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LOCAL ANESTHETIC BASE AND SOLUTION AND THEIR MANUFACTURE

Samuel D. Goldberg, Brooklyn, N. Y., assignor to Novocol Chemical Mfg. Co. Inc., Brooklyn, N. Y., a corporation of New York

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12 Claims. (Cl. 167—52)

This invention relates to local anesthetic bases and solutions and their manufacture.

Procaine is the accepted local anesthetic for hypodermic injection. It is usually employed as the hydrochloride salt which is soluble in water. If injected alone in small doses hypodermically, the anesthetic is carried away by the arteries and capillaries and oxidized by the body within 15 minutes. Under such circumstances anesthesia, although it occurs, is neither profound nor prolonged enough for surgical purposes. Furthermore there is no control of hemorrhage and if surgery is attempted using procaine alone under the above circumstances, profuse bleeding occurs.

To prevent this epinephrin or a similar vaso-constrictor is combined in standard practice with procaine hydrochloride in water solution. Its action is to contract the capillaries and arterioles and thus to localize the local anesthetic at the point of its introduction by the hypodermic needle and at the same time to minimize bleeding.

The usual dose for a single hypodermic injection is about 2 cc. of a 2% solution of procaine hydrochloride which, therefore, contains about 0.04 gr. of the anesthetic. With this is ordinarily employed approximately .002–.005% of epinephrin. These concentrations will give sufficient anesthesia for the usual operation. If the percent of epinephrin is reduced below .002% the solution becomes substantially ineffective as an anesthetic. It is important for anesthetic purposes to employ as small quantities of materials producing anesthesia and vaso-constriction as possible to produce the desired effects, in order to minimize the after effects of the ingredients injected, all of which must be consumed in some way by the body.

Procaine is valueless as a surface anesthetic such as required in eye operations requiring a 10% solution as compared with the usual 2% solution for hypodermic use.

The principal object of the present invention accordingly is to produce a series of local anesthetic bases and solutions having relatively low toxicity compared with their potency, which shall employ a smaller quantity of anesthetic and vaso-constrictor to produce equal or greater anesthetic effects and which in some instances may omit the addition of a vaso-constrictor entirely; as well as a series of local anesthetic bases in solutions which may be used as surface anesthetics requiring less than the quantity of procaine for this purpose and having other advantages. Another object is to provide simple methods for manufacturing these substances.

The invention comprises the novel products as well as the novel processes and steps of processes according to which such products are manufactured, the specific embodiments of which are described hereinafter by way of example and in accordance with which I now prefer to practice the invention.

I have found in accordance with my invention that the mono alkyl amino ethyl para amino benzoates, having the formula $NH_2C_6H_4COOC_2H_4NH$ alkyl, are superior in their action to the standard anesthetics. I have found that these substances having this formula when used hypodermically in single doses may be employed with a vaso-constrictor in smaller amounts with respect to both the anesthetic and the vaso-constrictor than in the standard solutions of procaine hydrochloride now on the market, to produce the same or greater anesthetic effects. I have found that I may add 50% less epinephrin than can be employed with procaine to these new solutions to produce the same or greater anesthetic effect than produced by the ordinary combinations of procaine hydrochloride and epinephrin. In addition I have indications that in some instances the epinephrin or other vaso-constrictor may be entirely omitted.

In accordance with my invention I have found that the mono alkyl amino ethyl para amino benzoates can be prepared by combining a mono alkyl amino ethanol with para nitro benzoyl chloride to form a mono alkyl amino ethyl para nitro benzoate, which is then reduced by hydrogen or other reducing agent to form a mono alkyl amino ethyl para amino benzoate. In order to carry out this process it is necessary accordingly to secure the intermediate ethanols. I accordingly will describe the methods employed for producing these ethanol intermediates as follows:

1. The production of normal mono propyl amino ethanol

100 grams of normal propyl bromide and 50 grams of ethanolamine were refluxed in 100 cc. of ethyl alcohol for twenty-four hours. The alcohol was then distilled off and to the residue was added a 30% aqueous solution of sodium hydroxide. Solid sodium hydroxide was then added until the solution separated into two layers. The aqueous solution was then discarded and the oily layer extracted with ether, which caused a complete separation from any unreacted ethanolamine, which is insoluble in ether. The ethereal

layer was dried over sodium hydroxide and distilled. The normal mono propyl amino ethanol distilled without any forerunnings at a temperature of 181° C. There was no high boiling residue and the yield was 39 grams, or 67% of theory.

2. The preparation of normal mono butyl amino ethanol

The preparation of this substance follows the same procedure as given for normal propyl amino ethanol with the exception of the quantity of materials used and the use of the normal butyl amine as the starting material. The normal mono butyl amino ethanol distills without any forerunning at a temperature of 198° C. and there is no high boiling residue and the yield is 65% of theory.

3. The preparation of mono isobutyl amino ethanol

The preparation of this substance follows the same procedure as given for normal propyl amino ethanol with the exception of the quantity of materials used and the use of the isobutyl amine as the starting material. The normal mono isobutyl amino ethanol distills without any forerunning at a temperature of 186° C. and there is no high boiling residue and the yield is 60% of theory.

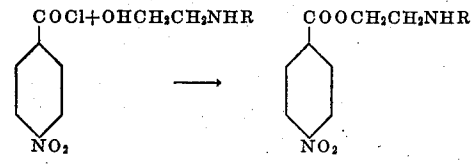
4. The preparation of mono normal amyl amino ethanol

The preparation of this substance follows the same procedure as given for normal propyl amino ethanol with the exception of the quantity of materials used and the use of the mono normal amyl amine as the starting material. The mono normal amyl amino ethanol distills without any forerunning at a temperature of 216° C. and there is no high boiling residue and the yield is 65% of theory.

As an alternative method of preparation of the above secondary alcohols, I may employ the following method:—Into a pressure flask is placed 149 grams of normal mono butyl aniline to which is added directly 40 grams (or .95 mol) of ethylene oxide. The flask was immediately stoppered and well shaken. It was then allowed to stand at room temperature for about three weeks. At the end of this time the contents of the flask were transferred to a distilling flask and distilled. The yield of butyl hydroxy ethyl aniline was quantitative. There was no low boiling fraction. The yield was 155 grams or 96% of theory. Boiling point 300° at 760 millimeters. To 50 grams (1 mol) of butyl hydroxy ethyl aniline thus prepared was added 19 grams of hydrochloric acid (2 mols) and the mixture cooled to 5° C. While agitated 1 mol of sodium nitrite was added slowly until the test with starch iodide paper indicated a slight excess of nitrous oxide. The nitrosated material was then dropped slowly on a boiling solution of 50% sodium hydroxide and steam-distilled. The steam distillation was continued until the distillate was no longer cloudy. The distillate was then extracted with ether, the ether dried and distilled. The yield was 10 grams of the normal mono butyl amino ethanol boiling at 198° to 200° or 33⅓% of theory.

This alternative method may be employed for preparing the other mono alkyl secondary alcohols, namely, the mono-isobutyl-, the mono-normal-amyl- and mono-isoamyl-, mono-normal-propyl-, the mono-isopropyl- and the mono-ethyl amino ethanol.

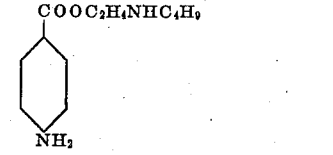
The condensation of the secondary amino alcohols just mentioned proceeds smoothly when reacted under proper conditions. Reaction is as follows:



It is important that the conditions be such that the hydrogen of the hydroxyl group of the secondary amino alcohols shall be replaced. Otherwise the hydrogen may be eliminated from the amine group leaving the hydroxyl group unaffected, or a second molecule of para nitro benzoyl chloride may take part in the reaction, these side reactions producing different products from those represented in the above equation. If the temperature is raised too high, the above reaction fails and para nitro benzoyl chloride is saponified into para nitro benzoic acid. Since the condensation with the nitrogen group yields a substituted amide, upon raising the temperature the amide is also saponified to the para nitro benzoic acid and the secondary amino alcohol is regained. This saponification occurs through the presence of sodium hydroxide. In addition the quantity of sodium hydroxide is essentially the same for all of the reactions involving the alkyl amino ethanols used. If the temperature is kept too low, the reaction indicated by the equation above may take place partially but in addition there will be a reaction with two molecules of the para nitro benzoyl chloride.

When alkyl amino alcohols below butyl amino ethanol are used, the para nitro benzoyl chloride should be added in small quantities to the aqueous solution to avoid saponification of the para nitro benzoyl chloride. The reaction materials are preferably used in molecular equivalents since an excess of para nitro benzoyl chloride is detrimental to the reaction.

The following is the preferred procedure which is used in effecting condensations producing local anesthetic bases in accordance with my invention: The preparation of the mono normal butyl amino ethyl para amino benzoate,



10 grams of mono normal butyl amino ethanol, 16 grams of para nitro benzoyl chloride and 5 grams of sodium hydroxide in 175 cc. of water were allowed to react. The temperature was maintained between 30° to 40° C. during reaction. The reaction mixture was extracted with ether, the ether evaporated, and the resultant oil washed with water to remove any unreacted secondary amino alcohol and then dried. The yield was 21 grams or 91% of theory. The compound responded positively when tested for the presence of the amine configuration and also the nitro group. The yellow viscous oil which was formed was mono-butyl amino ethyl para nitro benzoate. 20 grams of this latter material was directly reduced with 15 grams of tin and 50 cc. of concentrated hydrochloric acid. The temperature of the reduction was controlled by addition from time to time of small quantities of cold water to

maintain the temperature at or near 70° C. When the reaction was completed 150 cc. of sodium hydroxide was added and the solution then cooled to 15° C. The oil which gradually formed combined with undissolved tin to form a pasty mass which soon settled. The supernatant liquid was decanted and the residue washed two or three times with water to remove all traces of alkali. The oily mass, freed from most of its water, was then extracted with ether and filtered. The filtrate was evaporated to dryness and the yield of the base obtained was 13 grams or 73.5% of theory. In order to get the melting point of the base, the mono-hydrochloride was first formed and purified, then the hydrochloride was dissolved in water and just neutralized with ammonia water. The colorless oil formed soon crystallized into a white solid, which after filtration and air drying, had a melting point of 74° to 74.5° C. The hydrochloride was made when the oily base was dissolved in propyl alcohol and the calculated quantity of aqueous hydrochloric acid added to form the mono-hydrochloride of this compound. After repeated recrystallizations, a white needle crystal was formed which had a melting point at 146° C.

The mono isobutyl amino ethyl para amino benzoate, the n-mono amyl amino ethyl para amino benzoate and the mono isoamyl amino ethyl para amino benzoate are prepared in a similar manner to that just described, with suitable well-known variation in the quantity of the reacting materials according to their molecular weights. The following are the properties of the compounds just mentioned as determined by me:

Compound	Melting point of base	Melting point of hydrochloride
Mono n-butyl amino ethyl p-amino benzoate	74. 5–75. 5	146
Mono isobutyl amino ethyl p-amino benzoate	----------	192–194
Mono n-amyl amino ethyl p-amino benzoate	64. 5–65	152–153
Mono iso-amyl amino ethyl p-amino benzoate	----------	148–149

In addition to the amyl and butyl derivatives mentioned above, my work indicates that the corresponding propyl derivatives, for example mono propyl amino ethyl para amino benzoate also has similar properties to these materials described above and apparently it has a high anesthetic efficiency.

The group of hydrochloride salts of mono alkyl amino ethyl p-amino benzoates just described form definite crystals with sharp melting points. They are all soluble in water and ethyl alcohol and sparingly soluble in propyl alcohol. The bases, on reprecipitation, formed white powdery flakes, insoluble in water, but readily soluble in acetone, ethyl alcohol and benzene, and soluble in an excess of ether.

All the bases, before being converted to the hydrochloride, were strongly anesthetic to the tongue. After their conversion to the hydrochloride, it was found that all these compounds seemed to retain their anesthetic properties when tested by the tongue. They differ in this respect from procaine hydrochloride, since that salt has no anesthetic effect whatsoever when placed upon the tongue.

The condensates so obtained were tested for their anesthetic properties. Tests were also made to determine whether the materials had vaso-constrictive properties and in some instances as noted below this was found to be the case. In testing for these properties the procedure of Sollmann (Journal of Pharmacology and Experimental Therapeutics, 1918, and his handbook) was followed. These tests were the following:

(1) Conduction anesthesia on the sciatic nerve of a frog (corresponding to nerve block).
(2) Surface anesthesia—
  (*a*) On the surface of a frog's leg.
  (*b*) On cornea of a rabbit's eye.
(3) Intracutaneous—wheal method on the arm of a human being (corresponding to infiltration anesthesia).
(4) Toxicity—minimum lethal dose on white mice.
(5) Excised arterial spiral.

Since their behavior under test conditions is well established, cocaine, butyn, procaine and epinephrin were the criteria used to prove the accuracy of the technique and to afford a baseline against which the new compounds were standardized.

Results of Test No. 1 for the conduction anesthesia on the sciatic nerve of a frog shows as follows: In accordance with this test the mono amyl amino ethyl para amino benzoate and the mono iso-amyl amino ethyl para amino benzoate were about four times as strong as procaine. The mono isobutyl amino ethyl para amino benzoate as an anesthetic was about three times as strong as procaine and mono butyl ethyl amino para amino benzoate was equivalent to procaine in strength.

Test No. 2.—Surface anesthesia on the surface of a frog's leg showed that mono amyl amino ethyl para amino benzoate and mono iso-amyl amino ethyl para amino benzoate were practically four times as strong as cocaine; mono butyl ethyl amino para amino benzoate and mono isobutyl amino ethyl para amino benzoate about one-half as strong as cocaine as a surface anesthetic. (*b*) Surface anesthesia of the same relative strength as obtained on the frog's leg was also obtained on the cornea of the rabbit's eye.

Test No. 3.—The intracutaneous or wheal method showed that mono isobutyl amino ethyl para amino benzoate, mono amyl amino ethyl para amino benzoate and mono iso-amyl amino ethyl para amino benzoate were four times as strong as procaine and mono butyl amino ethyl para amino benzoate twice as strong as procaine.

Test No. 5.—Vaso-constriction by means of the arterial spirals indicate that at certain concentrations mono amyl amino ethyl para amino benzoate and mono iso-amyl amino ethyl para amino benzoate exhibit this property.

From the above it will be noted that the mono alkyl amino ethyl para amino benzoates possess excellent anesthetic properties, some of the members of the series also exhibiting vaso-constrictor action. The toxicity of these compounds is relatively low especially in consideration of their high anesthetic potency.

The local anesthetics herein described are compatible with epinephrin and may be employed therewith in water solution. Those anesthetics which have a vaso-constrictor action as herein described may be employed without epinephrin where anesthetic concentration in the dose given is a sufficient concentration to produce the desired constriction of the arterioles or capillary walls. If the anesthetic concentration is insufficient for this purpose, I prefer to add epinephrin

or other compatible vaso-constrictor to produce a proper constrictive effect for local anesthesia.

The following are specific examples of the use of anesthetic solutions according to my invention: 5 grams of mono amyl ethyl amino ethyl para amino benzoate hydrochloride with 6 grams of sodium chloride are dissolved in sufficient water to make one liter. Epinephrin is added to the extent of one part per 100,000. 1 gram of sodium bisulfite is added per liter. The solution as prepared above is suitable for subcutaneous injection.

Instead of mono amyl ethyl amino ethyl para amino benzoate hydrochloride used in the above example, I may substitute any one of the other anesthetics mentioned—mono isobutyl amino ethyl para amino benzoate, mono butyl amino ethyl para amino benzoate, mono iso-amyl amino ethyl para amino benzoate, using the same proportion namely 5 grams per liter as mentioned in the above example.

For surface anesthesia I prefer to use the following formula: 10 grams of mono normal amyl amino ethyl para amino benzoate hydrochloride, 6 grams of sodium chloride dissolved in sufficient water to make one liter of solution. In place of the mono normal amyl I have also employed the mono iso-amyl amino ethyl para amino benzoate in the same proportion as employed in the above example for surface anesthesia.

The solutions described have been employed by me to give successful local anesthesia.

The expression "mono butyl amino" as employed in the claims is intended to cover both mono normal butyl amino compounds as well as compounds containing the isomers of the mono butyl group. Similarly the expressions "mono-amyl amino" and "mono propyl amino" are intended to cover both the normal compounds and the isomers thereof. The expression "mono lower alkyl amino ethyl amino benzoate" is used to cover not only the compounds herein specifically given as the preferred form of my invention, but as well compounds having the same general properties as my preferred compounds for the purpose stated.

In the claims where the compound "a mono alkyl amino ethyl para amino benzoate" or similar compound is claimed, it is intended not only to cover this compound, which is not easily soluble in water, but also, where the context permits, the more readily soluble form such as for example the hydrochloride.

While I have described my improvements in great detail and with respect to preferred forms thereof, I do not desire to be limited to such details and forms since many changes and modifications may be made and the invention embodied in widely different forms without departing from the spirit and scope thereof in its broader aspects. Hence I desire to cover all modifications, forms and embodiments coming within the language or scope of any one or more of the appended claims.

What I claim as new and desire to secure by Letters Patent is:

1. As a new compound a mono lower alkyl amino ethyl amino benzoate having the formula $NH_2C_6H_4COOC_2H_4NH$ alkyl.

2. As a new compound a mono amyl amino ethyl para amino benzoate having the formula $NH_2C_6H_4COOC_2H_4NHC_5H_{11}$.

3. As a new compound a mono butyl amino ethyl par amino benzoate having the formula $NH_2C_6H_4COOC_2H_4NHC_4H_9$.

4. As a new compound a mono alkyl amino ethyl para amino benzoate having the formula $NH_2C_6H_4COOC_2H_4NH$ alkyl, in which the alkyl group contains not more than five carbon atoms in the chain.

5. An anesthetic solution containing a salt of a mono alkyl amino ethyl para amino benzoate in which the alkyl radical is a derivative of a lower aliphatic hydrocarbon dissolved in water.

6. An anesthetic solution containing a salt of a mono alkyl amino ethyl para amino benzoate, in which the alkyl group contains not more than five carbon atoms in the chain dissolved in water.

7. An anesthetic solution containing a salt of a mono amyl amino ethyl para amino benzoate, dissolved in water.

8. An anesthetic solution containing a salt of a mono butyl amino ethyl para amino benzoate, dissolved in water.

9. A process for the preparation of a local anesthetic which comprises combining a mono alkyl amino ethanol in which the alkyl radical is a derivative of a lower aliphatic hydrocarbon with para nitro benzoyl chloride to form the mono alkyl amino ethyl para nitro benzoate and reducing the nitro compound to form the mono alkyl amino ethyl para amino benzoate.

10. An anesthetic solution containing a salt of a mono alkyl amino ethyl para amino benzoate, in which the alkyl group contains not more than five carbon atoms in the chain, and vaso-constrictive material.

11. An anesthetic solution containing a salt of a mono alkyl amino ethyl para amino benzoate, in which the alkyl group contains not more than five carbon atoms in the chain, and less than 0.002% of epinephrin.

12. As a new compound a mono propyl amino ethyl amino benzoate having the formula $NH_2C_6H_4COOC_2H_4NHC_3H_7$.

SAMUEL D. GOLDBERG.

CERTIFICATE OF CORRECTION.

Patent No. 2,139,818. December 13, 1938.

SAMUEL D. GOLDBERG.

It is hereby certified that error appears in the printed specification of the above numbered patent requiring correction as follows: Page 4, second column, line 16, claim 3, for "par amino" read para amino; lines 42 and 43, claim 9, before "mono" insert corresponding; and that the said Letters Patent should be read with this correction therein that the same may conform to the record of the case in the Patent Office.

Signed and sealed this 31st day of January, A. D. 1939.

Henry Van Arsdale

(Seal) Acting Commissioner of Patents.