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STABLE THIOBARBITURIC ACID SOLUTION

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This invention relates in general to the preparation of stable solutions of barbituric acid type compounds and more particularly to improved stable preparations of thiobarbituric acid compounds and the salts thereof and to a method of preparing said stable solutions.

The barbituric acid type compounds, and more particularly the thiobarbituric acid type compounds and the salts thereof, are important as anesthetic and hypnotic agents. An important use of the thiobarbiturates is for inducing surgical anesthesia of relatively short duration and for such use dilute aqueous solutions of thiobarbiturates are injected parenterally in relatively large amounts. Aqueous solutions of the thiobarbiturates, however, are notoriously unstable and decompose within a very short time by forming a precipitate and frequently giving off an objectionable odor. Consequently, it has generally been found necessary to form the dilute aqueous solutions of the thiobarbiturates shortly prior to administration by dissolving a dry thiobarbiturate salt in water. Because of the inconvenience of handling dry salts and preparing solutions thereof, however, attempts have been made to prepare stable solutions of the thiobarbituric acid type compounds by dissolving the thiobarbiturates in a solvent consisting of water and an organic solvent. These efforts have not been entirely successful, however, since the aqueous solutions begin to decompose within a relatively short time and serious decomposition of thiobarbiturate solutions cannot be avoided during prolonged periods. And, although thiobarbituric acids per se are soluble in certain organic solvents, such solutions are of little practical importance, since it is unsafe to administer parenterally large volumes of non-aqueous solvents; and when these thiobarbituric acid solutions are diluted with water the thiobarbituric acids precipitate from solution.

It is therefore an object of the present invention to provide a highly stable solution of a barbituric acid type compound.

A further object of the invention is to provide a highly stable concentrated solution of a barbituric acid type compound having a viscosity which makes the solution suitable for convenient handling and measuring.

It is another object of the invention to provide a highly stable solution of a thiobarbituric acid type compound which can be diluted with water in all proportions without forming a precipitate.

It is also an object of the invention to provide a highly concentrated solution of a thiobarbiturate type compound in an organic solvent medium which when admixed with water in therapeutic dilutions for parenteral administration will have a sufficiently high concentration of the active thiobarbiturate compound to be highly effective and a sufficiently low concentration of the organic solvent medium to be safely administered.

Other objects of the invention will be apparent from the detailed description and claims to follow.

The foregoing and other objects of the invention are achieved by preparing a solution of the thiobarbituric acid type compounds or the parenterally acceptable salts thereof in a parenterally acceptable substantially water-free organic solvent. It has been found that remarkably stable concentrated solutions of a thiobarbiturate type compound can be prepared with a solvent comprising a water miscible, parenterally acceptable, substantially non-aqueous organic solvent, such as the parenterally acceptable, water miscible mono, di, and polyhydroxy alcohols. Since it is generally considered undesirable to inject a large volume of even a normally non-toxic water miscible organic solvent intravenously, the stable solutions of the present invention must contain a sufficiently high concentration of the said thiobarbiturate to be effective when diluted with water and a sufficiently low concentration of the organic solvent medium when therapeutic dilutions thereof are prepared to permit safe administration intravenously. Thus, the present invention is principally concerned with the use of a solvent medium substantially free of appreciable amounts of water comprising one or more parenterally acceptable, water miscible alcoholic solvents, such as ethyl alcohol, propylene glycol, polypropylene glycol-150, polypropylene glycol-425, glycerin, and 1,2,4-butanetriol and other alcoholic solvents having properties similar to the foregoing.

It has been further discovered that by combining two parenterally acceptable, water miscible, non-aqueous organic solvents, such as propylene glycol and ethyl alcohol as the solvent medium, the solubility of the thiobarbiturate compounds in the said solvent medium is sufficient to form highly concentrated, low viscosity non-aqueous thiobarbiturate solutions having a low concentration of organic solvent upon therapeutic dilution with water to permit safe administration and provide solutions having a remarkably prolonged stability. In general the proportion of the ethyl alcohol to propylene glycol, for example, in the mixed solvent medium can be varied widely without departing from the objects of the invention. Since it is desirable for most preparations of the type under consideration to have a concentration of about 20 grams of thiobarbiturate per 100 ml. of solution prior to making therapeutic dilutions with water, a minimum of about 10% by weight propylene glycol is included in the mixed solvent medium to provide the required solubility of the thiobarbiturate therein. If desired, solutions containing 50 grams or more of a thiobarbiturate per 100 ml. of solution can be prepared in accordance with the present invention. For example, when a 50% w./v. thiobarbiturate solution is desired, a solvent medium containing about 50% propylene glycol and 50% absolute ethyl alcohol provides highly satisfactory results. For general use solutions of thiobarbiturate having a concentration of between about 20 and 35 grams thiobarbiturate per 100 ml. of solution wherein the solvent contains a minimum of between 10 and 30% by weight propylene glycol are preferred. For example, it has been found possible to form very stable solutions containing in excess of about 25 grams of thiobarbiturates per 100 ml. of solution by employing a solvent containing about 20% by weight propylene glycol and the balance ethyl alcohol. Solutions having the foregoing composition remain unchanged in their anesthetic and hypnotic effect after being heated in a sealed ampoule for prolonged periods at elevated temperatures or held for many months at 40° C. in accelerated aging tests. These thiobarbiturate solutions as prepared in accordance with the present invention are also capable of being diluted with water in all proportions without forming a precipitate.

Unlike solutions of barbiturates which do not contain sulfur, solutions of the thiobarbiturate compounds, such as sodium ethyl-(1-methylbutyl)-thiobarbiturate and sodium allyl-(1-methylbutyl)-thiobarbiturate, normally form precipitates of the thiobarbituric acids when an organic solvent solution thereof is diluted with water. It has been found that by incorporating in a concentrated thiobarbiturate organic solvent solution a parenterally acceptable alkaline regent which is soluble in the said solvent, it is possible to dilute the concentrated thiobarbiturate solutions in all proportions with water without causing a precipitate to form. Since it is necessary that the thera-

peutic aqueous dilutions of the thiobarbiturates have a pH of about 10 and preferably about 10.5 to avoid a precipitate forming on diluting with water, it is highly desirable to include in the thiobarbiturate concentrated organic solvent solution a parenterally acceptable alkaline reagent in an amount sufficient to provide the aqueous dilution thereof with a pH of about 10 and preferably 10.5. For example, sufficient alkali metal alkoxide is incorporated in the concentrated non-aqueous thiobarbiturate solution to provide an amount of an alkali metal between about 5 and 30% by weight in excess of the weight of the alkali metal contained in the alkali metal salt of the thiobarbiturate composition in solution to effectively prevent precipitation on dilution with water. Sodium ethoxide is particularly suitable for use as the alkaline reagent since it is readily soluble in the preferred solvent mixture and provides the desired alkalinity for complete solubility on dilution with water as it hydrolyzes to form sodium hydroxide and ethyl alcohol, both of which aid in solubilizing the thiobarbiturate in an aqueous solution without introducing additional ions into the solution. The sodium ethoxide may be formed in situ or, if desired, the sodium ethoxide may be added directly to the solvent containing the thiobarbiturate dissolved therein.

Other parenterally acceptable alkaline reagents which are soluble in the herein disclosed solvent medium can be used in addition to sodium ethoxide. For example, monoethanolamine has been used in amounts equivalent to that of the sodium ethoxide employed herein. The reaction product of sodium and propylene glycol can also be used in place of the sodium or sodium ethoxide, or, if desired, anhydrous alkali metal hydroxide can also be used to provide the necessary alkalinity by dissolving the hydroxide in the alcohol of the solvent medium. The amount of the alkaline reagent employed should, of course, be maintained below that which causes irritation or other untoward effects upon injecting the usual aqueous therapeutic dilution of between ½ and 5% aqueous thiobarbiturate solution and above the amount required to maintain complete water miscibility and solubility after dilution. It should also be understood that the amount of alkaline reagent required to insure solubility upon dilution with water varies with the concentration of the carbon dioxide present in the water used for dilution. Thus, the concentration of alkaline reagent in the thiobarbiturate solution can vary considerably depending primarily on the relative alkalinity or acidity of the water used for dilution prior to administration. If an alkaline reagent such as sodium carbonate is added to the dilution water, however, the excess of alkaline reagent in the concentrated thiobarbiturate solution can be omitted without departing from the other novel concepts of the present invention. Also, in the preferred form of the invention having the alkaline reagent dissolved in the organic solvent solution, it should be observed that the organic solvents used must be stable in contact with the alkaline material and at the relatively high pH of the aqueous solutions formed when diluted with water so as to avoid polymerization, gelling, and the like.

In preparing a stable solution of a thiobarbituric acid type compound, for example, in accordance with the preferred form of the present invention, a calculated amount of metallic sodium sufficient to provide the desired excess alkalinity, for example, about 30% by weight excess sodium based on the weight of the sodium in the sodium salt of the thiobarbituric acid to be solubilized, is dissolved in an excess of pure ethyl alcohol, preferably under an inert atmosphere of protective nitrogen to prevent absorption of carbon dioxide and water from the air, thereby forming an alcoholic solution of sodium ethoxide. The ethoxide solution is then mixed with the desired amount of propylene glycol and the mixed solvents comprising ethyl alcohol and propylene glycol containing dissolved sodium ethoxide is used to dissolve the sodium ethyl-(1-methylbutyl)-thiobarbiturate or an anhydrous alcoholic solvent solution thereof. The resulting solution is then filtered to provide a clear, pale greenish yellow solution which can be held for prolonged periods at a temperature of 100° C. or heat sterilized at a temperature of 125° C. without decomposing. Other methods of preparing the stable solution of the present invention will be apparent from the specific examples and claims to follow.

In order to rapidly determine the stability of the concentrated thiobarbiturate solutions of the present invention, the thiobarbiturate solutions are placed in sealed glass ampoules and heated for periods of 1 to 24 hours at 100° C. in a water bath. At the end of the heating periods each thiobarbiturate solution is examined for changes in appearance and each is diluted with water in therapeutic proportions and allowed to stand for at least 24 hours to determine whether a precipitate forms. The usual aqueous thiobarbiturate solution when heated at 100° C. exhibits evidence of decomposition in about one hour, whereas the non-aqueous solutions of the present invention remain unchanged when held for periods substantially in excess of 1 hour at 100° C. Comparative pharmacological tests show that the above non-aqueous solutions after heating for periods as long as 24 hours at 100° C. when diluted with water to form a dilute aqueous solution and injected intravenously retain their original potency. Accelerated shelf-life studies have also been conducted by holding samples of the concentrated solution of the present invention at 40° C. for periods in excess of 13 months without any evidence of decomposition or decrease in potency.

The following specific examples are shown by way of illustration only and should not be construed to restrict the invention to the precise proportions or ingredients disclosed therein.

Example I

A stable solution containing 25 g. of sodium ethyl-(1-methylbutyl)-thiobarbiturate per 100 ml. of solution is prepared with the following ingredients:

Sodium metal	g.	0.44
Sodium ethyl-(1-methylbutyl)-thiobarbiturate	g.	50.0
Propylene glycol	ml.	40
Absolute ethyl alcohol	ml.	120

In preparing the above solution the sodium metal is finely divided, rinsed free of protective solvent, added to the absolute ethyl alcohol, and allowed to stand until the sodium completely reacts with the ethyl alcohol to form the sodium ethoxide solution. Thereafter the specified amount of propylene glycol is added to the ethoxide solution. The sodium ethyl-(1-methylbutyl)-thiobarbiturate is then dissolved in the alkaline propylene glycol-ethyl alcohol solution to form a pale greenish yellow solution. The solution is then filtered through a porcelain filter candle in order to remove any haze or fine materials which may be present and filled into containers and sealed.

The above thiobarbiturate solution is placed in sealed glass ampoules and heated for a period of 5 hours at 100° C. in a water bath. At the end of the heating period the thiobarbiturate solution is unchanged in appearance, can be diluted in all proportions with water without forming a precipitate, and has its original potency when injected intravenously.

Example II

A stable solution containing 35 g. of sodium ethyl-(1-methylbutyl)-thiobarbiturate per 100 ml. of solution is prepared with the following ingredients:

	G.
Sodium metal	0.65
Sodium ethyl-(1-methylbutyl)-thiobarbiturate	70.0
Propylene glycol	50.0
Absolute ethyl alcohol	50.0

50:50 propylene glycol:absolute ethyl alcohol (percent by weight), q.s. 200 ml.

The above solution of thiobarbiturate is prepared by reacting the sodium metal in a finely divided state with the ethyl alcohol and combining the alcoholic solution of sodium ethoxide with the specified amount of propylene glycol. To the above solvent solution is added the specified amount of sodium ethyl-(1-methylbutyl)-thiobarbiturate and the volume of the solution adjusted to 200 ml. by addition of the mixed solvent and the solution is filtered as in Example I.

The above thiobarbiturate solution is placed in sealed glass ampoules and heated for a period of 5 hours at 100° C. in a water bath. At the end of the heating period the thiobarbiturate solution is unchanged in appearance, can be diluted in all proportions with water without a precipitate forming, and has its original potency when injected intravenously. Shelf-life tests comprising holding the ampoules prepared in the above manner for a period of 13 months at 40° C. show no loss in in vivo anesthetic potency nor any change in physical appearance of the solution.

Example III

A stable solution containing 30 g. of sodium ethyl-(1-methylbutyl)-thiobarbiturate per 100 ml. of solution is prepared with the following ingredients:

	G.
Sodium metal	0.60
Sodium ethyl-(1-methylbutyl)-thiobarbiturate	60.0
Propylene glycol	50.0
Absolute ethyl alcohol	50.0

70:30 propylene glycol:absolute ethyl aclohol (percent by weight), q.s. 200 ml.

The above solution of thiobarbiturate is prepared by reacting sodium metal in a finely divided state with the ethyl alcohol and combining the alcoholic solution of sodium ethoxide with the specified amount of propylene glycol. To the above solvent solution is added the specified amount of sodium ethyl-(1-methylbutyl)-thiobarbiturate and the solution is filtered as in Example II.

The thiobarbiturate solution is placed in sealed glass ampoules and heated for a period of 5 hours at 100° C. in a water bath. At the end of the heating period the thiobarbiturate solution is unchanged in appearance, can be diluted in all proportions with water without a precipitate forming, and has substantially its original potency when injected intravenously. Shelf-life tests comprising holding the ampoules prepared in the above manner for a period of 13 months at 40° C. show no loss in in vivo anesthetic potency for any change in physical appearance of the solution.

Example IV

A stable solution containing 25 g. of sodium ethyl-(1-methylbutyl)-thiobarbiturate in 100 ml. of solution is prepared with the following ingredients:

Sodium metal	g.	4.80
Ethyl-(1-methylbutyl)-thiobarbituric acid	g.	45.9
Absolute ethyl alcohol	ml.	80

Propylene glycol, q.s. 200 ml.

The sodium metal in a finely divided state is reacted with the absolute ethyl alcohol under a protective atmosphere of nitrogen gas. To the clear solution of sodium ethoxide containing an excess of sodium above that required to form the sodium salt of the thiobarbituric acid in ethyl alcohol is added 25 ml. of freshly distilled propylene glycol and the specified amount of ethyl-(1-methylbutyl)-thiobarbituric acid. Approximately 155 ml. of thiobarbiturate solution is formed and it is completely miscible with water in all proportions. For convenience in handling and measuring the volume of the solution is adjusted to 200 ml. by adding propylene glycol.

The resulting yellow solution is allowed to stand for 24 hours in a closed container under an atmosphere of nitrogen gas and then filtered through a plug of glass wool into 10 ml. ampoules.

Ampoules of the thiobarbiturates are heated for 5 hours at 100° C. and show no loss in anesthetic properties at the end of the heating period. Also, ampoules of the above thiobarbiturate solution after being held for a period of three months at 40° C. show no loss in anesthetic properties.

Example V

A stable solution of sodium allyl-(1-methylbutyl)-thiobarbiturate is prepared containing the following ingredients:

Sodium metal	g.	6.0
Allyl-(1-methylbutyl)-thiobarbituric acid)	g.	46.1
Propylene glycol	ml.	50

Absolute ethyl alcohol, q.s. 200 ml.

The sodium metal is reacted with 80 ml. of absolute alcohol under a protective atmosphere of nitrogen and the allyl-(1-methylbutyl)-thiobarbituric acid added to the alkaline solution. The entire quantity of acid readily dissolves but within a few minutes a heavy crystalline precipitate begins to form. Upon adding the specified amount of freshly distilled propylene glycol to the solution containing the precipitate, a clear yellow solution is formed which does not precipitate on standing. The volume of the solution is adjusted to 200 ml. with ethyl alcohol. The solution contains 25 g. of sodium allyl-(1-methylbutyl)-thiobarbiturate in 200 ml. of solvent. The solution is allowed to stand for two days in a closed container having a protective atmosphere of nitrogen and is then filtered through a plug of glass wool. The clear solution is filled into 10 cc. ampoules and sealed.

Example VI

A solution containing 25 g. sodium allyl-(1-methylbutyl)-thiobarbiturate per 100 ml. solution in an ethyl alcohol-propylene glycol mixture having a 30:70 solvent weight ratio and containing approximately 10% by weight excess sodium is prepared with the following ingredients:

	G.
Sodium metal	0.06
Absolute ethyl alcohol	3.0
Propylene glycol	7.0
Sodium allyl-(1-methylbutyl)-thiobarbiturate	6.25

30:70::ethyl alcohol:propylene glycol mixture, q.s. 25 ml.

A solution containing the foregoing ingredients is prepared in accordance with the procedure described in Example II to form a stable solution of sodium allyl-(1-methylbutyl)-thiobarbiturate having a concentration of 25 g. per 100 ml. of solution. Upon heating the latter solution for 5 hours at 100° C. there is no evidence of decomposition and the pharmacological activity of the dilute aqueous solution of thiobarbiturate remains unchanged when compared with the dilute aqueous solution of the control sample of the thiobarbiturate.

Example VII

A solution of sodium ethyl-(1-methylbutyl)-thiobarbiturate is formed containing the following ingredients:

Sodium metal	g.	6.2
Ethyl-(1-methylbutyl)-thiobarbituric acid	g.	27.6
Propylene glycol	ml.	10
Absolute ethyl alcohol	ml.	90

The sodium metal is dissolved in 80 ml. of absolute ethyl alcohol and this sodium ethoxide alcoholic solution is added to an alcohol thiobarbituric acid solution. Complete solution of the acid is effected by adding an additional 10 ml. absolute ethyl alcohol to bring the volume of solution to 120 ml. but upon standing the sodium salt of the acid precipitates. Upon adding 10 ml. of propylene glycol to the ethyl alcohol solution containing the thiobarbituric acid salt, a clear solution forms which does not precipitate on standing and which may be diluted with water in all proportions.

Example VIII

A stable solution of sodium ethyl-(1-methylbutyl)-

thiobarbiturate containing 25 g. barbiturate per 100 ml. of solution consisting of ethyl alcohol-propylene glycol in a 1:1 weight ratio and containing a 10% excess of sodium is prepared with the following ingredients:

	G.
Sodium metal	0.44
Absolute ethyl alcohol	25.0
Propylene glycol	25.0
Sodium ethyl-(1-methylbutyl)-thiobarbiturate	50.0
Ethyl alcohol-propylene glycol, 1:1 mixture (weight ratio), q.s. 200 ml.	

The above ingredients are combined in accordance with the procedure described in Example II to form a clear fluid solution of the thiobarbiturate. After filtering and filling into ampoules the thiobarbiturate is heated for 24 hours at 100° C. without decomposition or otherwise adversely affecting the anesthetic activity of the thiobarbiturate composition.

Example IX

A stable solution of sodium ethyl-(1-methylbutyl)-thiobarbiturate having a concentration of 25 g. per 100 ml. of solvent comprising ethyl alcohol-propylene glycol in a weight ratio of 20:80 and containing about 30% excess sodium is prepared with the following ingredients:

	G.
Sodium metal	1.31
Absolute ethyl alcohol	20.0
Propylene glycol	80.0
Sodium ethyl-(1-methylbutyl)-thiobarbiturate	50.0
Absolute ethyl alcohol-propylene glycol, 20:80 weight ratio, q.s. 200 ml.	

The solution of the thiobarbiturate in the mixed solvent high in propylene glycol and 30% excess sodium is prepared in the same manner described in Example II to produce a low-viscosity solution which is stable when heated at temperatures sufficient to sterilize the ampoules and there is no decrease in anesthetic potency after heating for 24 hours at 100° C. On dilution with water either before or after heating for prolonged periods there is no precipitation of the thiobarbiturate or thiobarbituric acid.

Example X

A solution of sodium ethyl-(1-methylbutyl)-thiobarbiturate having a concentration of 25 g. per 100 ml. solution in a mixed solvent comprising 30 parts by weight ethyl alcohol and 70 parts by weight propylene glycol and containing sodium ethoxide equivalent to an excess of approximately 30% sodium by weight based on the weight of the sodium salt of the thiobarbiturate is prepared with the following ingredients:

	G.
Sodium metal	1.31
Sodium ethyl-(1-methylbutyl)-thiobarbiturate	50.0
Absolute ethyl alcohol	30.0
Propylene glycol	70.0
Absolute ethyl alcohol-propylene glycol mixed solvent (30:70 weight ratio), q.s. 200 ml.	

The solution of the thiobarbiturate is prepared by reacting the sodium metal with an excess of ethyl alcohol (30 g.) under a protective atmosphere of nitrogen in accordance with the procedure in the several examples. Propylene glycol (70 g.) is then mixed with the ethyl alcohol containing the alkaline reagent and the sodium ethyl-(1-methylbutyl)-thiobarbiturate is dissolved in the mixed solvent. The volume of the solution is adjusted to 200 ml. by adding the mixed solvent. The solution is then filtered and stored in ampoules. A very stable thiobarbiturate solution is obtained which can be diluted with water in all proportions without forming a precipitate.

Example XI

A solution of sodium ethyl-(1-methylbutyl)-thiobarbiturate having a concentration of 25 g. per 100 ml. solution in a mixed solvent comprising ethyl alcohol and propylene glycol containing sodium hydroxide equivalent to approximately 20% sodium by weight based on the weight of the sodium thiobarbiturate is prepared with the following ingredients:

Sodium hydroxide	g.. 1.52
Sodium ethyl-(1-methylbutyl)-thiobarbiturate	g.. 50.0
Absolute ethyl alcohol	ml.. 110
Propylene glycol, q.s. 200 ml.	

The solution of the thiobarbiturate is prepared by dissolving the sodium hydroxide in the ethyl alcohol and the sodium thiobarbiturate dissolved in the ethyl alcohol solution. The volume of the solution is adjusted to 200 ml. by the addition of propylene glycol. After filtering a clear thiobarbiturate solution is obtained which may be diluted with water in all proportions.

Example XII

A solution of sodium ethyl-(1-methylbutyl)-thiobarbiturate containing 25 grams of the said thiobarbiturate per 100 ml. of solution is formed with the following ingredients:

Sodium metal	g.. 1.4
Sodium ethyl-(1-methylbutyl)-thiobarbiturate	g.. 50.0
Absolute ethyl alcohol	ml.. 70
Glycerin, redistilled	ml.. 70
Absolute ethyl alcohol, q.s. 200 ml.	

The sodium metal (1.4 g.) is dissolved in 70 ml. of absolute ethyl alcohol and 70 ml. of redistilled glycerin containing about 0.015% water is added to form an alkaline alcoholic solvent medium. The sodium ethyl-(1-methylbutyl)-thiobarbiturate (50.0 g.) is dissolved in the said alcoholic solvent with stirring. A quantity of absolute ethyl alcohol is added sufficient to adjust the volume of the solution to 200 ml. A nitrogen atmosphere is used throughout. The clear solution thus formed is filteded through a porcelain filter candle (Selas #10) and filled into ampoules under nitrogen atmosphere.

The ampouled concentrated thiobarbiturate solution prepared in the foregoing manner after heating for 10 hours at 100° C. remains clear with no evidence of decomposition and on forming therapeutic dilutions thereof with distilled water remains clear on standing for a period in excess of 48 hours. There is no apparent difference in the toxicity and anesthetic effectiveness between the aqueous solutions prepared after heating the said concentrated solutions for 10 hours at 100° C. and the aqueous control sample of sodium ethyl-(1-methylbutyl)-thiobarbiturate prepared by dissolving the dry commercial sodium ethyl-(1-methylbutyl)-thiobarbiturate preparation in water for injection, both solutions having the same therapeutic dilution.

Example XIII

A solution of sodium ethyl-(1-methylbutyl)-thiobarbiturate containing 25 grams of the said thiobarbiturate per 100 ml. of solution is formed with the following ingredients:

Sodium metal	g.. 1.31
Sodium ethyl-(1-methylbutyl)-thiobarbiturate	g.. 50.0
Absolute ethyl alcohol	ml.. 60
Polypropylene glycol-150	ml.. 60
Polypropylene glycol-150–absolute ethyl alcohol, 50:50 (volume basis), q.s. 200 ml.	

The sodium metal (1.31 g.) is dissolved in 60 ml. of absolute ethyl alcohol and 60 ml. of polypropylene glycol-150 is added to form an alkaline alcoholic solvent medium. The sodium ethyl-(1-methylbutyl)-thiobarbiturate (50.0 g.) is dissolved in the said alcoholic solvent medium with agitation and the volume of the solution adjusted to 200 ml. by adding a mixed solvent consisting of polypropylene glycol-150 and absolute ethyl alcohol (50:50, volume basis). The clear solution thus formed is filtered

through a porcelain filter candle (Selas #01) and filled into 10 ml. ampoules. A nitrogen atmosphere is used throughout.

After heating the ampouled concentrated thiobarbiturate solution prepared in the foregoing manner for 8 hours at 100° C. and preparing therapeutic aqueous dilutions thereof, a clear solution is formed with no evidence of decomposition. Pharmacological tests show that there is no apparent difference in toxicity and anesthetic activity between the aqueous control sample of thiobarbiturate and the therapeutic dilution of the heated ampoule of thiobarbiturate solution.

Example XIV

A solution of sodium ethyl-1-(methylbutyl)-thiobarbiturate containing 25 grams of the said thiobarbiturate per 100 ml. of solution is formed with the following ingredients:

Sodium metal	g—	1.31
Sodium ethyl-(1-methylbutyl)-thiobarbiturate	g—	50.0
Absolute ethyl alcohol	ml—	70
Polypropylene glycol-425	ml—	30

Absolute ethyl alcohol-polypropylene glycol-425, 70:30 (volume basis), q.s. 200 ml.

The sodium metal (1.31 g.) is dissolved in 70 ml. of absolute ethyl alcohol and 30 ml. of polypropylene glycol-425 is added to form an alkaline alcoholic solvent medium. The sodium ethyl-(1-methylbutyl)-thiobarbiturate (50.0 g.) is dissolved in the said alcoholic solvent medium with agitation, and the volume of the solution is adjusted to 200 ml. by the addition of a mixed solvent consisting of absolute ethyl alcohol and polypropylene glycol-425, 70:30 (volume basis). The clear solution thus formed is filtered through a porcelain filter candle (Selas #10) and filled int 10 ml. ampoules. A nitrogen atmosphere is used throughout.

After heating the ampouled concentrated thiobarbiturate solution for 8 hours at 100° C. and preparing therapeutic aqueous dilutions thereof (2.5% thiobarbiturate) there is no apparent difference in the toxicity and anesthetic activity betwen the aqueous control sample of thiobarbiturate and the therapeutic dilution of the heated ampoule of thiobarbiturate solution.

Example XV

A solution of sodium ethyl-(1-methylbutyl)-thiobarbiturate containing 25 grams of the said thiobarbiturate per 100 ml. of solution is formed with the following ingredients:

Sodium metal	g—	0.50
Sodium ethyl-(1-methylbutyl)-thiobarbiturate	g—	25.0
Absolute ethyl alcohol	ml—	35
1,2,4-butanetriol	ml—	15

Absolute ethyl alcohol:1,2,4-butanetriol, 70:30 (volume basis), q.s. 100 ml.

The sodium metal (0.50 g.) is dissolved in 35 ml. absolute ethyl alcohol and 15 ml. of 1,2,4-butanetriol is added to form an alkaline alcoholic solvent medium. The sodium ethyl-(1-methylbutyl)-thiobarbiturate (25.0 g.) is dissolved in the said alcoholic solvent medium with stirring and the volume of the solution adjusted to 100 ml. by adding a mixed solvent consisting of absolute ethyl alcohol–1,2,4-butanetriol (70:30, volume basis). The solution thus formed is filtered through a porcelain filter candle (Selas #01) and the clear solution filled into 10 ml. ampoules. A nitrogen atmosphere is used throughout.

After heating the ampouled concentrated thiobarbiturate solution prepared in the foregoing manner for 8 hours at 100° C. and a therapeutic aqueous dilution thereof prepared (2.5% thiobarbiturate) pharmacological tests show no apparent difference in the toxicity and anesthetic activity between the aqueous control sample of thiobarbiturate and the said therapeutic dilution of the heated ampoule.

It should be understood that the preferred method of preparing the remarkably stable substantially water-free concentrated solutions of the barbituric acid compounds disclosed herein comprises first forming an alcoholic solvent solution containing an alkaline reagent by reacting an alkali metal, such as sodium, with an excess of one of the alcohols which is employed in the solvent medium and thereafter dissolving an alkali metal salt of the barbituric acid compound in the alkaline solvent, said solvent containing sufficient alkaline reagent to maintain the barbituric acid in solution when therapeutic aqueous dilutions of the solvent solution are prepared. It is also possible, however, to form the solutions of the present invention by adding to a substantially water-free alcoholic solvent solution containing the barbituric acid or water soluble salt thereof sufficient alkaline reagent, such as sodium ethylate, as an anhydrous solid or dissolved in a substantially water-free mono-, di-, or polyhydroxy alcohol which is employed in the alcoholic solvent as a constituent part thereof. In each procedure it is desirable to employ an inert atmosphere, such as a nitrogen atmosphere, to reduce the uptake of moisture to a minimum.

In the foregoing specific examples the substantially water-free alcoholic solvent media illustrating the present invention, the preferred solvent medium has comprised a parenterally acceptable aliphatic monohydric alcohol, ethyl alcohol, admixed with a parenterally acceptable aliphatic polyhydric alcohol in a proportion which provides the medium with a great solubilizing power for the thiobarbiturate compound while maintaining a relatively low viscosity therefor to permit ready handling during manufacturing operations and administration, each of said alcohols being stable in the presence of an alkaline reagent which is present in an amount sufficient to solubilize the thiobarbituric acid compound upon preparing therapeutic aqueous dilutions thereof. While ethyl alcohol has been found most useful in forming low-viscosity highly concentrated solutions of the barbituric acid type compounds disclosed herein, it should be understood that other parenterally acceptable relatively low-viscosity alcohols, such as ethylene glycol, can be used in place of ethyl alcohol. It also should be understood that in addition to the aliphatic polyhydric alcohols heretofore employed, other parenterally acceptable polyhydric alcohols, such as diethylene glycol, trimethylene glycol, and the four butylene glycols, can be used.

The principal thiobarbituric acid compound used to illustrate the present invention has been the readily available thiobarbiturate compound, sodium ethyl-(1-methylbutyl)-thiobarbiturate, more generally known as "Pentothal" sodium. It should be understood, however, that the herein disclosed invention is applicable to other barbituric acid compounds containing an atom or functional group which causes the barbituric acid compound to form a precipitate when admixed with water in the absence of a strongly alkaline reagent, such as most of the thio-barbituric acid compounds. Included within the latter group are thiobarbituric acid compounds containing one or more aryl, alkyl, alkylene, alkenyl, cyclopentyl, and cyclohexyl substituents. Of particular importance are the 5,5-disubstituted 2-thiobarbituric acid compounds, including the spiro thiobarbituric acids, and the N-methyl thiobarbituric acids, in addition to the phenyl-ethyl thiobarbituric acids, the cyclohexyl-ethyl thiobarbituric acids, the cyclopentyl-ethyl thiobarbituric acids, the cyclohexenyl-allyl thiobarbituric acids, the methylbutyl-ethyl thiobarbituric acids, and the methylbutyl-allyl thiobarbituric acids. Included among the spiro thiobarbituric acids are those containing the substituted cyclopentyl ring, such as spiro(2,3,5 - trimethylcyclopentane-1,5'-thiobarbituric acid), spiro(2 - ethyl-3,5-dimethylcyclopentane-1,5'-thiobarbituric acid), and spiro(2-methyl-5-ethylcyclopentane-

1,5'-thiobarbituric acid). Among the N-methyl thiobarbituric acid compounds useful in the present invention are 1-methyl-5-ethyl-5-(1'-methylbutyl)-thiobarbituric acid and 1-methyl-5-allyl-5-(1'-methylbutyl)-thiobarbituric acid. The parenterally acceptable water soluble salts of each of the above thiobarbituric acid compounds, such as the alkali metal, sodium salt, are possessed of the greatest utility in the present invention.

It is evident that in addition to providing an improved highly stable solution of barbituric acid compounds, such as the thiobarbiturates, the present invention also makes it possible for those desiring to use only small amounts of a thiobarbiturate at any one time to purchase thiobarbiturate solutions in large vials from which the individual therapeutic dilutions can be readily prepared and thereby avoid purchasing small individual dose ampoules of the dry acid salt as was heretofore necessary. Thus, the small purchaser such as the individual doctor can now obtain the same economic advantages as was heretofore possible only for the large institutional users.

Others may readily adapt the invention for use under various conditions of service, by employing one or more of the novel features disclosed or equivalents thereof. As at present advised with respect to the apparent scope of our invention, we desire to claim the following subject matter.

This is a continuation-in-part of the applicants' copending patent application Serial No. 328,532, filed December 29, 1952, now abandoned.

We claim:

1. A stable solution of a thiobarbituric acid compound having anesthetic or hypnotic properties comprising a water-free solution of a thiobarbituric acid compound selected from the group consisting of a therapeutically useful thiobarbituric acid and the water soluble salts thereof, dissolved in an anhydrous alcoholic solvent consisting of a mixture of a parenterally acceptable water-miscible lower aliphatic monohydroxy alcohol and a parenterally acceptable water-miscible lower aliphatic polyhydroxy alcohol, said solvent having dissolved therein a soluble alcoholate of a parenterally acceptable lower aliphatic alcohol and an alkali metal in an amount providing an alkali metal concentration substantially in excess of that required to maintain the said thiobarbituric acid compound dissolved in said solvent as an alkali metal salt.

2. A stable concentrated solution of a thiobarbituric acid compound having anesthetic or hypnotic properties comprising a substantially water-free solution of a thiobarbituric acid compound selected from the group consisting of a therapeutically useful thiobarbituric acid and the water soluble salts thereof, dissolved in an anhydrous alcoholic solvent consisting of a mixture of a parenterally acceptable water-miscible lower alphatic monohydroxy alcohol and a parenterally acceptable water soluble lower aliphatic polyhydroxy alcohol, said solvent having dissolved therein a soluble alcoholate of a parenterally acceptable lower aliphatic alcohol and an alkali metal in an amount providing an excess of between about 5% and 30% by weight alkali metal above the weight of the alkali metal in an alkali metal salt of the said thiobarbituric acid compound dissolved in said solvent.

3. A composition according to claim 2 wherein the said alcoholate is sodium ethylate.

4. A stable concentrated solution of a thiobarbituric acid compound comprising a water-free solution of a thiobarbituric acid compound selected from the group consisting of a therapeutically useful thiobarbituric acid and the water soluble salts thereof dissolved in an anhydrous alcoholic solvent consisting of ethyl alcohol and a polyhydroxy compound selected from the group consisting of propylene glycol, polypropylene glycol, glycerol, 1,2,4-butanetriol, and mixtures thereof, said solvent having dissolved therein a soluble alcoholate of a parenterally acceptable lower aliphatic alcohol and an alkali metal in an amount providing an alkali metal ion concentration substantially in excess of that required to maintain the said thiobarbituric acid compound as an alkali metal salt.

5. A stable concentrated solution of a thiobarbituric acid compound comprising a water-free solution of a thiobarbituric acid compound selected from the group consisting of a therapeutically useful thiobarbituric acid and the water soluble salts thereof dissolved in an anhydrous alcoholic solvent consisting of ethyl alcohol and a polyhydroxy compound selected from the group consisting of propylene glycol, polypropylene glycol, glycerol, 1,2,4-butanetriol, and mixtures thereof, said solvent having dissolved therein a soluble alcoholate of a parenterally acceptable lower aliphatic alcohol and an alkali metal in an amount providing an excess of between about 5% and 30% by weight alkali metal above the weight of the alkali metal in an alkali metal salt of the said thiobarbituric acid compound dissolved in said solvent.

6. A composition according to claim 5 wherein the anhydrous alcoholic solvent is comprised essentially of a mixture of anhydrous ethyl alcohol and glycerol.

7. A composition according to claim 5 wherein the anhydrous alcoholic solvent is comprised essentially of a mixture of anhydrous ethyl alcohol and 1,2,4-butanetriol.

8. A composition according to claim 5 wherein the anhydrous alcoholic solvent is comprised essentially of a mixture of anhydrous ethyl alcohol and polypropylene glycol.

9. A composition according to claim 5 wherein the anhydrous alcoholic solvent is comprised essentially of a mixture of anhydrous ethyl alcohol and propylene glycol.

10. A stable concentrated solution of a thiobarbituric acid compound consisting of a water-free solution of sodium ethyl-(1-methylbutyl)-thiobarbiturate in a non-aqueous solvent consisting of a mixture of ethyl alcohol and propylene glycol, said solvent having dissolved therein sodium ethylate in an amount providing an excess of between about 5% and 30% by weight sodium metal above the weight of the sodium in the sodium salt of the said thiobarbiturate dissolved in said solvent.

11. A stable concentrated solution of a thiobarbituric acid compound consisting of a water-free solution of sodium allyl-(1-methylbutyl)-thiobarbiturate in a non-aqueous solvent consisting of a mixture of ethyl alcohol and propylene glycol, said solvent having dissolved therein sodium ethylate in an amount providing an excess of between about 5% and 30% by weight sodium metal above the weight of the sodium in the sodium salt of the said thiobarbiturate dissolved in said solvent.

12. A stable concentrated solution of a thiobarbituric acid compound consisting of a water-free solution of sodium 5-Δ^2-cyclohexenyl-5-allyl-2-thiobarbiturate in a non-aqueous solvent consisting of a mixture of ethyl alcohol and propylene glycol, said solvent having dissolved therein sodium ethylate in an amount providing an excess of between about 5% and 30% by weight sodium metal above the weight of the sodium in the sodium salt of the said thiobarbiturate dissolved in said solvent.

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