but, because of the tannin content, they are apparently disagreeable

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