BARBITURIC ACIDS. V. 5-SUBSTITUTED-
MERCAPTO DERIVATIVES OF
5-ISOAMYLBARBITURIC ACID

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THESIS

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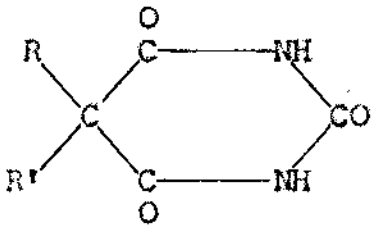
CHAPTER I

INTRODUCTION

The hypnotic activity of substituted barbituric acids has long been known. Hundreds of disubstituted barbituric acids have been prepared in order to evaluate their usefulness as sedatives or anesthetics. They may be represented by the general formula:

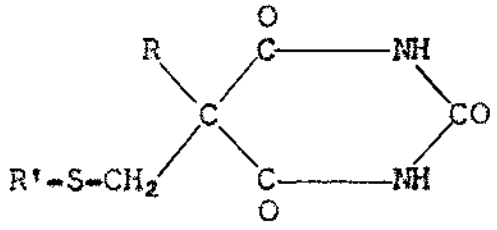


Among those in general use are barbital, 5,5-diethylbarbituric acid; phenobarbital, 5-ethyl-5-phenylbarbituric acid; amytal, 5-ethyl-5-isoamylbarbituric acid; pentobarbital, 5-ethyl-5-(1-methylbutyl)barbituric acid; and seconal, 5-allyl-5-(1-methylbutyl)barbituric acid. Phenobarbital has anticonvulsant as well as hypnotic activity. Amytal and pentobarbital act more quickly and have a shorter duration of action than either barbital or phenobarbital. Seconal acts still more quickly and for a relatively short period.

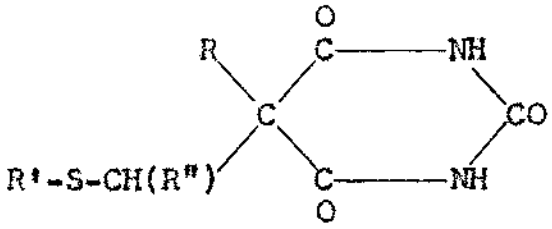
Included in the types of barbituric acids reported are a limited number containing sulfur in the carbon chain of an alkyl group attached to the barbituric acid nucleus.

L. A. Walter, L. H. Goodson, and R. J. Fosbinder have prepared compounds of four general types:

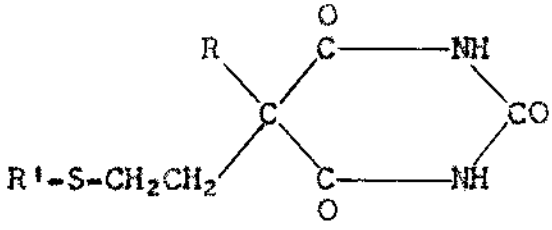
Type 1.[1]



Type 2.[2]



Type 3.[3]



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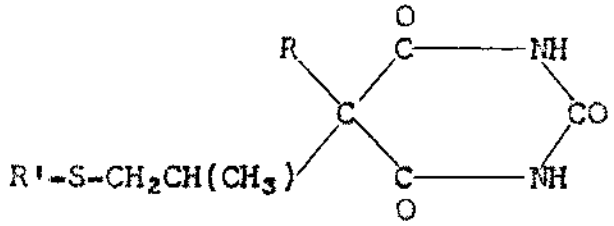
[1]L. A. Walter, L. H. Goodson, and R. J. Fosbinder, J. Am. Chem. Soc., 67, 655-657 (1945).

[2]Ibid., pp. 657-659. [3]Ibid., pp. 659-660.

Type 4.[4]



Wm. H. Hunt, Russel J. Fosbinder, and O. W. Barlow have reported that for these types, duration of hypnotic effect decreases and toxicity increases as the molecular weight increases.[5] In a comparative study of compounds represented by Type 1, and by Type 2 where R" is a methyl group, they found that Type 2 compounds produced a greater duration of activity.[6]

Ramond L. Cahen[7] has reported the anticonvulsant activity of some Type 1 and Type 3 compounds. Most were effective only in doses sufficient to produce ataxia. A few compounds of higher molecular weight exhibited some anticonvulsant activity independent of any depressant activity.

Since no mention has been found in the literature of any 5-substituted-mercapto-5-alkyl derivatives of barbituric acid, it was thought to be of interest to prepare a series of compounds containing sulfur attached directly to the

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[4]Ibid., p. 661.

[5]Wm. H. Hunt, Russel J. Fosbinder, and O. W. Barlow, J. Am. Pharm. Assoc., 35, 231-43 (1946); C. A., 41, 518 (1947).

[6]Wm. H. Hunt, Russel J. Fosbinder, and O. W. Barlow, J. Am. Pharm. Assoc., Sci. Ed., 37, 1-5 (1948); C. A., 42, 4671 (1948).

[7]Ramond L. Cahen, J. Pharmacol., 88, 343-52 (1946); C. A., 41, 4581 (1947).

barbituric acid nucleus. 5-Substituted-mercapto-5-isoamyl-barbituric acids were chosen as representative of barbituric acids in which the alkyl group has a fairly high molecular weight.

Several reactions suggested themselves as possible methods for preparing 5-substituted-mercapto-5-alkyl barbituric acids. Those investigated were the following:

Method 1.

$$RCH(COOC_2H_5)_2 + Br_2 \longrightarrow RCBr(COOC_2H_5)_2 + HBr$$

$$RCBr(COOC_2H_5)_2 + R'SH + C_5H_5N \longrightarrow R(R'S)C(COOC_2H_5)_2 + C_5H_5NHBr$$

$$R(R'S)C(COOC_2H_5)_2 + CO(NH_2)_2 \xrightarrow{M^+B^-} R(R'S)C\underline{CONHCONHCO} + C_2H_5OH$$

Method 2.

$$RCH(COOC_2H_5)_2 + CO(NH_2)_2 \xrightarrow{NaOC_2H_5} RC\underline{HCONHCONHCO} + C_2H_5OH$$

$$RC\underline{HCONHCONHCO} + Br_2 \longrightarrow RC\underline{BrCONHCONHCO} + HBr$$

$$RC\underline{BrCONHCONHCO} + R'SAg \longrightarrow R(R'S)C\underline{CONHCONHCO} + AgBr$$

Alternately, the 5-bromo-5-alkylbarbituric acid was reacted with a mercaptan in the presence of pyridine:

$$RC\underline{BrCONHCONHCO} + R'SH + C_5H_5N \longrightarrow R(R'S)C\underline{CONHCONHCO} + C_5H_5NHBr$$

The compounds reported in this work were prepared by the latter variation.

CHAPTER II

EXPERIMENTAL

Preparation of Diethyl Ethylbromomalonate

$$C_2H_5CH(COOC_2H_5)_2 + Br_2 \longrightarrow C_2H_5CBr(COOC_2H_5)_2 + HBr$$

In a 200-ml. 3-necked flask fitted with a mercury-sealed stirrer, drying tube, and dropping funnel was placed 100 grams (0.532 mole) of diethyl ethylmalonate. By means of the dropping funnel 42.5 grams (0.532 mole) of bromine was added slowly. If the reaction did not start soon after the first drops of bromine were added, the reaction mixture was heated slightly. When once started the reaction proceeded at room temperature. At the end of the reaction a jet of air was blown over the reaction mixture until the hydrogen bromide and any excess bromine were removed. The resulting material was vacuum distilled. One hundred and twenty grams of diethyl ethylbromomalonate distilling at 87-90°/3 mm. was obtained. This represents a yield of 85 per cent of the theoretical.

Preparation of Diethyl Ethyl-n-butylmercaptomalonate

$$C_2H_5CBr(COOC_2H_5)_2 + C_4H_9SH + C_5H_5N \longrightarrow C_2H_5(C_4H_9S)C(COOC_2H_5)_2 + C_5H_5NHBr$$

In the reaction vessel of a 1-liter autoclave were placed 40 grams (0.15 mole) of diethyl ethylbromomalonate, 12 grams

(0.15 mole) of pyridine, 13.5 grams (0.15 mole) of n-butyl mercaptan, and 200 ml. of anhydrous ether. The mixture was heated with stirring at 100° for 10 hours. After it had cooled, the mixture was filtered to remove the pyridine hydrobromide. The ether was removed by distillation and the remaining material was vacuum distilled. The greater part of the material distilled at 55-85°/3 mm. and was discarded. The diethyl ethyl-n-butylmercaptomalonate then distilled at 105-110° at the same pressure. About 6.2 grams, 15 per cent of the theoretical, was obtained.

Preparation of 5-n-Butylmercapto-5-ethylbarbituric Acid

$$C_2H_5(C_4H_9S)C(COOC_2H_5)_2 + CO(NH_2)_2 \xrightarrow{Mg(OCH_3)_2} C_2H_5(C_4H_9S)C\underline{CONHCONHCO} + C_2H_5OH$$

Twenty-four hundredths of a gram of magnesium (0.01 mole) was dissolved in 10 ml. of anhydrous methyl alcohol in a 50-ml. flask fitted with a reflux condenser protected with a drying tube. Then 2.78 grams (0.01 mole) of ethyl-n-butylmercaptomalonate and 0.6 grams (0.01 mole) of urea dissolved in 10 ml. of anhydrous methyl alcohol were added. The mixture was refluxed 22 hours. A white precipitate began to form soon after the refluxing was begun. At the end of this time the alcohol solution was decanted and the precipitate was washed with a little anhydrous methyl alcohol, which was decanted and added to the first alcohol solution. The precipitate contained no sulfur or nitrogen. The alcohol

solution was evaporated and the resulting material was stirred with ether and the ether solution decanted. About two-thirds of the material dissolved in the ether, but extraction of the ether solution with sodium bicarbonate solution and acidification of the sodium bicarbonate layer gave no acid. The ether insoluble portion was a solid. When hydrochloric acid was added, the solid changed to an oil. The oil was extracted with 5 per cent sodium carbonate. Acidification of the sodium carbonate layer gave an oil which soon solidified. After recrystallization from alcohol-water, 0.05 grams of material melting at 89.5-90.5° was obtained. This represents only 2 per cent of the amount theoretically obtainable.

Preparation of Diethyl Isoamylmalonate

$$CH_2(COOC_2H_5)_2 + (CH_3)_2CHCH_2CH_2Br + NaOC_2H_5 \longrightarrow$$
$$(CH_3)_2CH(CH_2)_2CH(COOC_2H_5)_2 + C_2H_5OH + NaBr$$

In a 2-liter three-necked flask fitted with a mercury-sealed stirrer, reflux condenser, and dropping funnel were placed 600 ml. of anhydrous alcohol and 29.9 grams (1.3 moles) of sodium. After the sodium had dissolved, 204 grams (1.3 moles) of diethyl malonate was added and the mixture was heated to boiling. Then 197 grams (1.3 moles) of isoamyl bromide was added rapidly with stirring by means of the dropping funnel. The mixture was stirred and refluxed 12 to 16 hours, after which it was heated on a steam bath and the alcohol evaporated using a jet of air. Enough water was added to dissolve the sodium bromide, and the ester layer was separated,

dried with calcium chloride, and distilled under vacuum. A first fraction of about 25 ml. was discarded, and the remainder of the material, except about 25 ml. remaining in the distillation flask, was collected. It distilled at about 90°/4 mm., and the yield was 200 grams, 67 per cent of the theoretical.

Preparation of 5-Isoamylbarbituric Acid

$$(CH_3)_2CH(CH_2)_2CH(COOC_2H_5)_2 + CO(NH_2)_2 \xrightarrow{NaOC_2H_5}$$

$$(CH_3)_2CH(CH_2)_2\underset{\llcorner\!\!\lrcorner}{CH}CONHCONHCO + 2\ C_2H_5OH$$

In a 1000-ml. flask fitted with a condenser protected with a drying tube were placed 400 ml. of anhydrous alcohol and 19.3 grams (0.84 mole) of sodium. The resulting sodium ethylate solution was placed in the reaction vessel of a 1-liter autoclave, and to it were added 162 grams (0.7 mole) of diethyl isoamylmalonate and 50.4 grams (0.84 mole) of urea dissolved in 400 ml. of anhydrous alcohol. The mixture was heated in the autoclave with stirring at 100° for 20 hours. After the autoclave had cooled to 70°, the reaction mixture was removed and filtered. The crystalline sodium salt of isoamylbarbituric acid was dissolved in water, and the solution was acidified with hydrochloric acid to give a precipitate of isoamylbarbituric acid. This was separated by filtration, suspended in boiling dilute alcohol, dissolved by further addition of alcohol, and filtered while hot. The crystals which formed on cooling were separated by filtration

and dried. One hundred and five grams of isoamylbarbituric acid melting at 238-240° was obtained. This represents a yield which is 76 per cent of the theoretical.

Preparation of 5-Bromo-5-isoamylbarbituric Acid

$$(CH_3)_2CH(CH_2)_2\underline{CHCONHCONHCO} + Br_2 \longrightarrow$$
$$(CH_3)_2CH(CH_2)_2\underline{CBrCONHCONHCO} + HBr$$

Twenty grams of isoamylbarbituric acid was suspended in 1000 ml. of boiling water, and bromine dissolved in sodium bromide solution was added with stirring until a permanent bromine color remained. The resulting suspension was diluted to 2 liters, heated to boiling, and the resulting solution was cooled. The crystals of 5-bromo-5-isoamylbarbituric acid were removed by filtration. Twenty-four and three-tenths grams of material melting at 168-169° was obtained, this representing a yield of 86 per cent of the theoretical.

Preparation of 5-Substituted-mercapto-5-isoamylbarbituric Acids

Method I

$$(CH_3)_2CH(CH_2)_2\underline{CBrCONHCONHCO} + RSAg \longrightarrow$$
$$(CH_3)_2CH(CH_2)_2(RS)\underline{CCONHCONHCO} + AgBr$$

The procedures used to prepare various 5-substituted-mercapto-5-isoamylbarbituric acids by this method are exactly analogous to the procedure used to prepare 5-n-butylmercapto-5-isoamylbarbituric acid, as follows: In a 200-ml. 3-necked

flask fitted with a mercury-sealed stirrer and reflux condenser protected with a drying tube were placed 100 ml. of anhydrous dioxane, 10 grams (0.0362 mole) of 5-bromo-5-isoamylbarbituric acid, and 7.12 grams (0.362 mole) of silver n-butylmercaptide.[1] The mixture was refluxed one hour with stirring. It was then allowed to stand until the solid material had settled, and a 2 ml. sample was drawn from the supernatant liquid by means of a volumetric pipette. The sample was placed in a beaker containing 3 ml. of 1.8 M potassium iodide, 1.5 ml. of 6 N hydrochloric acid, 6 ml. of ethyl alcohol, and 10 ml. of water. The unreacted 5-bromo-5-isoamylbarbituric acid in the sample liberates iodine according to the equation:

$$(CH_3)_2CH(CH_2)_2\underline{CBrCONHCONHCO} + 2\ KI + HCl \longrightarrow$$
$$(CH_3)_2CH(CH_2)_2\underline{CHCONHCONHCO} + I_2 + KBr + KCl$$

The iodine was titrated with standard sodium-thiosulfate solution to determine the number of moles of unreacted 5-bromo-5-isoamylbarbituric acid, and this number of moles of silver n-butylmercaptide was added to the reaction mixture. The mixture was refluxed an additional hour and allowed to cool. The solution was separated from silver bromide and unreacted silver mercaptide by filtration, and the dioxane was distilled from the solution under reduced pressure. The resulting

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[1]The silver mercaptides were prepared by dissolving silver acetate in water at 80° and adding with stirring the calculated amount of mercaptan dissolved in a little cold alcohol. The resulting mercaptide was separated by filtration.

oil was diluted with a little alcohol, and enough potassium iodide solution was added to reduce the 5-bromo-5-isoamylbarbituric acid present to 5-isoamylbarbituric acid. The iodine liberated was converted to potassium iodide by adding sodium thiosulfate solution to the mixture. Ether was then added to dissolve the barbituric acids present, and inorganic salts were removed by washing the ether layer with water. The ether solution was next washed with sodium bicarbonate solution in order to remove the 5-isoamylbarbituric acid. Finally the ether solution was extracted with 25 ml. portions of 0.1 N sodium hydroxide until no further material precipitated on acidification. The material obtained by acidification of the sodium hydroxide extracts was a viscous oil containing sulfur and nitrogen. The yield of this crude 5-n-butylmercapto-5-isoamylbarbituric acid was estimated from the amount of sodium hydroxide required to extract the product from ether. It amounted to only about 12 per cent of the theoretical.

Method II

$$(CH_3)_2CH(CH_2)_2\underline{CBrCONHCONHCO} + RSH + C_5H_5N \longrightarrow (CH_3)_2CH(CH_2)_2(RS)\underline{CCONHCONHCO} + C_5H_5NHBr$$

The procedure for preparing the 5-alkylmercapto-5-isoamylbarbituric acids by this method is exactly analogous to that used for preparing 5-n-butylmercapto-5-isoamylbarbituric acid except for the details of purification, which require individual discussion.

Preparation of 5-n-Butylmercapto-5-isoamylbarbituric Acid.--Ten grams (0.0361 mole) of 5-bromo-5-isoamylbarbituric acid dissolved in 50 ml. of anhydrous ether was placed in a 3-necked flask fitted with mercury-sealed stirrer, dropping funnel, and drying tube. The mixture was cooled in an ice-salt bath, and a solution of 3.28 grams (0.0361 mole) of n-butylmercaptan and 2.86 grams (0.0361 mole) of pyridine in 50 ml. of anhydrous ether was added dropwise with stirring. A white precipitate formed soon after the first drops were added. After all the solution had been added, the presence of unreacted 5-bromo-5-isoamylbarbituric acid was detected by its liberation of iodine from potassium iodide. An additional 3.28 grams of n-butylmercaptan and about 0.3 ml. of pyridine were dissolved in 50 ml. of anhydrous ether, and this solution was added dropwise with stirring to the reaction mixture until no 5-bromo-5-isoamylbarbituric acid was detected. The cold reaction mixture was then filtered to remove the precipitate, which consisted of pyridine hydrobromide and 5-isoamylbarbituric acid. The latter is formed according to the following equation.[2]

$$(CH_3)_2CH(CH_2)_2\underline{CBrCONHCONHCO} + 2\ RSH + C_5H_5N \longrightarrow$$
$$(CH_3)_2CH(CH_2)_2\underline{CHCONHCONHCO} + RSSR + C_5H_5NHBr$$

[2]p-Tolyl disulfide formed by the reaction of 5-bromo-5-phenylbarbituric acid and p-thiocresol under the above conditions has been isolated and identified by its melting point. (Howard Shahan, "Barbituric Acids as Anticonvulsants IV. 5-Substituted-mercapto Derivatives of 5-Phenylbarbituric Acid.," Unpublished Master's Thesis, Department of Chemistry, North Texas State College, 1951.)

The precipitate was saved and used to estimate the per cent yield of desired product.[3] The filtrate was washed with water and then extracted with 10 ml. portions of 5 per cent sodium bicarbonate solution until acidification of the bicarbonate layer gave no solid.[4] The ether solution was finally extracted with 25 ml. portions of 0.2 N sodium hydroxide until acidification with hydrochloric acid gave no insoluble oil.

The above preparation was carried out three times in order to investigate possible methods for purifying the crude 5-n-butylmercapto-5-isoamylbarbituric acid which was obtained as an oil on acidification of the sodium hydroxide extracts. Despite long standing in the refrigerator with occasional stirring, the material from the first two preparations remained an oil. One of the acidified extracts from the third preparation, however, turned to a solid after standing about two weeks in the refrigerator. Although the

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[3]The precipitate was dried and weighed, carefully washed with water, and again dried and weighed. The per cent yield of pyridine hydrobromide (water soluble portion) was calculated. The water insoluble portion was found to be 5-isoamylbarbituric acid. To correct its weight for loss during transfer, its weight was multiplied by the factor which, when multiplied by the weight of pyridine hydrobromide, would convert that weight to the theoretical amount.

[4]The precipitate was found to be 5-isoamylbarbituric acid. It was separated by filtration, dried, and weighed. This weight was added to the weight of the same material which was filtered from the original reaction mixture. The number of moles of isoamylbarbituric acid recovered was subtracted from the number of moles of brominated acid used, to give the estimated number of moles of brominated acid used in the formation of the desired mercaptobarbituric acid.

remaining extracts of the material from this preparation stood in the refrigerator in separate beakers during the same period, they did not solidify even after an additional week. When some of the solid material was stirred into these oils, however, they turned to a solid within a day or two. Recrystallization was accomplished by dissolving 1 gram of this solid in 170 ml. of alcohol, decolorizing with norit, filtering, and adding 550 ml. of cold water with shaking. The resulting milky suspension was seeded with a little of the solid and allowed to stand in the refrigerator for several days with occasional shaking. During this time crystals slowly formed, but the yield of recrystallized material was less than 50 per cent. Material melting at 77-80.5° was obtained after one recrystallization. The yield of crude product was estimated to be 53 per cent.[5] Per cent nitrogen: calcd., 9.78; found, 9.62.

Preparation of 5-Methylmercapto-5-isoamylbarbituric Acid.--This compound and those of the succeeding syntheses were prepared using the same molar quantities as in the previous experiment. Acidification of the sodium hydroxide extract corresponding to that in the above preparation gave an oil which turned to a solid within a few seconds. The solid

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[5]Because it would have been difficult to dry and weigh the material in the individual extracts, the yield of crude product was estimated in this and succeeding syntheses from the amount of 5-isoamylbarbituric acid recovered. In some cases the yield of purified compound was much less because of the poor yield on recrystallization.

crystallized without difficulty from alcohol-water, but five recrystallizations were necessary to obtain material melting at 158-159°. Alternately, purification was accomplished by dissolving the solid in enough 0.1 N sodium hydroxide to form the monosodium salt, and then adding half that amount of 0.1 N acetic acid. The crystals which formed on cooling this solution were found to melt at a higher temperature than those obtained by recrystallizing some of the same material from alcohol-water, indicating that greater purification had been accomplished. The yield of crude material was estimated to be 61 per cent. Per cent nitrogen: calcd., 11.47; found 11.48.

Preparation of 5-Ethylmercapto-5-isoamylbarbituric Acid.--After the preparation was carried out as in the previous experiment, acidification of the sodium hydroxide extract gave an oil which turned to a solid after standing several days in the refrigerator. One gram could be recrystallized by dissolving in 37 ml. of alcohol, adding 230 ml. of cold water, seeding the resulting milky suspension of oil with a little solid, and allowing the mixture to stand in the refrigerator for about 24 hours. It was found that if a greater concentration of compound than that specified above was used, the suspension of oil would not crystallize even on longer standing. After three recrystallizations, the compound melted at 105.8-106.8°. The yield of crude product was estimated to be 73 per cent. Per cent nitrogen: calcd., 10.85; found, 10.73.

Preparation of 5-n-Propylmercapto-5-isoamylbarbituric Acid.--After the preparation was carried out as in the previous experiment, acidification of the sodium hydroxide extract gave an oil which turned to a solid after standing several days in the refrigerator. One gram was recrystallized by dissolving in 65 ml. of alcohol, decolorizing, adding 300 ml. of cold water, seeding, and allowing the suspension to stand in the cold with occasional shaking for a day or more. After three recrystallizations the compound melted at 98.5-99.5°. The yield of crude product was estimated to be 64 per cent. Per cent nitrogen: calcd., 10.29; found, 10.36.

Preparation of 5-Isopropylmercapto-5-isoamylbarbituric Acid.--The oil obtained from the preparation carried out as in the previous experiments solidified on standing overnight. The material was recrystallized with greater ease than any compound in the series except the methylmercapto derivative. One gram was recrystallizable from 20 ml. of alcohol and 50 ml. of water. After four recrystallizations the compound melted at 112.6-113.8°. The yield of crude product was estimated to be 75 per cent. Per cent nitrogen: calcd., 10.29; found, 10.30.

Preparation of 5-Isobutylmercapto-5-isoamylbarbituric Acid.--The oil in some of the extracts obtained as in the previous experiments solidified on standing in the refrigerator about 24 hours. The remaining oils solidified when seeded with some of the solid material. One gram of the

solid was recrystallized by dissolving in 75 ml. of alcohol, decolorizing, adding 800 ml. of cold water, seeding, and allowing the resulting suspension of oil to stand in the cold for about 12 hours. After three recrystallizations, the compound melted at 88.7-90°. The yield of crude product was estimated to be 60 per cent. Per cent nitrogen: calcd., 9.78; found, 9.78.

Preparation of 5-Allylmercapto-5-isoamylbarbituric Acid.--The oil obtained from the preparation carried out as in the previous experiments solidified on standing in the cold overnight. One gram of the solid was recrystallized by dissolving in 45 ml. of alcohol, decolorizing, adding 200 ml. of cold water, seeding, and allowing the resulting suspension of oil to stand in the refrigerator about 24 hours with occasional shaking. The crystals obtained by this method were found to form an oil when placed under vacuum, indicating that they were a hydrate which underwent loss of water. The amount of water was determined by measuring the loss in weight when a 0.1 gram sample was heated at 80° under 4 mm. pressure for about 8 hours. Per cent water: calcd. for $C_{12}H_{18}O_3N_2S \cdot H_2O$, 6.25; found, 6.37. After three recrystallizations, the crystals of hydrate melted at 66-68.5°. The yield of crude product was estimated to be 45 per cent. Per cent nitrogen: calcd. for $C_{12}H_{18}O_3N_2S \cdot H_2O$, 9.72; found, 9.52.

CHAPTER III

DISCUSSION OF RESULTS

The methods for making mercapto-substituted barbituric acids which were tried may be placed in two groups: those in which the mercapto group was introduced prior to the formation of the barbituric acid nucleus, and those in which it was introduced after the formation of the barbituric acid nucleus.

In exploratory work using diethyl ethylmalonate, which was commercially available, attempts were made to prepare diethyl n-butylmercaptoethylmalonate from diethyl bromoethylmalonate by four procedures. No reaction occurred when this compound was mixed with n-butyl mercaptan and pyridine in cold ether solution. When it was refluxed with the mercaptan and pyridine without solvent, reaction occurred, but vacuum distillation gave substances of too low a boiling range to be diethyl n-butylmercaptoethylmalonate. When diethyl ethylbromomalonate was refluxed with the silver salt of n-butyl mercaptan in anhydrous dioxane, it was recovered unchanged on distillation. When it was heated with pyridine and n-butyl mercaptan in anhydrous ether at 100°, however, the desired product was obtained as a fraction distilling at 115-120°/2 mm. Despite variation of the reaction time and

temperature, the yield was never more than about 15 per cent of the theoretical.

Attempts were made to condense this material with urea using as condensing agents sodium ethoxide, magnesium methoxide, and sodium t-butoxide according to McElvain and Goese.[1] From a preparation using magnesium methoxide, an acid was isolated which contained sulfur and nitrogen and which melted at 89.5-90.5° after one recrystallization from alcohol-water. The yield of recrystallized material was only about 2 per cent of the theoretical, the remainder of the mercaptomalonic ester apparently reacting to give other products. 5-n-butylmercapto-5-ethylbarbituric acid has now been synthesized from 5-bromo-5-ethylbarbituric acid.[2] A sample prepared by this procedure melted at 86.5-88°. When this material was mixed with that prepared from the mercaptomalonic ester, the melting point was 87-89°, confirming the identity of the acid prepared from the above ester, and indirectly, of the ester.

Because of the low yields which were obtained when the above method was used, attempts were made to introduce the

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[1]S. M. McElvain and M. A. Goese, J. Am. Chem. Soc., 65, 2226 (1943), carried out the condensation of diethyl ethyl-2-pyridylmalonate with urea in the presence of sodium t-butoxide with t-butyl alcohol as a solvent. The ethyl alcohol formed in the condensation was removed continuously from the reaction mixture by distillation, along with some t-butyl alcohol. When sodium ethoxide was used as the condensing agent, this ester gave only a cleavage product, -(2-pyridyl)butyramide.

[2]C. B. Jeanes, unpublished notes, Department of Chemistry, North Texas State College, 1952.

mercapto group subsequent to the formation of the barbituric acid nucleus. 5-Bromo-5-isoamylbarbituric acid was easily prepared in good yield for use in this portion of the work.

When this material was refluxed with the silver salt of n-butyl mercaptan in anhydrous dioxane, a fair yield of crude product was obtained, as described in Chapter II. When the silver salt of ethyl mercaptan was used, however, the reaction proceeded at a much slower rate, as was determined by titrating the iodine liberated from potassium iodide by the unreacted 5-bromo-5-isoamylbarbituric acid in samples from the reaction mixture. Furthermore, the amount of crude product isolated from the reaction mixture after long refluxing was negligible. This result agreed with results obtained by using 5-bromo-5-(1-methylbutyl)barbituric acid, which could be prepared from commercially available 1-methylbutylmalonic ester. When this material was reacted under the above conditions with the silver salts of methyl, ethyl, n-propyl, and n-butyl mercaptans, respectively, the desired products were obtained only with the latter two mercaptans. It is possible that the failure of the lower molecular weight mercaptides to react is due to their having lower solubility in dioxane, which might be expected from their greater resemblance to inorganic salts. The slow disappearance of the bromobarbituric acid on refluxing with these mercaptides may be due to the instability of the bromobarbituric acid at higher temperatures. 5-Bromo-5-isoamylbarbituric acid turns dark and evolves a gas when kept at its melting point, 175°, for a few minutes.

It was evident from the above results that the above method could not be used to prepare methylmercapto- and ethylmercaptobarbituric acids. Furthermore, it is likely that the crude products obtained from other mercaptides were contaminated by the unidentified substances arising from the decomposition of the bromobarbituric acid. Accordingly, the reaction of 5-bromo-5-isoamylbarbituric acid with mercaptan and pyridine in cold ether solution was studied. This reaction was finally used for the preparation of the compounds reported in this work. Although part of the brominated acid was used in each case in the oxidation of the mercaptan to disulfide, the materials resulting from this competing reaction were successfully separated from the mercaptobarbituric acids. Nevertheless, all compounds prepared by this method have been very difficult to purify, as evidenced by the fact that even after three to five recrystallizations, the melting points of the compounds could be raised by additional recrystallizations. Furthermore, 5-n-butylmercapto-5-ethylbarbituric acid prepared by this method melted 2.5° lower than the same material prepared from the mercaptomalonic ester, despite the fact that it had been recrystallized several additional times. Apparently an unidentified impurity is present in the crude products, which has chemical properties resembling those of the desired compounds.

It can be concluded, then, that the method used to prepare the compounds reported in this work is not wholly

satisfactory in its present form. Additional work with large quantities of reactants might make possible the identification of the unknown impurity. The effect of further purification of the intermediate compounds might be studied in an attempt to make the method more usable. On the other hand, additional attempts might be made to prepare mercaptobarbituric acids from mercaptomalonic esters, as there is some evidence that the compounds prepared in this way would be more easily purified.

BIBLIOGRAPHY

Articles

Cahen, Ramond L., J. Pharmacol., 88, 343-52 (1946); C. A., 41, 4561 (1947).

Hunt, Wm. H., Fosbinder, Russel J., and Barlow, O. W., J. Am. Pharm. Assoc., 35, 231-43 (1946); C. A., 41, 516 (1947).

Hunt, Wm. H., Fosbinder, Russel J., and Barlow, O. W., J. Am. Pharm. Assoc., Sci. Ed., 37, 1-5 (1948); C. A., 42, 4671 (1948).

McElvain, S. M., and Goese, M. A., J. Am. Chem. Soc., 65, 2226 (1943).

Walter, L. A., Goodson, L. H., and Fosbinder, Russel J., J. Am. Chem. Soc., 67, 655-7 (1945).

Walter, L. A., Goodson, L. H., and Fosbinder, Russel J., J. Am. Chem. Soc., 67, 657-9 (1945).

Walter, L. A., Goodson, L. H., and Fosbinder, Russel J., J. Am. Chem. Soc., 67, 659-60 (1945).

Walter, L. A., Goodson, L. H., and Fosbinder, Russel J., J. Am. Chem. Soc., 67, 661 (1945).

Unpublished Material

Jeanes, C. B., Unpublished notes, Department of Chemistry, North Texas State College, 1952.

Shahan, Howard, "Barbituric Acids as Anticonvulsants IV. 5-Substituted-mercapto Derivatives of 5-Phenylbarbituric Acid.," Unpublished Master's Thesis, Department of Chemistry, North Texas State College, 1951.