Patented May 30, 1944 2,350,318

UNITED STATES PATENT OFFICE

2,350,318

AMINOALKANES

Horace A. Shonle and Ewald Rohrmann, Indianapolis, Ind., assignors to Eli Lilly and Company, Indianapolis, Ind., a corporation of Indiana

No Drawing. Application April 9, 1942, Serial No. 438,304

6 Claims. (Cl. 167—65)

This invention relates to aminoalkanes and more particularly to 2-amino-4-methylhexane.

Ephedrine and amphetamine (1-phenyl-2-aminopropane) have long been employed as vasoconstrictors. Ephedrine is obtained from Ma Huang and is also produced synthetically. Whether derived from natural sources or produced synthetically, the preparation of ephredrine is relatively expensive. Ephedrine and its salts are substantially nonvolatile and, as a result, their methods of application are limited to oral, parenteral, and topical administration. Amphetamine, on the other hand, is volatile, may be inhaled and considerable relief obtained in many cases of congestion of the nasal passage by this mode of administration. Amphetamine, however, has the decided disadvantage of markedly stimulating the central nervous system and is relatively toxic.

The compositions of this invention possess the desirable properties of both ephedrine and amphetamine but do not manifest some of the undesirable characteristics of these two materials. The compositions of this invention are 2-amino-4-methylhexane and the acid addition salts of 2 - amino - 4 - methylhexane. The 2 - amino - 4-methylhexane may be administered for the treatment of congestion of the nasal passage by inhalation, for it is more volatile than amphetamine. The 2-amino-4-methylhexane and its acid addition salts are substantially less toxic than amphetamine and its acid addition salts. Unlike ephedrine, which inhibits the action of smooth muscles, the compositions of this invention stimulate these muscles. The 2-amino-4-methylhexane and its acid addition salts increase the nasal volume to a greater extent than ephedrine or amphetamine. In addition, 2-amino-4-methylhexane and its salts have a negligible effect on the nervous system and are relatively nontoxic.

Aqueous solutions or solutions in physiological saline of 2-amino-4-methylhexane sulfate up to 4 percent are well tolerated by the human mucosa and produce no subjective discomfort of any kind in the patient. There is a notable absence of local tingling and of subsequent systematic reaction, such as tremor, excitement or insomnia which are some of the more common subjective symptoms produced by ephedrine and its acid addition salts.

The 2-amino-4-methylhexane may be administered topically, while the acid addition salts of 2-amino-4-methylhexane may be administered orally, parenterally, or topically. For topical administration of the 2-amino-4-methylhexane, it may be dissolved in a suitable solvent, such as cottonseed oil or liquid petrolatum, or it may be incorporated in a jelly or ointment, or it may be utilized directly by inhalation. The acid addition salts of the 2-amino-4-methylhexane are preferably dissolved in water or physiological saline solution or a sugar solution, such as glucose. For topical administration, a water solution, such as an isotonic water solution, can be conveniently used, while for parenteral administration physiological saline, an aqueous solution, or an isotonic solution of the desired acid addition salt may be employed. Jellies may also be used for topical administration and may be prepared by incorporating an acid addition salt of 2-amino-4-methylhexane in water, glycerin, and some viscous medium or thickening agent, such as gum tragacanth, sodium algenate or methyl cellulose.

In addition, the 2-amino-4-methylhexane or the acid addition salt of 2-amino-4-methylhexane may be combined with local anesthetic bases. Preferably, an acid addition salt of 2-amino-4-methylhexane is employed with an acid addition salt of the local anesthetic base or the local anesthetic base itself. Such combinations may be used in any suitable form, such as solutions, jellies, or ointments. An especially useful combination is that obtained by incorporating the acid addition salt of 2-amino-4-methylhexane with the acid addition salt of a local anesthetic base in an aqueous solution.

Examples of local anesthetic bases as such or as their acid addition salts for the purposes of this invention are:

Cocaine—methylbenzoylecgonine
Procaine—p-aminobenzoyldiethylaminoethanol
Δ-[2-methyl-piperidino]-propyl benzoate
p-Amino-benzoyl-dimethylamino-methylbutanol
p-Aminobenzoyl-Δ-di-n-butylaminopropanol
p - Aminobenzoyl - 2 - 2 - dimethyl - 3 - diethylaminopropanol
Monoisobutylaminoethyl-p-aminobenzoate
Piperidinopropanediol-di-phenylurethane
2 - butyloxyquinolinecarboxylic acid - 4 - diethyl ethylene-diamine
Δ-diethylaminopropylcinnamate

The compositions of this invention are prepared by any one of the following methods:

1. One molecular equivalent of 4 - methylhexanone-2 is reacted with slightly more than one molecular equivalent of hydroxylamine. Desirably, the hydroxylamine is prepared in the pres-

ence of the 4-methylhexanone-2 by reacting the hydrochloride or sulfate or other salt of the hydroxylamine with a suitable base, such as sodium carbonate or sodium hydroxide. Desirably, the reaction mixture is agitated for a few hours to insure the conversion of the 4-methylhexanone-2 to 4-methylhexanone-2 oxime. The resulting 4-methylhexanone-2 oxime separates and is dried by any suitable means, such as with a dehydrating agent, for example, sodium sulfate or magnesium sulfate. After drying, 4-methylhexanone-2 oxime is reduced with hydrogen by means of a catalyst, such as Raney nickel, or by reaction of sodium and a primary alcohol, such as ethanol. The resulting 2-amino-4-methylhexane may be purified by distillation.

2. Another method of preparing the 2-amino-4-methylhexane of this invention is to react one molecular equivalent of 4-methylhexanone-2 with approximately four molecular equivalents of formamide or ammonium formate. The mixture is heated to a temperature of 185°–190° C. and maintained at that temperature until the liberation of ammonium carbonate ceases. This condition may be readily ascertained by observing a condenser attached to the reaction mixture. The reaction product is separated from the excess formamide by adding water to the mixture, agitating, and separating the reaction product, which is insoluble in water, from the water solution. The reaction product is then refluxed with an excess of mineral acid, such as concentrated hydrochloric or dilute sulfuric acid. Desirably, the reaction product is refluxed for a period of from one to two hours, during which time the acid addition salt of 2-amino-4-methylhexane is formed. If the base 2-amino-4-methylhexane is desired, the acid addition salt is treated with a suitable base, such as sodium carbonate or sodium hydroxide. If purification is desired, it may be distilled.

3. A third method of preparing compositions of this invention is to subject a quantity of 4-methylhexanone-2 to the action of ammonia and hydrogen in the presence of a suitable catalyst, such as Raney nickel. Desirably, an excess of ammonia and hydrogen is used and the reaction may be conveniently performed in a bomb by dissolving the ammonia in a solvent, such as ethanol.

If acid addition salts of the base, 2-amino-4-methylhexane, are desired, the 2-amino-4-methylhexane is reacted with an equivalent of the desired acid. The reaction is almost immediate and can be carried out in a suitable solvent, such as ethyl ether, ethanol, or water. In this manner the acid addition salts of 2-amino-4-methylhexane may be formed, such as the acetic, hydrobromic, hydrochloric, sulfuric, maleic, propionic, or malonic acid salts of 2-amino-4-methylhexane.

In the preparation of the 2-amino-4-methylhexane or the acid addition salts of 2-amino-4-methylhexane by the methods outlined herein, racemic mixtures of the *d* and *l* forms of 2-amino-4-methylhexane or the acid addition salts of 2-amino-4-methylhexane result. These racemic mixtures may be removed, if desired, by any of the well-known methods and, after resolution, the *d* or the *l* form may be used alone as a vasoconstrictor or for other purposes instead of the racemic mixtures.

Typical examples of the compositions of this invention and the methods of preparing them are as follows:

Example 1.—Preparation of 2-amino-4-methylhexane.

In a 2-liter flask equipped with a stirrer and thermometer is placed 85 g. (0.52 mol) of hydroxylamine hydrochloride and 175 cc. of cold water. This mixture is stirred until solution is complete. To this solution is added 115 g. (1 mol) of 4-methylhexanone-2. The mixture is stirred and a solution of 50 g. (0.5 mol) of anhydrous sodium carbonate in about 150 cc. of water is added through a dropping funnel. This addition is regulated so that the temperature does not rise above 50° C. During this time 4-methylhexanone-2 oxime is formed. The stirring is continued for 1 to 2 hours after the addition is completed. The mixture separates into two layers, a water layer and a water-immiscible layer. The water-immiscible layer, which contains the 4-methylhexanone-2 oxime, is washed with water and dried with magnesium sulfate or sodium sulfate.

A solution of 80 g. of crude dry 4-methylhexanone-2 oxime in 1800 cc. of absolute ethanol is heated to boiling in a 5-liter flask equipped with an efficient reflux condenser. The source of heat is withdrawn and approximately 200 g. of sodium metal is added as rapidly as possible without essential loss of the ethanol. During this time the 2-amino-4-methylhexane is formed. When all of the sodium is added and reacted, the mixture is cooled and diluted with about 1500 cc. of water. The mixture is distilled through an efficient condenser until no more 2-amino-4-methylhexane comes over. The distillate is adjusted to about pH 6 with hydrochloric acid and the solvents removed by heating in vacuum. The residual material is cooled and made alkaline with strong sodium hydroxide solution. The 2-amino-4-methylhexane is separated from the lower water layer and dried first over solid potassium hydroxide and then over magnesium sulfate. The product, which is 2-amino-4-methylhexane, may be distilled as a colorless liquid, B. P. about 131°–133° C. uncorrected.

Example 2.—Preparation of 2-amino-4-methylhexane.

To a mixture of 20 g. of Raney nickel catalyst and 50 g. of 4-methylhexanone-2 contained in a steel bomb is added 170 cc. of cold absolute ethanol which has been saturated with anhydrous ammonia at −5° C. The resulting mixture is shaken for 3 hours with hydrogen at a pressure of 10 to 150 atmospheres at a temperature of 70° to 100° C. The catalyst is removed by filtration and the filtrate subjected to fractional distillation through an efficient fractionating column. The fraction boiling at about 131°–133° C. consists of 2-amino-4-methylhexane.

Example 3.—Preparation of 2-amino-4-methylhexane.

A mixture of 250 g. (4 mols) of ammonium formate and 115 g. (1 mol) of 4-methylhexanone-2 is heated in a 1-liter flask equipped with a thermometer well and an 8-inch Vigreaux column. The top of the Vigreaux column is connected to a condenser of large bore set for distillation. The mixture is heated from 150° to 185° C. until distillation stops. The ketone which has distilled over is separated and returned to the reaction flask and the heating continued. Water, carbon dioxide and ammonia are formed as by-products in the reaction. The reaction re-

quires approximately 8 to 10 hours to complete. During this time the formyl derivative of 2-amino-4-methylhexane is formed. When the reaction is completed the mixture is shaken with water and the water-insoluble material separated. The water-insoluble material is refluxed with 150 cc. of concentrated hydrochloric acid for about two hours. During this time the hydrochloride of 2-amino-4-methylhexane is formed. The aqueous solution of the hydrochloride after being freed from any unchanged ketone, as by steam distillation, is cooled and made alkaline with strong sodium hydroxide solution. The separated 2-amino-4-methylhexane is dried first with solid potassium hydroxide and then with anhydrous magnesium sulfate. The 2-amino-4-methylhexane is distilled as a colorless liquid, boiling at about 131°–133° C. uncorrected.

In this preparation formamide may be used instead of ammonium formate with good results. As in the case with ammonium formate best results are obtained by using an excess of formamide.

Example 4.—Preparation of 2-amino-4-methylhexane.

A mixture of 97 g. (0.75 mol) of 4-methylhexanone-2 oxime, 100 cc. of ethanol and 8.0 g. of Raney nickel catalyst is shaken with hydrogen at 15 to 150 atmospheres pressure and a temperature of 75°–100° C. for 5 hours. During this time 2-amino-4-methylhexane is formed. The catalyst is removed by filtration and the filtrate subjected to fractional distillation. The material boiling at about 131°–133° C. uncorrected is collected separately and comprises the desired amine, 2-amino-4-methylhexane.

Example 5.—Preparation of 2-amino-4-methylhexane sulfate.

A mixture of 75 g. of 2-amino-4-methylhexane, 200 cc. of absolute ethanol and 340 cc. of aqueous 2N sulfuric acid is evaporated to dryness on a steam bath. During this time the 2-amino-4-methylhexane sulfate is formed. The white solid is powdered and washed on a Buchner funnel first with ethyl ether-ethanol (1:1) and then with dry ethyl ether. The white solid is dried at 60°–70° C. in an air oven. The product, which is 2-amino-4-methylhexane sulfate, does not have a definite melting point. It is very soluble in water and sparingly soluble in absolute ethanol. It contains a molecule of water of crystallization.

Other acid addition salts of 2-amino-4-methylhexane may be formed by reacting the 2-amino-4-methylhexane with the required acid. For example, 2-amino-4-methylhexane-n-hexyl sulfonate may be produced by reacting 2-amino-4-methylhexane dissolved in a suitable solvent, such as ethyl ether, with a solution of n-hexyl sulfonic acid dissolved in ethyl ether. Likewise, 2-amino-4-methylhexane malate, 2-amino-4-methylhexane benzoate, 2-amino-4-methylhexane glycolate, 2-amino-4-methylhexane nicotinate, 2-amino-4-methylhexane maleate, 2-amino-4-methylhexane gluconate, 2-amino-4-methylhexane phosphate, and 2-amino-4-methylhexane succinate may be prepared by reacting 2-amino-4-methylhexane, dissolved in a suitable solvent, with malic acid, benzoic acid, glycolic acid, nicotinic acid, maleic acid, gluconic acid, phosphoric acid, or succinic acid respectively.

Example 6.—Preparation of 2-amino-4-methylhexane inhalant compound.

An effective 2-amino-4-methylhexane inhalant compound is prepared by incorporating the following in approximately 100 cc. of liquid petrolatum:

2-amino-4-methylhexane	g.	1
Menthol	do	.75
Camphor	do	.75
Oil of thyme	cc.	.3
Liquid petrolatum to make	do	100

Example 7.—Preparation of 2-amino-4-methylhexane sulfate jelly.

An effective 2-amino-4-methylhexane sulfate jelly is prepared by compounding the following ingredients:

	Grams
2-amino-4-methylhexane sulfate	1
Glycerin	15
Tragacanth	1
Methyl salicylate	.01
Sodium phosphate	.2
Water to make	100

Example 8.—Preparation of 2-amino-4-methylhexane ointment.

An effective ointment of 2-amino-4-methylhexane is compounded from the following ingredients:

	Grams
2-amino-4-methylhexane	1
Menthol	.7
Camphor	.7
Oil of wintergreen	.3
Anhydrous wool fat	5
Liquid petrolatum	25
White petrolatum to make	100

Example 9.—Preparation of solution of acid addition salts of 2-amino-4-methylhexane.

An effective solution of 2-amino-4-methylhexane sulfate for use as a nasal spray is compounded from the following ingredients:

Chlorobutanol	g.	.5
2-amino-4-methylhexane sulfate	do	1
Physiological saline solution	cc.	100

In Examples 7 and 8, acid addition salts of 2-amino-4-methylhexane such as those described in Example 5 may be used instead of 2-amino-4-methylhexane, while in Example 6 oil-soluble acid addition salts such as 2-amino-4-methylhexane oleate may be employed instead of the 2-amino-4-methylhexane. In addition, various other therapeutic compositions may be substituted for the menthol, camphor, methyl salicylate and other ingredients used in the typical Examples 6, 7, and 8. The proportion of all ingredients in these examples may be varied within wide limits, it being understood that these examples are merely typical of a wide variety of solutions, jellies, and ointments which may be prepared with the compositions of this invention.

What is claimed is:

1. A composition selected from the class which consists of 2-amino-4-methylhexane and acid addition salts of 2-amino-4-methylhexane.

2. 2-amino-4-methylhexane.

3. An acid addition salt of 2-amino-4-methylhexane.

4. A solution of a composition selected from the class consisting of 2-amino-4-methylhexane and acid addition salts of 2-amino-4-methylhexane.

5. An isotonic solution of an acid addition salt of 2-amino-4-methylhexane.

6. A 2-amino-4-methylhexane sulfate.

HORACE A. SHONLE
EWALD ROHRMANN.