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THE SUPPRESSION OF APPETITE WITH 1-(O-CHLOROPHENYL)-2-METHYL-2-PROPYLAMINE AND ACID-ADDITION SALTS THEREOF

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7 Claims. (Cl. 424—330)

ABSTRACT OF THE DISCLOSURE

Novel anoretic compositions comprising essentially a pharmacologically effective amount of 1 - (o - chlorophenyl)-2-methyl-2-propylamine or a pharmaceutically acceptable acid-addition salt thereof as the active anoretic ingredient, and a pharmaceutically acceptable carrier.

This is continuation-in-part application of our application Ser. No. 393,360, filed Aug. 31, 1964, which in turn is a continuation-in-part application of our application Ser. No. 285,885, filed June 6, 1963, which in turn is a continuation-in-part application of our application Ser. No. 200,048, filed June 5, 1962, all of which are now abandoned.

Known appetite suppressant compositions usually contain as the anoretic principle compounds having as the common structural characteristic a 2-phenylethylamine portion, such as, for example, d, l-1-phenyl-2-propylamine (d, l-amphetamine)d-1-phenyl-2-propylamine (d-amphetamine), N-methyl-1-phenyl-2-propylamine (methamphetamine), 3-methyl-2-phenyl-morpholine (phenmetrazine) and the like. However, apart from their appetite suppressant effects, all of these compounds exert other pharmacological activities which limit their effectiveness in the treatment of obesity: At doses necessary to suppress the appetite, they show stimulating and very often hypertensive properties. Since many obese patients requiring suppression of the appetite often show a latent overstimulation and nervousness, such conditions can be seriously aggravated by administering an anoretic compound with stimulating properties. In order to counteract the stimulating effects of such compounds, many anoretic preparations are combination preparations, which in addition to the appetite suppressant compound contain a sedative agent, e.g. 5-ethyl - 5 - phenyl-barbituric acid (phenobarbital), 5-ethyl-5-(1-methyl-butyl) - barbituric acid (pentobarbital) and the like, or a tranquilizing or muscle relaxing compound, e.g. 1 - (p-chloro-α-phenylbenzyl)-4-(2-hydroxyethoxyethyl) - piperazine (hydroxyzine), 2-chloro-10-[3-(4-methyl-1-piperazino) - propyl]-phenothiazine (proclorperazine), 2-methyl-2-n-propyl-13-propanediol dicarbamate (meprobamate) and the like.

Holm et al., Acta pharmacol and toxicol, 17, pp. 121–136 (1960) discloses the 1-(o-chloro-phenyl)-2-methyl-2-propylamine used in the compositions of the present invention as well as the 1-(m-chloro-phenyl) and 1-(p-chloro-phenyl)-isomers of that compound, but indicate non-equivalence in concluding that the first named compound is useless as an anoretic agent in the manner in which it was compounded while the latter two compounds are useful for that purpose when tested in that manner; on page 134 of this reference, it is stated that "For chlorine substituted compounds anorexigenic action required the chlorine atom in the para or meta position."

Furthermore, compositions containing appetite suppressant compounds with blood pressure raising effects are usually not recommended and even contra-indicated for

the treatment of obese patients with hypertensive conditions.

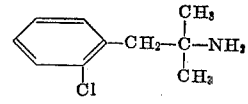
Either the addition of a sedative or tranquilizing drug to an anoretic composition to offset stimulating properties of the anoretic principle or the contra-indication of such compositions in the treatment of obese patients with hypertensive conditions is a serious drawback, because the proper balancing between stimulation and sedative depends largely on the reactions of the individual patient to the two types of drugs; furthermore, the majority of clinically obese patients require reduction of weight and suppression of the appetite because of hypertensive conditions.

A primary object of our invention is to provide a new method for the suppression of the appetite by administering to a host (e.g. human) requiring such treatment a new anoretic composition, which does not have or only to a negligible degree the undesirable side effects of known anoretic compositions.

It is another object of our invention to provide a new method for the suppression of the appetite by administering to a host (e.g. human) requiring such treatment a new anoretic composition which is free from any effects on the blood pressure.

A further object of our invention is the provision of a new method for the suppression of the appetite by administering to a host (e.g. human) requiring such treatment a new anoretic composition which at a dose controlling and suppressing the appetite does not have or only to a negligible degree effects on the central nervous system, such as the stimulating properties usually associated with known anoretic compositions.

We have now found that the appetite can be suppressed without noticeable side effects by administering a new composition comprising essentially a pharmacologically effective amount of 1-(o-chloro-phenyl) - 2 - methyl-2-propylamine, having the formula



or a pharmaceutically acceptable acid addition salt thereof, as the active anoretic ingredient, and a pharmaceutically acceptable carrier.

Pharmaceutically acceptable acid addition salts of 1-(o-chloro-phenyl)-2-methyl-2-propylamine are those with inorganic acids, e.g. hydrochloric, hydrobromic, sulfuric, phosphoric acids and the like, or with organic acids, such as organic carboxylic acids, e.g. acetic, propionic, glycolic, malonic, succinic, maleic, hydroxymaleic, fumaric, malic, tartaric, citric, glucuronic, benzoic, salicylic, 4-aminosalicylic, 2-acetoxybenzoic, pamoic, nicotinic acid and the like, or organic sulfonic acids, e.g. methane sulfonic, ethane sulfonic, 2-hydroxyethane sulfonic, ethane 1,2-disulfonic, benzene sulfonic, p-toluene sulfonic, naphthalene 2-sulfonic acid and the like.

We have found that 1-(o-chloro-phenyl)-2-methyl-2-propylamine or its acid addition salts exhibit anoretic properties without having any effects on the blood pressure; especially they do not elevate the latter above its normal value. Furthermore, we have found that these compounds, unlike others having similar 2-phenylethylamine structures, for example, 2 - methyl - 1 - phenyl-2-propylamine, 1 - (p - chloro-phenyl)-2-methyl-2-propylamine and the like, have no substantial stimulating effects at doses which effectively suppress the appetite. Behavior studies with monkeys show that with the exception of the appetite none of the normal reactions of the test animal, particularly its mood, are affected to any noticeable degree. These findings are in contrast with the re-

sults obtained with other anoretic drugs having the basic 2-phenylethylamine structure, which above all show pronounced stimulating effects in test animals.

A preferred method for the suppression of appetite comprises administering a new composition comprising essentially a pharmacologically effective amount of a pharmaceutically acceptable acid addition salt of 1-(o-chloro-phenyl)-2-methyl-2-propylamine, such as the 1-(o-chloro - phenyl) - 2-methyl-2-propylamine hydrochloride and the like, as the active anoretic ingredient, and a pharmaceutically acceptable carrier.

Also included within the scope of this invention are the new anoretic compositions, which comprise essentially a pharmacologically effective amount of 1 - (o - chloro-phenyl)-2-methyl-2-propylamine or a pharmaceutically acceptable acid addition salt thereof, as the active anoretic ingredient, and a pharmaceutically acceptable carrier.

Preferred compositions for the suppression of appetite comprise essentially a pharmacologically effective amount of a pharmaceutically acceptable acid addition salt of 1-(o-chlorophenyl)-2-methyl-2-propylamine, such as the 1-(o-chloro-phenyl)-2-methyl-2-propylamine hydrochloride and the like, as the active anoretic ingredient, and a pharmaceutically acceptable carrier.

The formulation of the compositions of this invention is carried out in the manner normally employed in the art, usually by combining the pharmacologically active ingredient with a pharmaceutically acceptable organic or inorganic carrier in specified proportions. The compositions of this invention are made up to contain at most equal amounts of the pharmacologically active compound and the carrier, such as from about 10 percent to at most 50 percent, by weight, of the active anoretic ingredient.

The tablet, capsule, dragee and the like provide for the oral form of administration. These orally applicable compositions are compounded to have per single dosage unit from about 0.025 g. to about 0.075 g., of the active anoretic ingredient; the latter is preferably used in the form of a pharmaceutically acceptable acid addition salt thereof, such as one of the above-mentioned salts with an inorganic or organic acid. It has been found that an average adult dose of about 25 to 75 mg. per day (preferably 50 mg. per day) is effective in humans.

Apart from the active anoretic ingredient, the orally applicable preparations contain carrier materials commonly employed in the pharmaceutical art for preparing dosage unit compositions, such as tablets, capsules, dragees. These include excipients, binders, fillers, lubricants, stabilizers and the like. Examples of such carrier materials are starches, e.g. corn starch, wheat starch and the like, sugars, e.g. lactose, sucrose and the like, stearic acid or salts thereof, e.g. magnesium stearate, calcium stearate and the like, aluminum magnesium silicate preparations (colloidal silica preparations), talcum, tragacanth, acacia, polyethylene glycol and the like. The quantities of these ingredients may vary widely and depend upon the physical characteristics (e.g. softness and the like) and size of the orally applicable composition, the method of its manufacture and the like. Encapsulation may also be effected using, if necessary, the same excipients as those employed for the manufacturing of the tablets. Any compatible color, approved and certified under the provisions of the Federal Food, Drug and Cosmetic law may be used as a means of identification and the like.

Special orally applicable compositions may also provide for a prolonged and sustained anoretic effect. For example, tablets, such as those described in U.S. Patent 2,887,-738, may contain the pharmacologically active ingredient embedded in a pharmaceutically acceptable waxy core (for prolonged absorption in the lower intestine), around which is compressed a granulated mixture of the active ingredient together with a pharmaceutically acceptable carrier (for immediate absorption in the stomach). Or, capsules having prolonged effects may contain micro-pills containing small amounts of the pharmacologically active ingredient with coats of different rates of degradation. These long-acting preparations are prepared according to well known methods.

Other suitable pharmaceutical preparations for the suppression of the appetite containing from about 10 percent to about 50 percent, of 1-(o-chloro-phenyl)-2-methyl-2-propylamine or a pharmaceutically acceptable acid addition salt thereof, as the active anoretic ingredient, are, for example, orally administered confectionery compositions, such as elixirs and syrups, parenteral solutions and the like. These preparations are manufactured according to methods established in the pharmaceutical arts using appropriate carrier materials. Elixirs are, for example, solutions of the pharmacologically active ingredient in water containing a small amount, for example, about five percent, of ethanol, and sugar substitute, as well as flavor and/or coloring preparations. In view of the fact that the active anoretic ingredient, particularly in the form of its acid addition salt, is a water-soluble substance, parenteral solutions contain water (purified for the use in parenteral solutions) as the primary solvent; other solvents are, for example, lower alkanols, e.g. ethanol and the like, or aqueous mixtures thereof. Other ingredients are added to ensure stable solutions, for example, stabilizers, such as anti-oxidants, e.g. thiourea, sodium sulfide, sodium metabisulfite, ascorbic acid, cysteine hydrochloride, sodium formaldehyde sulfoxylate, monothioglycerol, thiosorbitol and the like, solubilizers, e.g. N,N-diethylacetamide, polyethyleneglycols, ureas, urethanes and the like, buffers or buffer combinations, to maintain a preferable pH of about 7, for example, acetic acid, potassium phthalate and sodium hydroxide, potassium dihydrogen phosphate and disodium hydrogen phosphate, potassium dihydrogen phosphate and sodium hydroxide, acetic acid and sodium acetate, and the like, salts for isotonic solutions, e.g. sodium chloride and the like.

The following working examples are illustrative of the invention, but are in no way intended to limit its scope.

EXAMPLE 1

Tablets, each containing 0.05 g. of 1-(o-chloro-phenyl)-2-methyl-2-propylamine hydrochloride as the pharmacologically active ingredient, are prepared as follows (for 10,000 tablets):

Ingredients:	G.
1 - (o-chloro-phenyl) - 2 - methyl-2-propyl amine hydrochloride	500.00
Lactose, U.S.P.	1210.00
Tragacanth	50.00
Talcum, U.S.P.	50.00
Corn starch	50.00
Magnesium stearate	140.00
Alcohol 3A, 50 percent, q.s.	

The tragacanth, the 1-(o-chloro-phenyl)-2-methyl-2-propylamine hydrochloride and 1,000 g. of lactose are placed in a suitable mixer and blended to homogeneity. The balance of the lactose and the corn starch are added, and the granulate is formed by adding the alcohol. After passing the granulate through a mill, using a No. 4 screen and medium speed, it is dried with circulating dehumidified air, and again passed through a mill using a No. 2 screen. The broken granulate is returned to the mixer, the talcum and the magnesium stearate are added and mixing is continued. The resulting mass is compressed into tablets weighing 0.2 g. each, using $\frac{5}{32}$ inch punches and dies.

In the above example, the hydrochloride of 1-(o-chloro-phenyl)-2-methyl-2-propylamine may be replaced by another salt, such as the sulfate, tartrate, citrate, methane sulfonate, naphthalene 2-sulfonate and the like, of 1-(o-chloro-phenyl)-2-methyl-2-propylamine.

EXAMPLE 2

Tablets, each containing 0.075 g. of 1-(o-chloro-phenyl)-2-methyl-2-propylamine hydrochloride as the pharmacologically active ingredient, are prepared as follows (for 5,000 tablets):

Ingredients:	G.
1 - (o-chloro-phenyl) - 2 - methyl-2-propylamine hydrochloride	375.00
Lactose, U.S.P.	480.00
Tragacanth	25.00
Talcum, U.S.P.	25.00
Wheat starch	25.00
Magnesium stearate	70.00
Alcohol 3A, 50 percent, q.s.	

The tablets, each weighing 0.2 g., are prepared according to the procedure described in Example 1.

EXAMPLE 3

Tablets for the sustained release of the anoretic compound, consisting of a core having 0.067 g. of 1-(o-chloro-phenyl - 2 - methyl - 2 - propylamine hydrochloride, and a coating having 0.033 g. of 1-(o-chloro-phenyl)-2-methyl-2-propylamine hydrochloride as the pharmacologically active ingredient, are prepared as follows (for 10,000 tablets):

(A) Core formulation

Ingredients:	G.
1 - (o-chloro-phenyl) - 2 - methyl-2-propylamine hydrochloride	670.00
Carnauba wax	655.00
Stearyl alcohol	655.00
Magnesium stearate	20.00

The carnauba wax and the stearyl alcohol are melted, and the pulverized 1-(o-chloro-phenyl) - 2 - methyl-2-propylamine hydrochloride is added; the mixture is stirred until a uniform dispersion is obtained. The melt is permitted to flow onto a cooling drum; the resulting flakes are collected and passed through a No. 12 screen. The magnesium stearate is added, and the mixture is compressed on the Manesty Dry Cota machine into $^{10}/_{32}$ inch cores, weighing 0.2 g. each.

(B) Coating formulation

Ingredients:	G.
1 - (o-chloro-phenyl) - 2 - methyl-2-propylamine hydrochloride	330.00
Polyethyleneglycol 6000	132.50
Acacia	53.00
Tragacanth	53.00
Lactose	1551.45
Confectioners sugar	397.50
Talcum	132.55
Alcohol 3A, 50 percent, q.s.	

The 1-(o-chloro-phenyl)-2-methyl-2-propylamine hydrochloride, the acacia, the tragacanth, the lactose, the confectioners sugar and the talcum are mixed in a suitable mixer. The polyethyleneglycol 6000 is dissolved in the alcohol and added to the above mixture to form the granulate, which is passed through a No. 16 screen, dried and again passed through a No. 16 screen. A coating of this material, weighing 0.265 g. each, is then compressed around the previously-described core, using $^{13}/_{32}$ inch punches on the Manesty Dry Cota machine. The total weight of the sustained-release tablet is 0.465 g.

In the above formulation, the hydrochloride of 1-(o-chloro-phenyl)-2-methyl-2-propylamine may be replaced by another salt, such as the sulfate, tartrate, citrate, methane sulfonate, naphthalene 2-sulfonic and the like, of 1-(o-chloro-phenyl)-2-methyl-2-propylamine.

EXAMPLE 4

Capsules, each containing 0.05 g. of 1-(o-chloro-phenyl)-2-methyl-2-propylamine hydrochloride as the pharmacologically active ingredient, are prepared as follows (for 1,000 capsules):

Ingredients:	G.
1-(o-chloro-phenyl) - 2 - methyl - 2 - propylamine hydrochloride	50.00
Lactose, U.S.P.	130.00

The ingredients are blended in a suitable mixer, sieved through a No. 40 screen and again mixed; portions, each weighing 0.18 g. of the resulting mixture are filled into No. 4 capsules.

EXAMPLE 5

Capsules, each containing 0.075 g. of 1-(o-chloro-phenyl)-2-methyl-2-propylamine hydrochloride as the pharmacologically active ingredient are prepared as follows (for 1,000,000 capsules):

Ingredients:	G.
1 - (o - chloro - phenyl) - 2 - methyl - 2-propylamine hydrochloride	75,000.0
Magnesium Stearate	20,000.0
Lactose, U.S.P.	205,000.0

The ingredients are blended for twenty minutes in a suitable mixer, passed through a 20 mesh screen, and filled in portions of 0.3 g. into No. 2 capsules.

In the above formulation, the hydrochloride of 1-(o-chloro-phenyl)-2-methyl-2-propylamine may be replaced by another salt, such as the sulfate, tartarate, citrate, methane sulfonate, naphthalene 2-sulfonate and the like, of 1-(o-chloro-phenyl)-2-methyl-2-propylamine.

EXAMPLE 6

A syrup, formulated to provide a dosage unit of about 0.050 g. per dosage unit, is prepared as follows:

Ingredients:	Kg.
1-(o-chloro - phenyl)-2-methyl-2-propylamine hydrochloride	1.000
Sodium saccharin	0.020
Sodium sucaryl	0.200
Color FD&C Yellow No. 6	0.004
Orange flavor	0.020
Sodium benzoate	0.500
Purified water to make 100 lit.	

To a 150 liter vessel equipped with a stirrer is added 40 liters purified water and the 1-(o-chloro-phenyl)-2-methyl-2-propylamine hydrochloride and the mixture is stirred until complete dissolution is achieved. The remaining ingredients are then added while stirring in the following order: sodium saccharin, sodium sucaryl, sodium benzoate, color and flavor. Stirring is continued until complete dissolution is achieved and the volume is then adjusted to 100 liters with purified water with subsequent stirring to insure uniformity.

EXAMPLE 7

An elixir, formulated to provide a dosage unit of about 0.050 g. per dosage unit, is prepared as follows:

Ingredients:	Kg.
1-(o-chloro - phenyl)-2-methyl-2-propylamine hydrochloride	1.000
Sodium saccharin	0.020
Sodium sucaryl	0.200
Color FD&C Yellow No. 6	0.004
Orange flavor	0.020
Sodium benzoate	0.500
Alcohol 95%	10.000
Purified water to make 100 lit.	

The procedure used to prepare the elixir is identical with that given in Example 6 for the preparation of the syrup except that the flavor is dissolved in the alcohol and this solution is the last ingredient added.

The pharmacologically active ingredient of the above

compositions is prepared as follows (temperatures are given in degrees centigrade):

To a Grignard reagent (prepared from 50.0 g. of o,α-dichloro-toluene and 7.45 g. of magnesium in diethyl ether) is added 18.0 g. of acetone at such rate that constant reflux is maintained. The reaction mixture is allowed to stand overnight at room temperature, and is then poured onto a mixture of 20 percent sulfuric acid and ice. The organic layer is separated, washed with water, an aqueous solution of sodium hydrogen carbonate and again with water, dried over magnesium sulfate and evaporated to dryness. The residue is distilled under reduced pressure to yield 42.6 g. of 1-(o-chloro-phenyl)-2-methyl-2-propanol, B.P. 120–122°/12.5 mm.

To 29.0 ml. of glacial acetic acid, cooled to 15°, is added 11.5 g. of sodium cyanide (98 percent) while stirring, and then dropwise 32.4 ml. of concentrated sulfuric acid, dissolved in 29 ml. of glacial acetic acid, while maintaining a temperature of 20°. The 1-(o-chlorophenyl)-2-methyl-2-propanol is added moderately fast, allowing the temperature to rise spontaneously. After completing the addition, the reaction mixture is heated to 70° and stirred, and is then poured onto a mixture of water and ice. The aqueous mixture is neutralized with sodium carbonate and extracted with diethyl ether. The organic solution is washed with water, dried over magnesium sulfate and evaporated to dryness.

The oily residue is taken up in 100 ml. of 6 N aqueous hydrochloric acid and refluxed until a clear solution is obtained. The latter is made basic with aqueous ammonia and extracted with diethyl ether; the organic solution is separated, washed, dried and evaporated. The residue is distilled under reduced pressure to yield 26.3 g. of 1-(o-chloro-phenyl)-2-methyl-2-propylamine, B.P. 116–118°/16 mm.

The 1-(o-chloro-phenyl)-2-methyl-2-propylamine hydrochloride is prepared by adding ethanolic hydrogen chloride to an ice-cold solution of the free base in ethanol; the desired salt precipitates and is recrystallized from ethanol, M.P. 245–246°. Other salts, such as the sulfate, tartrate, citrate, methane sulfonate, naphthalene 2-sulfonate and the like, of 1-(o-chloro-phenyl)-2-methyl-2-propylamine are prepared according to analogous procedures.

What is claimed is:

1. A method for the suppression of the appetite of a human, which comprises orally administering to said human a composition comprising a pharmacologically effective amount of a member selected from the group consisting of 1-(o-chlorophenyl)-2-methyl-2-propylamine and a pharmaceutically acceptable acid addition salt thereof, as the active anoretic ingredient, and a pharmaceutically acceptable carrier.

2. A method of claim **1** for the suppression of the appetite of a human, which comprises orally administering to said human a composition comprising a pharmacologically effective amount of a pharmaceutically acceptable acid addition salt of 1-(o-chloro-phenyl)-2-methyl-2-propylamine as the active anoretic ingredient, and a pharmaceutically acceptable carrier.

3. A method of claim **1** for the suppression of the appetite of a human, which comprises orally administering to said human a composition comprising a pharmacologically effective amount of 1-(o-chloro-phenyl)-2-methyl-2-propylamine hydrochloride as the active anoretic ingredient, and a pharmaceutically acceptable carrier.

4. A method of claim **1** for the suppression of the appetite or a human, which comprises orally administering to said human a composition comprising from about 0.025 g. to about 0.075 g. of a member selected from the group consisting of 1-(o-chlorophenyl)-2-methyl-2-propylamine and a pharmaceutically acceptable acid addition salt thereof as the active anoretic ingredient, and a pharmaceutically acceptable carrier.

5. A method of claim **1** for the suppression of the appetite of a human, which comprises orally adminstering to said human a composition comprising from about 0.025 g. to about 0.075 g. of a pharmaceutically acceptable acid addition salt of 1-(o-chlorophenyl)-2-methyl-2-propylamine as the active anoretic ingredient, and a pharmaceutically acceptable carrier.

6. A method of claim **1** for the suppression of the appetite of a human, which comprises orally administering to said human a composition comprising from about 0.025 g. to about 0.075 g. of 1-(o-chloro-phenyl)-2-methyl-2-propylamine hydrochloride as the active anoretic ingredient, and a pharmaceutically acceptable carrier.

7. A method of claim **1** for the suppression of the appetite of a human, which comprises orally administering to said human a composition comprising about 0.050 g. of 1-(o-chloro-phenyl)-2-methyl-2-propylamine hydrochloride as the active anoretic ingredient, and a pharmaceutically acceptable carrier.

References Cited

Ferrari: Chem. Abst., vol. 54, 1960, pp. 2024*h* and 20925*c*.

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