Patented Apr. 18, 1950 2,504,122

UNITED STATES PATENT OFFICE

2,504,122

N-ALLYL-1,2-DIPHENYLETHYLAMINE

Louis H. Goodson, Kansas City, Mo., and Robert B. Moffett, Kalamazoo, Mich., assignors to George A. Breon & Company, Kansas City, Mo., a corporation of Missouri

No Drawing. Original application August 22, 1946, Serial No. 692,378. Divided and this application November 2, 1948, Serial No. 58,014

1 Claim. (Cl. 260—570.9)

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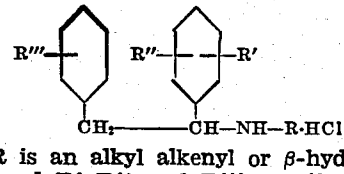
This invention relates to therapeutic compositions and more particularly to analgesics.

Among the several objects of the invention may be noted the provision of new analgesic compositions; the provision of new analgesic compositions that are readily soluble in available solvents to form stable solutions; the provision of new analgesic compositions that are readily administered; the provision of analgesic compositions that are relatively non-toxic and cause no serious complications or side reactions following administration; the provision of methods for manufacturing analgesic compositions of the class indicated that are characterized by their high yield, inexpensive and readily procurable reaction materials, and the facility with which they may be carried out; and the provision of new secondary amines having analgesic properties. Other objects will be in part apparent and in part pointed out hereinafter.

The invention accordingly comprises the ingredients and combinations of ingredients, the proportions thereof, steps and sequence of steps, and features of composition and synthesis, analysis, or metathesis, which will be exemplified in the products and processes hereinafter described, and the scope of the application of which will be indicated in the following claim.

According to the present invention analgesic compositions having desirable properties are provided. They are easily soluble in desired proportions in water, and are capable of being stored for long periods of time without being chemically, therapeutically or physically affected. The amount administered for effective analgesic action is substantially lower than that which is toxic. It has been found that analgesic compositions of the class described can be readily made in the form of powders, tablets, capsules, and ampules, to be used for any desired type of administration.

The analgesic compositions of the present invention have as an essential ingredient thereof, one or more compounds of the following formula:



where R is an alkyl alkenyl or β-hydroxyethyl radical and R' R'' and R''' are the same or different and are hydrogen, hydroxy, alkoxy or alkylenedioxy radicals.

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The analgesic compositions of the present invention were tested for their therapeutic efficacy by the following method. Adult male albino white mice were injected subcutaneously under the skin of the back just anterior to the tail. After a certain time interval, e. g. 10 minutes, a mouse so treated was placed on a hot circular plate surrounded by a hollow transparent cylinder. The time required for the mouse to show the effect of the heat, called hereinafter the reaction time, was determined by noting how long the mouse's hind feet would remain immobile or be normally active. The mouse would then be removed from the heated plate and after another time interval, e. g. 10 minutes, would be retested for reaction time. This procedure was repeated until the reaction time was less than a control time. This control time for each mouse was measured by determining how long the mouse, before injection, would remain on the heated plate without the abnormal movement of the hind feet referred to above.

The reaction time for the analgesic compositions described subsequently was found to be substantially greater than the control time, and no harmful after effects of any type were noted.

A sufficient number of normal mice were used in all tests to be sure that susceptibility due to age variations and other physical conditions were minimized. The fatal doses of the various compositions of the class described were also determined and found to be at concentrations substantially greater than the desired concentrations for effective analgesic action.

The amine ingredients of the analgesic compositions may be prepared by several general methods such as, for example, by the reaction of an appropriate benzyl phenyl ketone with an alkyl, alkanol or alkylene amine and formic acid and hydrolysis of the resulting amide, to give the desired N-substituted 1,2-diarylethylamine.

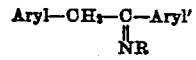
Also these compounds may be prepared by treating an appropriate aromatic aldehyde with a primary amine, treating the resulting Schiff's base with a substituted or unsubstituted benzyl magnesium halide and then isolating the desired N-substituted 1,2-diarylethylamine.

Furthermore these compounds may be prepared by the direct alkylation of the appropriate 1,2-diarylethylamine with agents such as dimethyl sulfate, ethylene chlorohydrin, and alkyl chloride or similar alkylating agents and then separating the desired secondary amine from the reaction product.

Another method of preparation is the treat-

ment of a 1,2-diarylethylhalide with the appropriate amine such as methyl amine, etc. and separating the secondary amine produced.

The reduction by catalytic or other means, of a Schiff's base of the formula



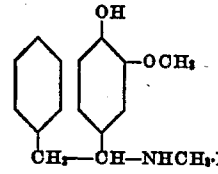
gives a secondary amine of this type also.

A secondary amine of this type also may be prepared by the hydrogenation of a ketone of the type Aryl-CH_2-CO-Aryl' in the presence of a catalyst and a primary amine.

While there are other methods of preparing the amines used in making the analgesic compositions of the present invention, the methods already outlined are preferred. The following examples illustrate the present invention. They are exemplary only.

EXAMPLE 1

N-methyl-1-(3-methoxy-4-hydroxyphenyl)-2-phenylethylamine hydrochloride

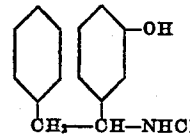


3-methoxy-4-hydroxybenzalmethylamine was prepared by heating a suspension of 76.07 g. of vanillin and 18.6 g. of methylamine in 300 ml. of benzene and removing the water formed in the reaction by refluxing the benzene with a continuous water separating device. The product was crystallized first from benzene and then from dioxane giving white crystals. M. P. 131–134.5° C.

A solution of 33.8 g. of this product in 100 ml. of hot dry dioxane was added to a stirred solution of benzyl magnesium chloride (prepared from 19.5 g. of magnesium, 92 ml. of benzyl chloride, and 300 ml. of dry ether). After refluxing for some time, the mixture set to a solid and the lumps were then broken up and added to ice and hydrochloric acid. On standing a crystalline precipitate separated which was recrystallized from methanol giving white crystals of the hydrochloride which melts at 178–180° C. and on continued heating of the sample it resolidified and melted again at 227–230° C. This product was dissolved in triple-distilled water to make an analgesic composition of the desired concentration, suitable for administration.

EXAMPLE 2

N-methyl-1-(3-hydroxyphenyl)-2-phenylethylamine hydrochloride

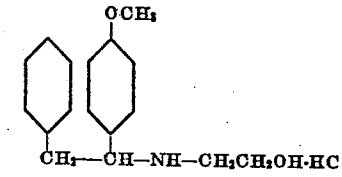


By a method similar to that described in Example 1, m-hydroxybenzalmethylamine was prepared from 24 g. of m-hydroxybenzaldehyde and 9.3 g. of methylamine. It was insoluble in benzene and upon recrystallization from dioxane had a M. P. of 150–153° C.

A solution of 19 g. of m-hydroxybenzalmethylamine in 71 ml. of dry dioxane was added to benzyl magnesium chloride (prepared from 13.6 g. of magnesium, 65 ml. of benzyl chloride and 200 ml. of dry ether). The mixture became very thick and 100 ml. of dry benzene were added to facilitate stirring. After decomposing the reaction mixture with ice and hydrochloric acid, the layers were separated and the aqueous layer was concentrated in vacuo. The hydrochloride crystallized out and was recrystallized from methanol. The M. P. was 201–202° C. This product was dissolved in triple-distilled water to make an analgesic composition of the desired concentration, suitable for administration.

EXAMPLE 3

N-(β-hydroxyethyl)-1-(4-methoxyphenyl)-2-phenylethylamine hydrochloride



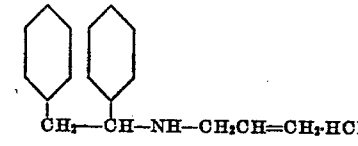
A mixture of 68 g. of anisic aldehyde, 34 g. of ethanolamine and 200 ml. of benzene was vigorously shaken for one hour and the water liberated in the reaction was removed by drying over anhydrous potassium carbonate. The organic solution was distilled and the fraction boiling at 106–109° C. at about 0.03 mm., freezing point 35° C., was collected.

To a solution of benzyl magnesium chloride prepared from 19.5 g. of magnesium, 92 ml. of benzyl chloride and 300 ml. of dry ether was added a solution of 32.6 g. of the above intermediate in 100 ml. of dry ether. After refluxing for one hour the mixture was treated with ice water and hydrochloric acid. The aqueous layer was separated and washed with ether and made strongly basic with sodium hydroxide. The aqueous suspension of magnesium hydroxide was extracted repeatedly with ether and the ether solution was washed with water and dried over potassium carbonate. The ether solution was distilled and the colorless amine, B. P. 160° C. at 13 mm., was collected, n_D^{25} 1.5727; d_D^{25} 1.0982.

The amine was converted into its hydrochloride by passing a stream of hydrogen chloride gas through a solution of it in dry ether. The hydrochloride was recrystallized from absolute alcohol. The M. P. was 154–155.5° C. This product was dissolved in triple-distilled water to make an analgesic composition of the desired concentration for administration.

EXAMPLE 4

N-allyl-1,2-diphenylethylamine hydrochloride

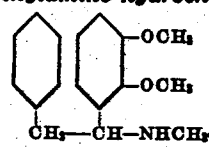


To a solution of benzyl magnesium chloride prepared from 19.5 g. of magnesium, 92 ml. of benzyl chloride and 300 ml. of dry ether, was added a solution of 29.1 g. of benzylallylamine in 50 ml. of dry ether. After refluxing for one hour the mixture was decomposed with ice and hydrochloric acid. The hydrochloride of the amine separated as a white crystalline precipitate and was collected on a filter, washed with water and ether and dried. After recrystallization from methanol it melted at 206–207.5° C. This product was dissolved in triple-distilled water to

make an analgesic composition of the desired concentration for administration.

EXAMPLE 5

N-methyl-1-(2,3-dimethoxyphenyl)-2-phenylethylamine hydrochloride

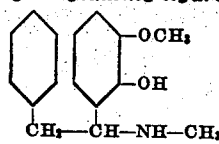


2,3-dimethoxybenzalmethylamine was prepared from 83.1 g. of 2,3-dimethoxybenzaldehyde and 18.6 g. of methylamine in 250 ml. of benzene by refluxing the benzene with a continuous water separating device. After removing the solvent in vacuo the product was distilled. The B. P. was 132° C. at 12 mm.

By a similar method to that described in Example 4, 35.8 g. of this product were allowed to react with benzyl magnesium chloride. The hydrochloride was crystallized from the decomposed reaction mixture and was recrystallized from methanol. The M. P. was 104–125° C. This product was dissolved in triple-distilled water to make an analgesic composition of the desired concentration for administration.

EXAMPLE 6

N-methyl-1-(2-hydroxy-3-methoxyphenyl)-2-phenylethylamine hydrochloride

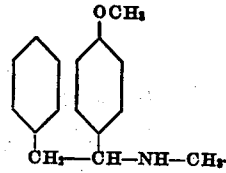


2-hydroxy-3-methoxybenzal methylamine was prepared from 83.1 g. of 2-hydroxy-1-methoxybenzaldehyde and 18.69 g. of methylamine by the method described in Example 5. It distilled at 132° C. at 12 mm.

A solution of 20 g. of this in 50 ml. of dry ether was allowed to react with benzyl magnesium chloride (prepared from 12.7 g. of magnesium, 60 ml. of benzyl chloride, and 200 ml. of dry ether). The reaction mixture was decomposed with ice and hydrochloric acid and an oily layer of the hydrochloride remained insoluble in both the water and ether layers. This was separated and dried in a vacuum desiccator and then crystallized from a mixture of absolute methanol and absolute ether. The M. P. was 176–179° C. This product was dissolved in triple-distilled water to make an analgesic composition of the desired concentration.

EXAMPLE 7

N-methyl-1-(4-methoxyphenyl)-2-phenylethylamine hydrochloride

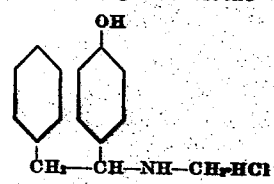


p-methoxyphenyl benzyl ketone 19 g. and methyl formamide 19.8 g. were heated at 180–210° C. for six hours in a distillation apparatus. The mixture was then refluxed six hours with a mixture of 40 ml. of concentrated HCl and 100 ml. of water. After cooling, the water solution was decanted and made strongly basic with sodium hydroxide. The crude product which separated was distilled at 116–126° C. at 0.05–0.13 mm., n_D^{27} 1.5643.

The hydrochloride was prepared by adding the amine to a solution of HCl in anhydrous alcohol. The amine hydrochloride was precipitated and washed with dry ether. The M. P. was 139–141° C. This product was dissolved in triple-distilled water to make an analgesic composition of the desired concentration.

EXAMPLE 8

N-methyl-1-(4-hydroxyphenyl)-2-phenylethylamine hydrochloride

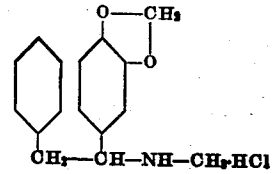


A mixture of 36.7 g. of p-hydroxybenzaldehyde, about 16 g. of methylamine, and 100 ml. of benzene was shaken vigorously for 1¼ hours, and then the solvent was refluxed, using a continuous water separating device. During the refluxing, the p-hydroxybenzal methylamine crystallized, and, after cooling, it was collected, dried, and recrystallized from dioxane; M. P. 175–177° C.

To a solution of benzyl magnesium chloride prepared from 19.5 g. of magnesium, 92 ml. of benzyl chloride and 300 ml. of dry ether, was slowly added a solution of 27 g. of the above p-hydroxybenzal methylamine in 250 ml. of warm dry dioxane. The mixture became very thick and 200 ml. of dry benzene were added to facilitate stirring. After refluxing for two hours with stirring, the mixture was decomposed with ice and hydrochloric acid. The layers were separated and after washing the aqueous layer with ether it was made basic by adding an excess of solid sodium carbonate. The mixture was extracted twice with n-butanol and then with ether and the combined extracts were dried over sodium sulfate. The solvent was distilled in vacuo and the residue was taken up in methanol, treated with decolorizing charcoal, and concentrated. Some 4-hydroxystilbene separated (M. P. 186–187° C.) which was discarded. The filtrate was saturated with hydrogen chloride gas and then diluted with ether to turbidity. After standing, the solution was filtered from a small amount of crystalline precipitate of unknown composition and poured into water. The aqueous solution was washed with ether and distilled in vacuo to a small volume which crystallized in cooling. The crystals were dissolved in methanol, diluted with ether, and cooled in the refrigerator. Crystals of the amine hydrochloride separated and were collected and dried. The M. P. was 170–173° C. On continued heating at the melting point of the sample, it crystallized and remelted at 220–224° C. This product was dissolved in triple-distilled water to make an analgesic composition of the desired concentration.

EXAMPLE 9

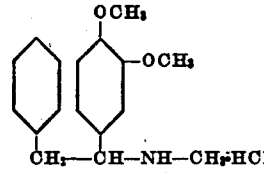
N-methyl-1-(3,4-methylenedioxyphenyl)-2-phenylethylamine hydrochloride



A solution of 32.6 g. of piperonal methylamine in 50 ml. of ether was allowed to react with benzyl magnesium chloride by a method similar to that described in Example 4. After recrystallization from methanol, the hydrochloride melted at 239–242° C. This product was dissolved in triple-distilled water to make an analgesic composition of the desired concentration.

EXAMPLE 10

N-methyl-1-(3,4-dimethoxyphenyl)-2-phenylethylamine hydrochloride

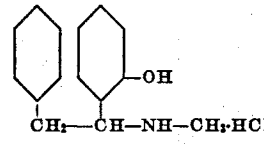


Veratral methylamine was made from 50 g. of veratraldehyde and an excess of methylamine by a method similar to that described in Example 5. It distilled at 144–152° C. at 11 mm.

By a method similar to that described in Example 3, 35.8 g. of veratral methylamine was allowed to react with benzyl magnesium chloride. The amine hydrochloride was recrystallized from a mixture of methanol and ether. The M. P. was 154–156° C. This product was dissolved in triple-distilled water to make an analgesic composition of the desired concentration.

EXAMPLE 11

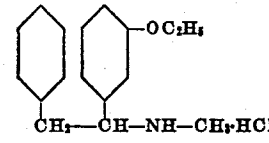
N-methyl-1-(2-hydroxyphenyl)-2-phenylethylamine hydrochloride



By a method similar to that described in Example 4 this amine hydrochloride was made from benzyl magnesium chloride and 27 g. of salicylal methylamine. After recrystallization from a mixture of absolute ethanol and absolute ether, the amine hydrochloride melted at 185–189° C. This product was dissolved in triple-distilled water to make an analgesic composition of the desired concentration.

EXAMPLE 12

N-methyl-1-(3-ethoxyphenyl)-2-phenylethylamine hydrochloride

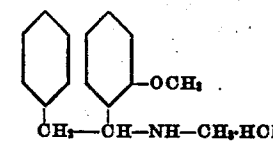


By a method similar to that described in Example 5, m-ethoxybenzal methylamine was prepared from 30 g. of m-ethoxybenzaldehyde and 10 g. of methylamine. The B. P. was 122° C. at 12 mm.

By a method similar to that described in Example 4, 22.7 g. of this product were allowed to react with benzyl magnesium chloride (prepared from 14.6 g. of magnesium, 69 ml. of benzyl chloride, and 200 ml. of dry ether). The amine hydrochloride was recrystallized from methanol. The M. P. was 171–175° C. This product was dissolved in triple-distilled water to make an analgesic composition of the desired concentration.

EXAMPLE 13

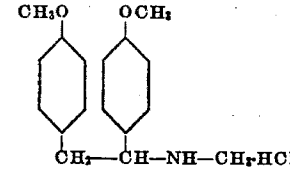
N-methyl-1-(2-methoxyphenyl)-2-phenylethylamine hydrochloride



By a method similar to that described in Example 4, 25.4 g. of o-methoxybenzal methylamine were allowed to react with benzyl magnesium chloride (prepared from 16.6 g. of magnesium, 79 ml. of benzyl chloride, and 275 ml. of dry ether). The amine hydrochloride separated from the decomposed reaction mixture as an oil which was separated and dried in a vacuum desiccator. It was crystallized from anhydrous acetone, M. P. 123–125° C. This product was dissolved in triple-distilled water to make an analgesic composition of the desired concentration.

EXAMPLE 14

N-methyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl) ethylamine hydrochloride

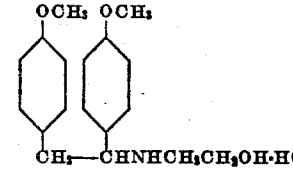


A mixture of 132 g. of desoxyanisoin, 118 g. of methyl formamide and 1 ml. of acetic acid was heated at 180–205° C. for twenty-eight hours. The mixture was cooled, washed with water, and the organic layer was boiled for six hours with a mixture of 200 ml. of concentrated hydrochloric acid and 500 ml. of water. After cooling, the aqueous layer was made strongly alkaline with sodium hydroxide. The resulting crude product (15 g.) melted at 56–58° C. and without purification was converted into its hydrochloride and crystallized from acetone with a yield of 7.1 g. The M. P. was 156–159° C. This product was dissolved in triple-distilled water to make an analgesic composition of the desired concentration.

In any of the amines described, one or more of the hydrogens on the phenyl groups can be replaced by an alkyl radical.

EXAMPLE 15

N-β-hydroxyethyl-1,2-di-p-methoxyphenylethylamine hydrochloride



Desoxyanisoin (30 g.), ethanolamine (8 g.), acetic acid (0.2 g.), and benzene (200 ml.) were refluxed using a continuous water separator until no more water was liberated (about six hours). The benzene was then removed under reduced pressure and replaced with absolute alcohol (140 ml.). Sodium metal (12 g.) was added rapidly to the boiling alcohol solution through a reflux condenser. When the sodium had dissolved the alcohol was removed and the residue was washed with water. The resulting crude N-β-hydroxy-

ethyl-1,2 - di - p - methoxyphenylethylamine was taken up into dilute hydrochloric acid and washed with benzene. The solution was made strongly basic with sodium hydroxide and extracted with ether. The ether layer was evaporated to dryness, finally under high vacuum, and the residue was converted to its hydrochloride in absolute alcohol. The hydrochloride melted at 210° C. This product was dissolved in triple-distilled water to make an analgesic composition of the desired concentration.

Analgesic compositions of other types than the solutions described above may be prepared. Tablets, capsules, ampules or powders, for example, may be made in the usual way employing the customary diluents, extenders, solvents, containers and the like, together with the amines described above. Such analgesic compositions may include more than one of the amines if desired, and the concentration of the amine or amines may be varied to vary the analgesic effect.

In view of the above, it will be seen that the several objects of the invention are achieved and other advantageous results attained.

As many changes could be made in the above processes and products without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

This application is a division of our copending U. S. Patent application S. N. 692,378, filed August 22, 1946.

We claim:

N-allyl-1,2-diphenylethylamine.

LOUIS H. GOODSON.
ROBERT B. MOFFETT.

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