

PATENT SPECIFICATION

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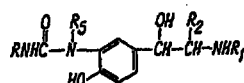
(54) α -AMINOALKYL-4-HYDROXY-3-UREIDOBENZYL ALCOHOLS

(71) We, SMITH KLINE & FRENCH LABORATORIES, of 1500 Spring Garden Street, City of Philadelphia, Commonwealth of Pennsylvania, 19101, United States of America, a corporation organized under the laws of the Commonwealth of Pennsylvania, one of the United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel α -aminoalkyl-4-hydroxy-3-ureidobenzyl alcohols which have useful pharmacodynamic activity. More specifically the compounds of this invention have utility as β -adrenergic stimulants with relatively greater activity on respiratory smooth muscle than on cardiac muscle. Therefore these compounds have direct bronchodilator action with minimal cardiac stimulation as demonstrated in standard pharmacological test procedures.

Two *in vitro* test systems used for determining selective β -stimulant activity are (1) effect on spontaneous tone of guinea pig tracheal chain preparations as a measure of β -stimulant (direct relaxant) effect on airway smooth muscle, and (2) effect on rate of spontaneously beating right atria of the guinea pig as a measure of β -stimulant effect on cardiac muscle. The compounds of this invention have selective broncho-dilating properties since they are active in (1) above at a dose lower than is required in (2) above resulting in a positive separation ratio.

The compounds of this invention are represented by the following general structural formula:

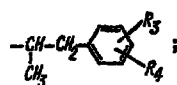


Formula I

in which:

R represents hydrogen, alkyl of from 1 to 5 carbon atoms, straight or branched chain, phenyl, dimethylaminoethyl or dimethylaminopropyl;

R₁ represents a branched chain alkyl group of from 3 to 5 carbon atoms, a cycloalkyl or cycloalkylmethyl group, the cycloalkyl moiety having from 3 to 6 carbon atoms, or



R₂ represents hydrogen, methyl or ethyl;

R₃ and R₄ represent hydrogen, hydroxy or methoxy; and

R₅ represents hydrogen or methyl.

Preferred compounds of this invention are represented by formula I above when

[Price 25p]

Price 33p

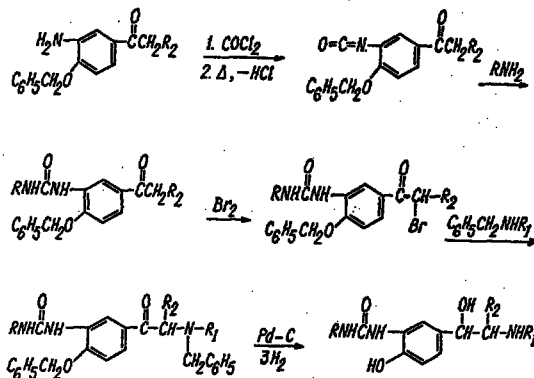
R is hydrogen or methyl; R₁ is isopropyl, t-butyl, cyclopropyl, cyclopentyl, 4-hydroxyphenylisopropyl or 3,4-dimethoxyphenylisopropyl; and R₂ and R₃ are hydrogen.

The compounds of this invention may be used in the form of a pharmaceutically acceptable acid addition salt having the utility of the free base. Such salts, prepared by methods well known to the art, are formed with both inorganic or organic acids, for example: maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, oxalic, propionic, tartaric, salicylic, citric, glyconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexyl sulfamic, phosphoric and nitric acids.

Compounds of this invention may be present as *d*, *l* optical isomers. Further the compounds of Formula I in which R₂ represents methyl or ethyl may be present as diastereoisomers and are designated as *erythro* and *threo* isomers which may be resolved into optical isomers. Resolution of optical isomers may be conveniently accomplished by fractional crystallization of their salts with optically active acids such as, for example, tartaric, camphor-10-sulfonic, *O,O*-dibenzoyltartaric, *O,O*-di(p-toluoxy)-tartaric, menthyloxyacetic, camphoric, or 2-pyrrolidone-5-carboxylic acids or *N*-acetyl-tryptophane from appropriate solvents. Unless otherwise specified in the claims, it is intended to include all isomers, whether separated or mixtures thereof.

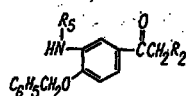
A preferred compound of this invention is α -(t-butylaminomethyl)-4-hydroxy-3-ureidobenzyl alcohol which relaxes the spontaneous tone of guinea pig tracheal ring preparation at an ED₅₀ of 0.0052 mcg/ml while increasing the rate of contraction of guinea pig right atria at an ED₂₅ of 0.168 mcg/ml. These activities give an absolute separation ratio of 33 which is a 66-fold improvement when compared to the corresponding activity of *d*, *l*-isoproterenol (absolute separation ratio=0.5) in similar *in vitro* preparations.

The compounds of this invention where R₃ is hydrogen are prepared as shown in the following sequence of reactions:



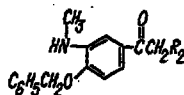
in which R, R₁ and R₂ are as defined in formula I. Thus, as shown above, an aminobenzoyloxyphenone is treated with phosgene and then heated to give the isocyanate which is reacted with ammonia or a monosubstituted alkyl or aryl amine to yield the ureidophenone derivative. The latter is treated with bromine or pyrrolidone hydrotribromide and the resultant α -bromophenone is reacted with an *N*-benzylamine to give the corresponding α -benzylaminophenone. This derivative is hydrogenated catalytically, preferably with palladium-on-carbon, to give the debenzylated ureido-benzyl alcohol product.

To prepare the compounds of this invention where R is hydrogen and R₃ is hydrogen or methyl, an aminobenzoyloxyphenone of the following formula:



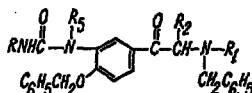
in which R₃ is as defined in formula I, preferably in acetic acid solution, is treated with aqueous sodium cyanate to yield the corresponding ureidophenone derivative which is then carried through the same sequence of reactions as described above to obtain the products.

The compounds of this invention where R is other than hydrogen as refined in formula I and R₃ is methyl are prepared from an aminobenzoyloxyphenone of the following formula:



in which R₂ is as defined in formula I, by treating with phosgene to give a carbamyl chloride derivative which is then reacted with an appropriately substituted amine to yield the N,N'-disubstituted ureidophenone. The latter is subsequently reacted according to the above described sequence to give the benzyl alcohol products. Alternatively the aminobenzoyloxyphenone is reacted with an appropriately substituted isocyanate to give the N,N'-disubstituted ureidophenone.

It will be appreciated that the benzylated derivatives of the following formula:



in which R, R₁, R₂ and R₃ are as defined in formula I, are useful intermediates in the preparation of the products of this invention and as such form a part of the invention.

The aminobenzoyloxyphenones used as starting materials herein are known or are prepared by methods known in the art. For example, a 4-hydroxyphenone is nitrated with nitric acid at -20 to -30°C. to yield the 4-hydroxy-3-nitrophenone which is reacted with benzyl chloride in the presence of potassium hydroxide or potassium carbonate to give the 4-benzoyloxy-3-nitrophenone and the latter is reduced to the 3-amino-4-benzoyloxyphenone using Raney nickel and hydrazine hydrate, platinum oxide and hydrogen or sodium sulfhydrylate (NaSH · 2H₂O) in dimethylformamide. The amino group is N-methylated by standard procedures.

The compounds of this invention may be administered orally or parenterally in conventional dosage unit forms such as tablets, capsules or injectables, by incorporating the appropriate dose of a compound of formula I, with carriers according to accepted pharmaceutical practices. Preferably a compound or an acid addition salt thereof is administered orally to an animal organism in a tablet or capsule comprising an amount sufficient to produce β-adrenergic stimulant activity. Each dosage unit will contain the active medicament in an amount of 3 mg. to 40 mg., preferably 5 mg. to 20 mg. Advantageously equal doses will be administered 2 to 4 times daily with the daily dosage regimen being 6 mg. to 160 mg. preferably 10 mg. to 80 mg.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate and stearic acid. Exemplary of liquid carriers are syrup, peanut oil, olive oil and water. Similarly the carrier or diluent can include any time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form, or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be 25 mg. to 1 g. If a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule, or an aqueous or nonaqueous liquid suspension.

Of particular applicability is an aerosol dispensing system wherein the active medicament is incorporated with a fluorohydrocarbon or other inert propellant in an aerosol container. Such an aerosol system will deliver a metered dose of 100 mcg. to 650 mcg., administered once or twice at a time as needed.

The foregoing is a general description of how to prepare the compounds of this invention. The following examples illustrate the preparation of specific compounds having β-adrenergic stimulant activity. However this should not be construed as a limitation of the invention since appropriate variations in the starting materials will produce other products set forth hereinabove.

EXAMPLE 1

A stirred solution of 40 g. (0.41 m.) of phosgene in 150 ml. of toluene is held at 25°C. with a cooling bath while a mixture of 25.2 g. (0.105 m.) of 3-amino-4-benzyloxyacetophenone and 220 ml. of toluene are added slowly. The mixture is heated to reflux and continued for 30 minutes. Nitrogen is passed through the mixture and then concentrated *in vacuo* to give a crystalline isocyanate, m.p. 105—106°C.

A stirred solution of the isocyanate (28.0 g.) in 500 ml. of dry benzene is saturated with ammonia. After one hour, the mixture is cooled to give the crystalline 4-benzyloxy-3-ureidoacetophenone, m.p. 184—186°C.

To a stirred solution of 5.7 g. (0.02 m.) of 4-benzyloxy-3-ureidoacetophenone in 100 ml. of chloroform is added 3.2 g. (0.02 m.) of bromine. The mixture is stirred at room temperature for about 45 minutes and the solution is concentrated *in vacuo* at 25—30°C. The amorphous residue (hydrobromide salt of 4-benzyloxy- α -bromo-3-ureidoacetophenone) is dissolved in 80 ml. of acetonitrile and 9.8 g. (0.06 m.) of N-benzyl-N-t-butylamine is added. The mixture is stirred and refluxed for 1.5 hours, then it is cooled to 0°C. in an ice-bath. Crystalline N-benzyl-N-t-butylamine hydrobromide is filtered. The filtrate is acidified with ethereal hydrogen chloride. The semi-crystalline product is filtered after diluting the mixture with a large excess of ether. Trituration of the product with 60 ml. of cold ethanol gives 4-benzyloxy- α -(N-benzyl-N-t-butylamino)-3-ureidoacetophenone hydrochloride, m.p. 220—221°C. (dec.).

A solution of 10.5 g. (0.0218 m.) of 4-benzyloxy- α -(N-benzyl-N-t-butylamino)-3-ureidoacetophenone hydrochloride in 65 ml. of methanol and 25 ml. of water is added to a suspension of 1.5 g. of 10% palladium-on-carbon in 10 ml. of water. The mixture is hydrogenated on the Parr apparatus at room temperature, using an initial pressure of 60 psi of hydrogen. After four hours about 80% of the theoretical volume of hydrogen has been absorbed. The mixture is filtered, an additional 1.5 g. of 10% palladium-on-carbon is added and the mixture is again hydrogenated on the Parr apparatus under the same conditions. After hydrogenating for an additional three hours, the mixture is filtered and the filtrate is concentrated *in vacuo*. The residue is stripped twice with toluene and crystallized with ether-ethanol to give α -(t-butylaminomethyl)-4-hydroxy-3-ureidobenzyl alcohol hydrochloride, m.p. 214—215°C.

EXAMPLE 2

Into a solution of 2.4 g. (0.008 m.) of the isocyanate prepared in Example 1 in 35 ml. of dry benzene is passed methylamine gas for one hour. The reaction mixture is cooled and filtered to give 4-benzyloxy-3-(N'-methylureido)acetophenone, m.p. 165—167°C.

To a suspension of 1.5 g. (0.005 m.) of the above ureidoacetophenone in 20 ml. of chloroform and 0.2 g. of benzoyl peroxide is added 0.84 g. (5% excess) of bromine in 2 ml. of chloroform. The reaction mixture is stirred at room temperature for 45 minutes and then concentrated *in vacuo* at 40—50°C. The residue is triturated with ethanol to give 4-benzyloxy- α -bromo-3-(N'-methylureido)-acetophenone, m.p. 182—184°C.

A mixture of 1.8 g. (0.005 m.) of 4-benzyloxy- α -bromo-3-(N'-methylureido)-acetophenone, 1.5 g. (0.01 m.) of N-benzylisopropylamine and 20 ml. of acetonitrile is stirred at 40—50°C. for one hour, then it is cooled and diluted with 20 ml. of ether. The reaction mixture is filtered (N-benzylisopropylamine hydrobromide) and the filtrate acidified (carefully) to give a flocculent solid. The solid is filtered, dissolved in 80 ml. of ethanol and 20 ml. of water, 1 g. of palladium-carbon is added and the mixture is hydrogenated on a Parr shaker (initial hydrogen pressure 60 psi and room temperature). The mixture is filtered, after hydrogen uptake is completed (about 45 minutes) and the filtrate is concentrated *in vacuo*. The residue is crystallized from ethanol-ether to give 4-hydroxy- α -isopropylaminomethyl-3-(N'-methylureido)benzyl alcohol hydrochloride.

Similarly, employing n-butylamine in the initial reaction with the isocyanate and proceeding in the above sequence of reactions yields the corresponding N'-n-butylureido derivatives and the product 3-(N'-n-butylureido)-4-hydroxy- α -(isopropylaminomethyl)-benzyl alcohol.

Reacting isopropylamine with the isocyanate and following through as above furnishes as the final product, 4-hydroxy- α -(isopropylaminomethyl)-3-(N'-isopropylureido)benzyl alcohol.

EXAMPLE 3

Following the procedures outlined in Example 1, the hydrobromide salt of 4-benzyloxy- α -bromo-3-ureidoacetophenone is reacted with N-benzylcyclopentylamine to

give 4-benzyloxy- α -(N-benzylcyclopentylamino)-3-ureidoacetophenone hydrochloride. Similar hydrogenation over palladium-on-carbon gives α -(cyclopentylaminomethyl)-4-hydroxy-3-ureidobenzyl alcohol.

Reacting 4-benzyloxy- α -bromo-3-ureidoacetophenone with N-benzyl-3,4-dimethoxyphenylisopropylamine followed by hydrogenation furnishes the product α -[2-(3,4-dimethoxyphenyl)-1-methylethylaminomethyl]-4-hydroxy-3-ureidobenzyl alcohol.

Similarly, employing N-benzylcyclopropylmethylamine in the above reaction followed by hydrogenation there is obtained α -(cyclopropylmethylaminomethyl)-4-hydroxy-3-ureidobenzyl alcohol.

EXAMPLE 4

Following the procedures of Example 2, 4-benzyloxy- α -bromo-3-(N'-methylureido)-acetophenone is reacted with N-benzylphenylisopropylamine to give 4-benzyloxy- α -(N-benzylphenylisopropylamino)-3-(N'-methylureido)-acetophenone which is hydrogenated to yield 4-hydroxy-3-(N'-methylureido)- α -(2-phenyl-1-methylaminomethyl)-benzyl alcohol.

Similarly, reaction of the 4-benzyloxy- α -bromo-3-(N'-methylureido)-acetophenone with N-benzyl-3,4-dibenzyloxyphenylisopropyl amine yields as the final product α -[2-(3,4-dihydroxyphenyl)-1-methylethylaminomethyl]-4-hydroxy-3-(N'-methylureido)-benzyl alcohol.

Reacting 4-benzyloxy- α -bromo-3-ureidoacetophenone with N-benzyl-4-benzyloxyphenylisopropylamine followed by hydrogenation gives α -[2-(4-hydroxyphenyl)-1-methylethylaminomethyl]-4-hydroxy-3-ureidobenzyl alcohol.

EXAMPLE 5

As described in Example 1, the isocyanate prepared from 3-amino-4-benzyloxyacetophenone is reacted with aniline to give 4-benzyloxy-3-(N'-phenylureido)-acetophenone which is brominated to 4-benzyloxy- α -bromo-3-(N'-phenylureido)-acetophenone. The latter is refluxed with N-benzyl-N-t-butylamine to give 4-benzyloxy- α -(N-benzyl-N-t-butylamino)-3-(N'-phenylureido)-acetophenone. Catalytic hydrogenation yields α -(t-butylaminomethyl)-4-hydroxy-3-(N'-phenylureido)-benzyl alcohol.

Similarly, reaction of the isocyanate with dimethylaminopropylamine to give 4-benzyloxy-3-(N'-dimethylaminopropylureido)-acetophenone followed by the above described reactions yields the product α -(t-butylaminomethyl)-3-(N'-dimethylaminopropylureido)-4-hydroxybenzyl alcohol.

By employing dimethylaminoethylamine as described above there is obtained the corresponding α -(t-butylaminomethyl)-3-(N'-dimethylaminoethylureido)-4-hydroxybenzyl alcohol.

EXAMPLE 6

A solution of 40 g. of phosgene in 150 ml. of toluene at 25°C. is treated with 28.1 g. of 3-amino-4-benzyloxybutyrophenone in 250 ml. of toluene. The mixture is refluxed for 30 minutes and concentrated *in vacuo* to give the isocyanate. The latter (31.2 g.) is dissolved in 500 ml. of dry benzene and the solution saturated with ammonia to yield 4-benzyloxy-3-ureidobutyrophenone.

To a stirred solution of 6.4 g. of the above prepared 3-ureidobutyrophenone in 125 ml. of chloroform is added 3.2 g. of bromine. After stirring at room temperature for about 45 minutes the reaction mixture is concentrated *in vacuo* at 25–30°C. The hydrobromide salt of 4-benzyloxy- α -bromo-3-ureidobutyrophenone thus obtained is dissolved in 100 ml. of acetonitrile and 9.8 g. of N-benzyl-N-t-butylamine is added. The mixture is refluxed for 1.5 hours, cooled and filtered. The filtrate is acidified with ethereal hydrogen chloride to give 4-benzyloxy- α -(N-benzyl-N-t-butylamino)-3-ureidobutyrophenone hydrochloride.

A solution of 11.7 g. of the above prepared hydrochloride in 75 ml. of methanol and 25 ml. of water is added to a suspension of 1.5 g. of 10% palladium-on-carbon in 10 ml. of water. The mixture is hydrogenated on the Parr apparatus at room temperature to yield α -(1-t-butylaminopropyl)-4-hydroxy-3-ureidobenzyl alcohol hydrochloride.

Similarly, by employing 3-amino-4-benzyloxypropiofenone in the initial reaction with phosgene and following through the above sequence of reactions there is obtained the corresponding product, α -(1-t-butylaminoethyl)-4-hydroxy-3-ureidobenzyl alcohol hydrochloride.

EXAMPLE 7

A solution of 23.4 g. (0.0785 m.) of 4-benzyloxy-3-(N'-methylureido)-acetophenone (prepared as in Example 2) and 6.7 g. (0.0785 m.) of 2-pyrrolidone in 785 ml. of dry tetrahydrofuran is stirred at room temperature while a solution of 39 g. (0.0785 m.) of pyrrolidone hydrotribromide in 785 ml. of dry tetrahydrofuran is added dropwise. The resulting solution is stirred overnight at room temperature, filtered and the filtrate evaporated *in vacuo* at 50°C. to give 4-benzyloxy- α -bromo-3-(N'-methylureido)-acetophenone (identical to material prepared in Example 2), m.p. 178.5—181.5°C.

A mixture of 7.56 g. (0.02 m.) of the above bromoacetophenone and 6.52 g. (0.04 m.) of N-benzyl-t-butylamine and 120 ml. of acetonitrile is stirred and refluxed for two hours. The cooled reaction mixture is diluted with 120 ml. of ether, filtered and the filtrate is acidified with ethereal hydrogen chloride to give the hydrochloride of 4-benzyloxy- α -(N-benzyl-N-t-butylamino)-3-(N'-methylureido)-acetophenone. The latter is dissolved in 70 ml. of ethanol and 30 ml. of water and reduced with 0.5 g. of palladium-on-carbon, at 60 psi hydrogen and room temperature to yield α -(t-butylaminomethyl)-4-hydroxy-3-(N'-methylureido)-benzyl alcohol hydrochloride, m.p. 185—187°C.

EXAMPLE 8

A mixture of 20 g. (0.083 m.) of 3-amino-4-benzyloxyacetophenone and 230 ml. of ethylformate is stirred and refluxed for 24 hours. The resulting solution is evaporated *in vacuo* and the residue is dissolved in methylene chloride and washed with dilute acid. The dried organic solution is evaporated *in vacuo* to give the N-formyl derivative, 119.5—122.5°C.

To a stirred solution of 13.5 g. (0.05 m.) of 4-benzyloxy-3-formamidoacetophenone in 60 ml. of dimethylsulfoxide under nitrogen is added 2.1 g. (0.05 m.) of a 57% dispersion of sodium hydride in mineral oil. The mixture is stirred for about 15 minutes, then cooled in an ice-bath and 8.0 g. (0.055 m.) of methyl iodide in 20 ml. of dimethyl sulfoxide is added dropwise. The resulting mixture is stirred at room temperature for about ten minutes, then heated to 55—60°C. for 30 minutes. The clear solution is poured into a large volume of ice-water, extracted with ethyl acetate and the dried extract is concentrated to yield 4-benzyloxy-3-(N-methylformamido)-acetophenone, m.p. 75—78°C.

To a solution of 10.0 g. (0.18 m.) of potassium hydroxide in 15 ml. of water is added a solution of 12.5 g. (0.044 m.) of 4-benzyloxy-3-(N-methylformamido)-acetophenone in 100 ml. of ethanol. The resulting mixture is refluxed for 90 minutes, concentrated *in vacuo* and the residue is diluted with water. This mixture is extracted with ether and the dried extract is concentrated to give 4-benzyloxy-3-methylaminoacetophenone, m.p. 66—67°C. The same material is obtained by a 30 minute reflux in 5% hydrochloric acid in 50% aqueous ethanol.

A solution of 40.8 g. (0.16 m.) of 4-benzyloxy-3-methylaminoacetophenone in 480 ml. of acetic acid and 160 ml. of water is stirred at 40°C. while a slurry of 23.5 g. of 90% sodium cyanate (21.2 g., 0.32 m.) in 160 ml. of water is added in portions. The resulting solution is stirred at 40°C. for one hour, diluted with 1600 ml. of water and extracted with methylene chloride. The extract is washed with sodium carbonate, dried and evaporated *in vacuo* to give 4-benzyloxy-3-(N-methylureido)-acetophenone, m.p. 143—146°C.; hydrochloride, m.p. 141—144°C.

A solution of 2.98 g. (0.01 m.) of 4-benzyloxy-3-(N-methylureido)-acetophenone in 25 ml. of chloroform is acidified with ethereal hydrogen chloride, then a stream of nitrogen is passed through the solution to remove the ether. This solution is stirred and 1.6 g. (0.01 m.) of bromine in 5 ml. of chloroform is added all at once. Nitrogen is passed through the solution to remove hydrogen bromide and the solution is washed with water/sodium bicarbonate. The dried solution is concentrated to a residue of α -bromo-4-benzyloxy-3-(N-methylureido)-acetophenone, m.p. 141—142°C. (dec.).

To a suspension of 2.5 g. (0.0067 m.) of the above bromo acetophenone in 20 ml. of acetonitrile is added 2.2 g. (0.0134 m.) of N-benzyl-N-t-butylamine. The solution is stirred and refluxed for one and one half hours, cooled, ether is added and the mixture is filtered. The filtrate is diluted with water and the separated ether layer is washed with water, dried and concentrated to give the free base 4-benzyloxy- α -(N-benzyl-N-t-butylamino)-3-(N-methylureido)-acetophenone; nitrate, m.p. 163—164°C. (dec.).

A solution of the above acetophenone in ethanol is acidified with ethereal hydrogen chloride and the filtered solid is dissolved in ethanol. A mixture of this solution and 10% palladium-on-carbon is hydrogenated on the Parr apparatus at room

temperature using an initial pressure of 60 psi hydrogen. The mixture is filtered and the filtrate is concentrated *in vacuo* to give an amorphous solid, α -(*t*-butylamino-methyl)-4-hydroxy-3-(*N*-methylureido)-benzyl alcohol hydrochloride.

EXAMPLE 9

To a solution of 12.0 g. (0.0446 m.) of 3-amino-4-benzyloxybutyrophenone in 25 ml. of water and 125 ml. of acetic acid at 40°C. is added a slurry of 5.88 g. (0.0905 m.) of sodium cyanate in water. The resulting mixture is stirred for one hour and filtered to give the solid 4-benzyloxy-3-ureidobutyrophenone, m.p. 164–165°C.

The above butyrophenone (12.2 g., 0.0391 m.) in 250 ml. of tetrahydrofuran with 3.33 g. (0.0391 m.) of 2-pyrrolidone at room temperature is reacted, dropwise, with a solution of 19.8 g. (0.0391 m.) of pyrrolidone hydrotribromide in about 250 ml. of tetrahydrofuran. The reaction mixture is shielded from light and stirred for 40 hours. After filtration the filtrate from the reaction mixture is evaporated, the residue is dissolved in chloroform and this solution is washed with aqueous sodium thiosulfate, then water. The dried solution is evaporated to yield 4-benzyloxy- α -bromo-3-ureido-butyrophenone, m.p. 170–172°C.

To a slurry of 10.0 g. (0.0255 m.) of the above bromo ketone in 300 ml. of acetonitrile is added an excess of *N*-benzyl-*N*-isopropylamine and the mixture is refluxed for two hours. The cooled reaction mixture is filtered and the filtrate is acidified with ethereal hydrogen chloride. The resulting hydrochloride is dissolved in 70 ml. of methanol and 30 ml. of water and hydrogenated with 10% palladium-on-carbon in the Parr apparatus at room temperature and 60 psi. The catalyst is filtered and the filtrate evaporated *in vacuo* to yield 4-hydroxy- α -(1-isopropylaminopropyl)-3-ureidobenzyl alcohol hydrochloride, m.p. 224°C.

EXAMPLE 10

A mixture of 25.5 g. (0.1 m.) of 4-benzyloxy-3-methylaminoacetophenone (prepared as in Example 8), 5.7 g. of methyl isocyanate and 100 ml. of toluene is stirred at 250 for two hours. Filtering the reaction mixture and evaporating the filtrate yields 4-benzyloxy-3-(*N,N'*-dimethylureido)-acetophenone.

Reaction of the above acetophenone as described in Example 8 to give the α -bromo derivative which is then treated with *N*-benzyl-*N*-*t*-butylamine followed by hydrogenation with palladium-on-carbon furnishes as the final product, α -(*t*-butylaminomethyl)-3-(*N,N'*-dimethylureido)-4-hydroxybenzyl alcohol hydrochloride.

EXAMPLE 11

Ingredients	Mg./Tablet
α -(<i>t</i> -Butylaminomethyl)-4-hydroxy-3-ureidobenzyl alcohol hydrochloride	5.68*
Lactose	107
Starch	7
Magnesium stearate	0.7

*Equivalent to 5 mg. of the free base

A granulation of the above ingredients is compressed with punches having 9/32 inch diameter.

EXAMPLE 12

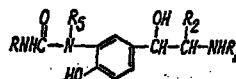
Ingredients	Mg./Dose
α -(<i>t</i> -Butylaminomethyl)-4-hydroxy-3-ureidobenzyl alcohol hydrochloride	0.125
Alcohol, U.S.P.	17
Propellant (20% Freon 12/ 80% Freon 114 mixture)	33

(FREON is a Registered Trade Mark)

The above ingredients in an aerosol dispensing system with a metered valve furnishes the indicated amounts per dose.

WHAT WE CLAIM IS:—

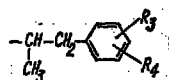
1. A compound of the formula:



or a pharmaceutically acceptable acid addition salt of said compound, wherein:

5 R is hydrogen, straight or branched chain alkyl of from 1 to 5 carbon atoms, phenyl, dimethylaminoethyl or dimethylaminopropyl;

R₁ is branched chain alkyl of from 3 to 5 carbon atoms, cycloalkyl or cycloalkylmethyl, the cycloalkyl moiety having from 3 to 6 carbon atoms, or



10 R₂ is hydrogen, methyl or ethyl;

R₃ and R₄ are hydrogen, hydroxy or methoxy; and
R₅ is hydrogen or methyl.

2. A compound according to claim 1 in which R₅ is hydrogen.

3. A compound according to claim 1 or claim 2 in which R is hydrogen.

15 4. A compound according to any one of claims 1 to 3 in which R₂ is hydrogen.

5. A compound according to any one of claims 1 to 4 in which R₁ is t-butyl.

6. α-(t-Butylaminomethyl)-4-hydroxy-3-ureidobenzyl alcohol.

7. α-(Cyclopentylaminomethyl)-4-hydroxy-3-ureidobenzyl alcohol.

8. A compound according to claim 2 in which R is methyl.

20 9. A compound according to claim 8 in which R₂ is hydrogen.

10. 4-Hydroxy-α-(isopropylaminomethyl)-3-(N'-methylureido)-benzyl alcohol.

11. α-(t-Butylaminomethyl)-4-hydroxy-3-(N'-methylureido)-benzyl alcohol.

12. A compound according to claim 3 in which R₂ is methyl or ethyl.

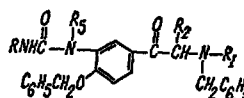
13. α-(1-t-Butylaminopropyl)-4-hydroxy-3-ureidobenzyl alcohol.

25 14. α-(1-t-Butylaminoethyl)-4-hydroxy-3-ureidobenzyl alcohol.

15. α-(t-Butylaminomethyl)-4-hydroxy-3-(N-methylureido)-benzyl alcohol.

16. A compound according to any one of the preceding claims as hereinbefore described in any one of the Examples.

17. A compound of the formula:



wherein R, R₁, R₂ and R₅ have the same significance as in the formula set out in claim 1.

18. A pharmaceutical composition in dosage unit form comprising a pharmaceutical carrier and a compound according to any one of claims 1 to 16.

19. A method of preparing any of the compounds of claim 1 substantially as described herein and particularly in any one of Examples 1—10.

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