Patented Jan. 16, 1951

2,537,988

UNITED STATES PATENT OFFICE

2,537,988

SYMPATHOLYTIC COMPOSITIONS

Louis Sanford Goodman and Mark Nickerson, Salt Lake City, Utah, assignors to Burton T. Bush, Inc., New York, N. Y., a corporation of New Jersey

No Drawing. Application February 6, 1946, Serial No. 645,961

8 Claims. (Cl. 167—65)

1

This invention relates to novel sympatholytic and adrenolytic compositions having specificity of action and being relatively non-toxic.

Prior to our invention there was no known sympatholytic or adrenolytic material which was not too toxic or which had sufficient potency, specificity, or duration of action to be very useful in therapeutics. The importance of such a material did not go unrecognized as indicated by the activity directed towards the development of an effective sympatholytic agent.

We need only cite a few examples to illustrate the importance of sympatholytic agents in the treatment of disease. The treatment of high blood pressure represents a crucial medical problem even today. This can easily be appreciated when it is noted that one out of three of all people over fifty years of age die of some disease related to the heart and blood vessels. At present, an operation known as the Smithwick operation is sometimes performed in the treatment of high blood pressure. This operation involves removal of certain parts of the sympathetic nervous system. Our present invention makes it possible to accomplish the desired purpose without any operation at all. In addition to eliminating the ordeal of such an operation, our present invention also avoids the consequences of the operation, namely, the permanent loss of the excised parts, inasmuch as the effects of our drugs can be eliminated by stopping their administration.

Again, in the treatment of certain types of diseases of the blood vessels of the arms and legs (peripheral vascular disease), operation on the sympathetic nervous system is often done, and this condition too could be treated medically in accordance with the present invention.

Also, in the use of the excellent anesthetic, cyclopropane, one of the great dangers to the patient, sometimes resulting in death, is the effect of cyclopropane on the heart, in the presence of even minute amounts of epinephrine or in the presence of overactivity of the sympathetic nervous system. A sympatholytic drug given to a patient to whom cyclopropane had been administered as an anesthetic would protect him against the harmful effects of cyclopropane on the heart, thereby allowing cyclopropane anesthesia to be safe as well as efficient.

Before proceeding to identify the novel sympatholytic and adrenolytic agents, we believe it will aid to a better understanding of our invention if we set forth some remarks concerning the

2

nervous system and the action of sympatholytic agents thereon.

In the more highly organized forms of life the nervous system is indispensable for existence and is necessary in order to keep the internal environment of the organism constant and to allow adaptation of the organism to its environmental surroundings. In mammals the nervous system is divided into two large parts, the somatic nervous system consisting of the brain, spinal cord and peripheral nerves, and the autonomic or visceral nervous system. The central nervous system controls such processes as thought, locomotion and sensation, as well as emotion. The visceral nervous system is concerned with regulating all the autonomic functions of the body including heart rate, blood pressure, circulation of blood to different parts of the body, secretion and motility of the stomach and intestine, size of the pupil, sweating, temperature control, respiration, urinary tract function, etc. It is also concerned with emotions, particularly in joy, anger and fear. Life would be impossible without the visceral nervous system which is also intimately connected anatomically and physiologically to the central nervous system.

The visceral nervous system is likewise traditionally divided into two parts, one known as the sympathetic nervous system and the other as the parasympathetic nervous system. Most organs of the body are supplied by nerves from both of these divisions and as a general rule the actions of these nerves stand in opposition. For example, the sympathetic nervous system causes dilatation of the pupil of the eye whereas the parasympathetic nervous system causes constriction. Again, the parasympathetic nervous system causes slowing of the heart beat whereas the sympathetic nervous system causes speeding of the heart rate. The sympathetic nervous system causes constriction of blood vessels and a rise in blood pressure, whereas the parasympathetic system causes dilatation of blood vessels and a fall in blood pressure. The intestinal tract is stimulated by the parasympathetic system and relaxed by the sympathetic system.

Within the last twenty years it seems to have been definitely established that when a nerve impulse travelling over a nerve reaches the muscle cell or gland cell, a chemical substance is released which acts on the muscle or gland cell causing it to respond in its characteristic fashion. In the sympathetic system this chemical substance is known as sympathin, and perhaps is identical

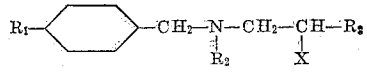
with the hormone of the adrenal medulla gland which is called adrenalin or epinephrine. In the parasympathetic nervous system the chemical is known as acetylcholine. In other words these two chemicals, acetylcholine and epinephrine, when given to animals or man will result in the same type of bodily reactions as caused by stimulation, respectively, of the parasympathetic and sympathetic nervous systems. Indeed, in the body, the sympathetic nervous system discharges not only sympathin but also epinephrine from the adrenal medulla.

Compositions which are the subject of this inventiion act in the body to prevent the usual excitatory action of either the sympathetic nervous system or epinephrine. In other words, an animal given the proper dose of these drugs will be protected against the effects of sympathetic nerve impulses of an excitatory nature and also against the excitatory effects of epinephrine, whether the latter is normally secreted in the body or injected by the physician.

Many diseases, syndromes, and symptoms experienced by patients are related to abnormal functions of the parasympathetic or sympathetic nervous system or to an imbalance between these two systems. In the parasympathetic field, excellent drugs such as the belladonna alkaloids are available to cause a blocking of either acetylcholine or parasympathetic nerve impulses. In the sympathetic field, no such drug is available. Indeed, as aforesaid, though some drugs have been suggested in this field, they have not been found to be suitable, because they are too toxic to be used extensively in man, because they are not sufficiently potent, or because they have so many side-effects that no specificity of action can be obtained.

The compositions described herein are known as sympatholytic and adrenolytic compounds because they prevent the previously described actions of the sympathetic nervous system and adrenalin.

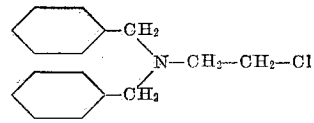
The novel sympatholytic and adrenolytic agents provided by this invention and having the above-indicated applications and uses include certain amines and their quaternary compounds as well as their salts with inorganic and organic acids. More specifically, these novel agents can be represented by the following general structural formula:



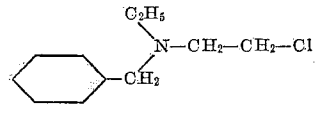
wherein R_1 is a member selected from the group consisting of H and CH_3, R_2 is a member selected from the group consisting of H, alkyl, aralkyl, aryl, haloalkylene and cycloalkyl radicals, R_3 is a member selected from the group consisting of H and CH_3, and X is halogen; organic and inorganic salts of said compounds; and quaternary salts of said compounds.

As specific examples of our novel sympatholytic and adrenolytic agents the following may be noted:

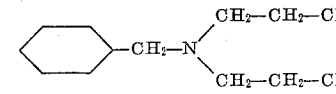
1



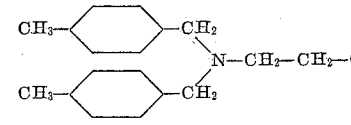
2



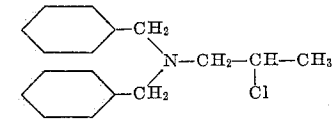
3



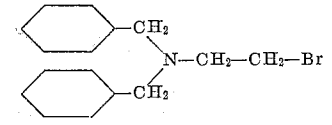
4



5



6



7. Hydrochlorides of compounds #1 to 5 above,
8. Hydrobromide of compound #6 above,
9. Salts of compounds #1 to 6 with acetic acid,
10. Salts of compounds #1 to 6 with benzoic acid,
11. Salts of compounds #1 to 6 with nitric acid,
12. Quaternary salts of compounds #1 to 6 with dimethyl sulfate or ethyl bromide.

The novel sympatholytic and adrenolytic compositions of this invention may be administered orally or parenterally. They may be employed in the form of tablets, made by incorporating inert carriers in the active ingredients, capsules, solutions, etc. For parenteral injections the water soluble compounds may be administered in the form of aqueous solutions. The non-water soluble salts may be administered in the presence of suitable solvents, as, for example, in the form of a 10% solution of the salts in propylene glycol. Such solution should be mixed with aqueous sodium chloride (0.9%) prior to intravenous injection.

The sympatholytic and adrenolytic agents herein have varying physical and chemical properties, depending, inter alia, on their structure, e. g., whether they are amines, salts with inorganic and organic acids, or quaternary ammonium salts. The amines are not water-soluble, but may be dissolved in ethyl alcohol, propylene glycol, and oxygenated solvents generally. The salts made with inorganic and organic acids are generally somewhat water-soluble, and also somewhat soluble in organic solvents such as those just mentioned. The quaternary salts are water-soluble and generally soluble in polar organic solvents.

In order to illustrate this invention more fully, but without thereby limiting it, the following examples are given.

EXAMPLE I

Dibenzyl-beta-chloroethylamine hydrochloride

To 610 grams of monoethanolamine, 1265 grams of benzyl chloride are added under stirring during five hours at a temperature of 100°–110° C. Stirring and heating at 100°–110° C. is continued for five more hours.

After cooling to about 70° C., a solution of 400 grams of sodium hydroxide in 600 cc. of water was gradually added under stirring and the mixture was heated in a boiling water bath for one hour. After cooling to room temperature, the contents were extracted with 800 cc. of benzene. The benzene solution was separated, washed with 1000 cc. of water, dried with anhydrous sodium

sulfate and filtered. The benzene was removed by distillation first under atmospheric pressure to a temperature of 90° C., and finally under vacuum of about 30 mm. mercury to about 100° C. The residual oil was then distilled at a vacuum of 5 mm. mercury and 848 grams of the desired material, boiling at 135°–192° C., were obtained. The liquid solidified on standing to a crystalline solid, congealing at 43° C.

A solution of 482 grams of dibenzyl aminoethanol in 500 cc. of chloroform was cooled in an ice bath and under stirring, a solution of 276 grams of thionyl chloride in 300 cc. of chloroform was added during two hours. Stirring was then continued for three hours under cooling. The reaction mixture was allowed to stand over night. The chloroform was distilled off under atmospheric pressure except near the end when vacuum was employed, and the crystalline mass was recrystallised from 700 cc. of ethanol containing 10 grams of decolorizing carbon. After filtration, 410 grams of white crystals of dibenzyl - beta - chloroethylamine hydrochloride, melting at 194°–195° C. were obtained; addition of ether to the mother liquor yielded a second crop of 90 grams (melting point 192°–194° C.).

Parenteral administration in man: this compound is dissolved in propylene gylcol (sterile technic) to the extent of 10%. It is stable in this solvent if the solution is acidified with anhydrous sulfuric acid (1:200 final concentration). Injection is made slowly intravenously (either by syringe technic directly or by injection into the tubing of an intravenous saline or glucose infusion) after dilution with 0.9% sodium chloride solution to at least 1:10. Evidence of physiological effect can usually be detected within 10 to 30 minutes, as indicated by paralysis of adrenergic excitatory effector cells. For example, the pupils become constricted, the peripheral vessels dilate if sympathetically constricted, the heart and blood vessels do not respond as before to sympathetic nerve impulses or to administered epinephrine, etc. Dosage: 5 to 10 mg./kg. per single dose. Effects may last several days.

Cats, rats and mice have been given this compound orally, acutely (single doses) and chronically (daily for as long as eight days), the dose used ranging from 5 to 20 times the intravenous dose. Effective oral doses are in the neighborhood of 5 times the parenteral dose. The action takes approximately an hour to become manifested and persists for days, even after a single dose.

Similar pharmacological results may be obtained with the materials prepared in accordance with the following examples.

EXAMPLE II

Dibenzyl-beta-chloroethylamine

300 grams of finely powdered dibenzyl-beta-chloroethylamine hydrochloride, prepared in accordance with Example I, were vigorously stirred for a half hour with 500 cc. of a saturated aqueous solution of potassium carbonate. The mixture was shaken with 400 cc. of benzene and the resulting benzene-containing layer was dried with anhydrous sodium sulfate, filtered, and the solvent was removed by distillation. The residual oil was distilled under high vacuum.

The desired dibenzyl-beta-chloroethylamine (210 grams) was obtained in the form of a yellowish oil, boiling at 176°–180° C. at 4 mm. Hg.

EXAMPLE III

Di-paramethyl benzyl-beta-chloroethylamine-hydrochloride

In a similar manner as in Example I, di-p-methylbenzyl amino ethanol (boiling point 205°–215° C. under 5 mm. Hg) was obtained from p-methyl benzyl chloride and monoethanolamine, and the di-p-methyl benzyl aminoethanol was converted into di-p-methyl benzyl-beta-chloroethylamine hydrochloride, melting at 171°–173° C. by means of thionyl chloride.

EXAMPLE IV

Benzyl-ethyl-beta-chloroethylamine hydrochloride

Benzyl chloride (253 grams) were dropped into ethyl monoethanolamine (356 grams) during two hours under stirring at a temperature of 100° C., and the mixture was kept at this temperature for six hours. A saturated solution of 150 grams of potassium carbonate was then added and after stirring and cooling, the reaction mixture was extracted with 500 grams of isopropyl ether. The isopropyl ether solution was dried over anhydrous sodium sulfate and distilled. After removal of the isopropyl ether, the residue was distilled at 10 mm. through a small Vigreux column. Obtained were 143 grams, boiling point 127°–135° C. and refractive index 20°, 1.5175 and 220 grams, boiling point 135° C. and refractive index 1.5190. The two fractions were combined for the preparation of the betachloroethyl derivative.

A solution of 190 grams of thionyl chloride in 100 cc. of chloroform was dropped under stirring into a solution of 268 grams of benzyl ethylamino ethanol in 300 cc. of chloroform which mixture was cooled in an ice bath. The time for the addition was about two hours, stirring was then continued for three hours under cooling. The reaction mixture was allowed to stand over night. The chloroform was then distilled off on the water bath, applying low vacuum at the end. 100 cc. of ethanol were added and the mixture evaporated to dryness in vacuo. The crystalline residue was dissolved in 300 cc. of isopropanol and the solution refluxed for about half an hour under the addition of 5 grams decolorizing carbon. To the filtered and cooled solution, petroleum ether (boiling point 60°–90° C.) was added until crystals started to separate. The crystals of benzyl ethyl-beta-chloroethylamine hydrochloride formed after standing were filtered, washed with petroleum ether and dried (300 grams, melting point 154°–155°).

EXAMPLE V

Benzyl-ethyl-beta-chloroethylamine

In accordance with the procedure of Example II, benzyl ethyl-beta-chloroethylamine (boiling point 114°–115° C. at 4 mm. Hg) was obtained from its hydrochloride (prepared as in Example IV).

EXAMPLE VI

Dibenzyl-beta-chloropropylamine hydrochloride

Into 150 grams of isopropanolamine, heated to 100° C. were dropped under stirring 253 grams of benzyl chloride during two hours; the mixture was then kept at 100°–110° C., for five hours. A concentrated solution of 90 grams of sodium hydroxide was then added and the reaction product extracted with 600 grams of benzene. The benzene solution was washed with water, dried over

anhydrous sodium sulfate and distilled. After removal of the benzene, the residual oil was distilled in vacuo and 168 grams of dibenzyl amino isopropanol, boiling point 170°–175° C., were collected.

Dibenzyl amino isopropanol (127 grams) were dissolved in 100 cc. of chloroform and cooled in an ice salt bath. To this solution, 70 grams of thionyl chloride in 100 cc. of chloroform were added under stirring during two hours. Stirring was then continued for another three hours under cooling. The reaction mixture was allowed to stand over night. The chloroform was distilled off, applying low vacuum at the end. Ethanol (50 cc.) was added and the mixture evaporated to dryness in vacuo. The crystalline residue was dissolved in 80 cc. of isopropanol and the solution purified by addition of 2 grams of decolorizing carbon and refluxing for thirty minutes. The filtered and cooled solution was brought to crystallisation by adding isopropylether. 92 grams of white crystals, melting at 165°–167° were obtained.

EXAMPLE VII

Dibenzyl-beta-chloropropylamine

In accordance with the procedure of Example II dibenzyl - beta - chloropropylamine (boiling point 176°–177° C. at 3 mm. Hg) was obtained from its hydrochloride (prepared as in Example VI).

EXAMPLE VIII

Benzyl di-beta-chloroethylamine hydrochloride

Benzyl chloride (190 grams) was slowly dropped under stirring into diethanolamine (315 grams), heated to 100° C. During the addition which took about one hour, the temperature rose to 125° C. Stirring was continued at this temperature for eight hours. Sufficient saturated potassium carbonate solution to neutralize the formed hydrochlorides was added and the mixture stirred for thirty minutes at 90° C. An oil separated; extraction with isopropyl ether (500 cc.) dissolved only small amounts of this oil. The oil and the isopropyl ether fraction were combined and enough ethanol added to obtain a homogeneous mixture. This solution was dried over anhydrous sodium sulfate and distilled. After removal of the solvent, the oil was distilled through a Vigreux column in vacuo. The fraction boiling at 174°–183° C. at 6 mm. was redistilled and 162 grams of pure di-beta-hydroxyethylbenzylamine, boiling point 176°–177° C. were obtained.

Into 97 grams of di-beta-hydroxyethyl benzyl amine, dissolved in 100 cc. of chloroform, and cooled with water, were dropped in under stirring 120 grams of thionyl chloride dissolved in 100 cc. of chloroform. The same procedure as described for benzyl ethyl-beta-chloroethylamine hydrochloride was applied, except that ethyl ether was used in place of petroleum ether, and 115 grams of white, crystalline di-beta-chloroethyl benzylamine hydrochloride, melting at 148°–150° C., were obtained.

EXAMPLE IX

Benzyl di-beta-chloroethylamine

In accordance with the procedure of Example II, di - beta - chloroethylbenzylamine (boiling point 148°–150° C. at 4 mm. Hg) was obtained from its hydrochloride (prepared as in Example VIII).

EXAMPLE X

Di-benzyl-beta-bromoethylamine hydrobromide

Melted dibenzyl aminoethanol (48 grams) prepared in accordance with Example I, were slowly added to 90 cc. of ice cold hydrobromic acid (d=1.42). The mass became solid and another 90 cc. of hydrobromic acid were added. The mixture was then refluxed for three hours and about 50 cc. liquid distilled off. After refluxing for another three hours, the reaction product was concentrated to about 50 cc. and twice shaken out with ether (100 cc. each). The residue was dried in vacuo and twice recrystallised from alcohol (50 cc.) under addition of ether until crystals separated. White crystals of dibenzyl-beta-bromoethylamine hydrobromide (38 grams) of melting point 176°–178° C. were obtained. The analysis showed 41.6% Br (theory 41.8%).

EXAMPLE XI

Di-benzyl-beta-bromoethylamine

In accordance with the procedure of Example II, di-benzyl-beta-bromoethyl amine (boiling point 177°–178° C. at 3 mm. Hg) was obtained from its hydrobromide (prepared in accordance with Example X).

EXAMPLE XII

Beta-chloroethyl-dibenzyl-methyl ammonium methosulfate

13 grams of dibenzyl-beta-chloroethyl amine (prepared as in Example II), 14 grams of dimethyl sulfate and 40 cc. of specially denatured #30 alcohol were boiled for 4 hours. The contents were passed into 200 cc. of ethyl ether under stirring, and then permitted to stand for a half hour. The ether was decanted and the residue was twice washed with 50 cc. of ethyl ether by thorough shaking followed by decantation of the supernatant liquid after settling. The resulting viscous oil was dried under high vacuum (4 mm. Hg) at 90° C. for one hour.

21 grams of a viscous brown oil were obtained. It is soluble in water, alcohol, acetone and propylene glycol, and insoluble in aromatic and petroleum hydrocarbons.

EXAMPLE XIII

Dibenzyl-beta-bromoethyl-methyl-ammonium methosulfate

In accordance with the procedure of Example XII, dibenzyl-beta-bromoethyl-methyl-ammonium methosulfate in the form of a brownish, very viscous liquid, was obtained from its amine (prepared in accordance with Example XI). This liquid is soluble in water, ethyl alcohol, methyl alcohol, acetone, propylene glycol, but is insoluble in ethyl ether, benzene and petroleum ether.

EXAMPLE XIV

Benzyl-di-beta-chloroethyl-methyl-ammonium methosulfate

In accordance with the procedure of Example XII, the above named material was obtained from its amine (prepared in accordance with Example IX) in the form of a brownish, very viscous liquid. This liquid is soluble in water, ethyl alcohol, methyl alcohol, acetone, propylene glycol, but is insoluble in ethyl ether, benzene and petroleum ether.

EXAMPLE XV

Benzyl-ethyl-beta-chloroethyl methyl ammonium methosulfate

In accordance with the procedure of Example XII, the above named material was obtained from its amine (prepared in accordance with Example V), in the form of a brownish, very viscous liquid. This liquid is soluble in water, ethyl alcohol, methyl alcohol, acetone, propylene glycol, but is insoluble in ethyl ether, benzene and petroleum ether.

EXAMPLE XVI

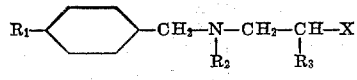
Dibenzyl-beta-chloropropyl-methyl ammonium methosulfate

In accordance with the procedure of Example XII, the above named material was obtained from its amine (prepared in accordance with Example VII, in the form of a brownish, very viscous liquid. This liquid is soluble in water, ethyl alcohol, methyl alcohol, acetone, propylene glycol, but is insoluble in ethyl ether, benzene and petroleum ether.

The foregoing illustrates the practice of this invention, which however, is not to be limited thereby but is to be construed as broadly as permissible in view of the prior art and limited solely by the appended claims.

What is claimed is:

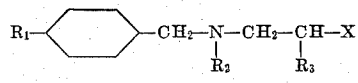
1. Therapeutic compositions having sympatholytic and adrenolytic properties, comprising propylene glycol and at least one material selected from the group consisting of salts of organic and inorganic acids with amines having the following general structural formula:



wherein R_1 is a member selected from the group consisting of H and CH_3, R_2 is a member selected from the group consisting of H, alkyl, aryl, aralkyl and haloalkyl radicals, R_3 is a member selected from the group consisting of H and CH_3, and X is a halogen selected from the group consisting of chlorine and bromine; and quaternary ammonium salts of said amines.

2. Therapeutic compositions having sympatholytic and adrenolytic properties, comprising dibenzyl-beta-chlorethylamine hydrochloride and propylene glycol.

3. Therapeutic compositions having sympatholytic and adrenolytic properties comprising non-toxic, organic oxygenated solvent and at least one material selected from the group consisting of salts of organic and inorganic acids with amines having the following general structural formula:



wherein R_1 is a member selected from the group consisting of H and CH_3, R_2 is a member selected from the group consisting of H, alkyl, aryl, aralkyl and haloalkyl radicals, R_3 is a member selected from the group consisting of H and CH_3, and X is a halogen selected from the group consisting of chlorine and bromine; and quaternary ammonium salts of said amines.

4. Therapeutic compositions having sympatholytic and adrenolytic properties, comprising dibenzyl-beta-chlorethylamine hydrochloride and non-toxic, organic oxygenated solvent.

5. Therapeutic compositions having sympatholytic and adrenolytic properties, comprising di-paramethylbenzyl-betachloroethylamine hydrochloride and propylene glycol.

6. Therapeutic compositions having sympatholytic and adrenolytic properties, comprising benzyl-ethyl-betachloroethylamine hydrochloride and propylene glycol.

7. Therapeutic compositions having sympatholytic and adrenolytic properties, comprising dibenzyl-beta-chloropropylamine hydrochloride and propylene glycol.

8. Therapeutic compositions having sympatholytic and adrenolytic properties, comprising dibenzyl-beta-bromoethylamine hydrobromide and propylene glycol.

LOUIS SANFORD GOODMAN.
MARK NICKERSON.

REFERENCES CITED

The following references are of record in the file of this patent:

FOREIGN PATENTS

Number	Country	Date
436,793	Great Britain	Oct. 14, 1935
538,456	Germany	Nov. 13, 1931
550,762	Germany	May 20, 1932

OTHER REFERENCES

Orth et al.: Squibb Abstract Bulletin, vol. 12, page 1194, Sept. 27, 1939. (Copy in Div. 43.)

Suter et al.: J. A. C. S. 63, 602–4 (1941). (Copy in P. O. S. L.)

J. A. P. A. Prac. Pharm Ed., June 1943, pp. 194, 195. (Copy in P. O. S. L.)

Introzzi: Squibb Abstract Bull., vol. 16, page 1964 (1943). Copy in Div. 43.

Jacobson et al.: J. A. M. A., Oct. 5, 1946, page 263. (Copy in P. O. S. L.)