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3,459,756

N-[2',6'-DIMETHYL-PIPERIDYL-(1')]-3-SULFAMYL-4-CHLORO-BENZOIC ACID AMIDE

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Claims priority, application Switzerland, Nov. 9, 1960, 12,547/60; June 6, 1961, 6,547/61

The portion of the term of the patent subsequent to May 20, 1986, has been disclaimed

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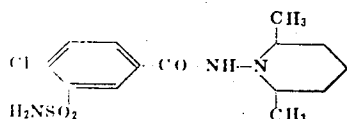
U.S. Cl. 260—293.4

1 Claim

ABSTRACT OF THE DISCLOSURE

This invention is directed to a new chemical compound, N-[2', 6'-dimethyl-piperidyl-(1')]-3-sulfamyl - 4 - chloro-benzoic acid amide, a compound having useful diuretic properties.

The present invention relates to a diuretic composition in unit dosage form containing as the active ingredient thereof N - [2', 6' - dimethyl - piperidyl - (1')] - 3 - sulfamyl - 4 - chloro - benzoic acid amide of the Formula I,



and is a division of application Ser. No. 560,062, filed June 24, 1966, which in turn is a continuation-in-part of our application Ser. No. 325,784, filed Nov. 22, 1963, now abandoned, which is in turn a continuation-in-part of application Ser. No. 153,776 filed Nov. 7, 1966, now abandoned. In the file of this co-pending application, Ser. No. 153,776, there was submitted a verified affidavit of Dr. Edward W. Fluckiger comparing the salidiuretic activity of the pharmaceutically active compound of the present invention, through testing in adult rats, with the structurally closest and most active prior art compound of the U.S. De Wald et al. Patent No. 3,043,874, namely N - [pyrrolidiny] - (1') - 3 - sulfamyl - 4 - chloro - benzoic acid amide, as well as with related compounds in the De Wald et al. patent in which the pyrrolidine ring was replaced by the morpholine ring. The verified affidavit demonstrated for the compound of the present invention a minimal effective dose in the adult rat at 0.01 mg./kg. (the dose necessary to increase sodium excretion by 0.5 meq. in 3 hours) and the maximally effective dose at 1 mg./kg. In contrast to the dose for the compound of said De Wald et al. patent, N-[pyrrolidiny]-(1') - 3 - sulfamyl - 4 - chloro - benzoic acid amide, the minimal dose for the compound of the invention is 10 times smaller than the minimal dose of the reference compound, the medium dose is 10 times smaller and the maximal effect dose which can be elicited is 5 times smaller, thereby demonstrating that the compound of the invention is unexpectedly superior to said De Wald et al. reference compound in respect to both effectiveness and clinical usefulness. Neither the compound of the present invention nor the compound of said De Wald et al. patent showed any notable effect on potassium excretion.

The acid addition salts of N - [2', 6' - dimethyl-piperidyl - (1')] - 3 - sulfamyl - 4 - chloro - benzoic acid and pharmaceutical compositions containing the aforesaid compound in addition to an inert carrier, as well as the pharmaceutically acceptable acid addition salt

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thereof, are effective in dosages for administration of 2-100 mg. per day and are also part of the present invention.

PRIOR DIURETICS FOR NaCl

Goodman and Gilman, in "The Pharmacological Basis of Therapeutics," 2nd Edition, MacMillan Company, New York (1955), at pages 840 and 841, classifies sodium chloride diuretics on the basis of structural composition, e.g. organic mercurials, xanthines, acetazoles, etc., and the physiological action, e.g. inhibition of renal tubular transport. It is observed that during a 24 hour period the average adult filters, through the glomeruli, about 180 liters of fluid containing over 1600 grams of sodium salts; and, under normal circumstances, 179 liters of fluid and 1590 grams of sodium salts are reabsorbed. The source of the glomerular filtrate is extracellular fluid. The reabsorption of sodium and accompanying anion by the renal tubule is the process which requires the greatest expenditure of energy by the kidney since the sodium ion is the principal cation of extracellular fluid. Interference with its reabsorption represents a significant mechanism for withdrawing sodium from the extracellular fluid, e.g. for the elimination of sodium from the body.

The organic mercurial inhibitors inhibit SH-activated enzyme systems through release of the mercuric ion. The diuretic action of the organic mercurial is inhibited by certain mercaptans. The sulfhydryl inhibition is believed to implicate the succinic dehydrogenase enzyme system. The extreme toxicity of mercury represents its principal disadvantage. Urine excreted in response to a mercurial diuretic contains chloride as the predominant ion and the loss of fixed sodium is secondary. Persistent systemic alkalosis develops quite readily and the patient becomes refractory to the desired action of the diuretic.

In contrast, acetazoleamide depresses tubular reabsorption transport of electrolyte by promoting the bicarbonate excretion and serves as a specific inhibitor of carbonic anhydrase enzyme. This compound shares with sulfanilamide the specific inhibition of carbonic anhydrase to thereby create acidification of the urine. Carbonic anhydrase enzyme is present in red blood cells, renal cortex, pancreas, and the gastric mucosa, and functions to provide a source of hydrogen and bicarbonate ions. In the renal tubular cell, hydrogen is exchanged with sodium. The source of the hydrogen is carbonic acid. By depressing the rate of formation of carbonic acid through the inhibitory action of the drug, the bicarbonate reabsorption is diminished, acid and ammonia disappear and the kidney elaborates an increased volume of alkaline urine. The net result is a loss of extracellular sodium bicarbonate and an osmotic equivalent of water. This treatment develops metabolic acidosis in contrast to the mercurial treatment which develops a metabolic alkalosis.

Both of the aforesaid types of prior art treatment, although of proven value, possess serious disadvantages, particularly in respect to the effect on the central nervous system. The anticonvulsant potency of sulfanilamide and acetazoleamide are correlated directly with the degree of inhibition of brain carbonic anhydrase which each compound produces in vivo. Large doses cause drowsiness and disorientation. It has always been thought that the inhibitory enzyme mechanism for the interaction of the sulfanilamide structure with carbonic anhydrase is a structural characteristic of the sulfonamide and the sulfanilamide radicals.

THE UNEXPECTED PROPERTIES OF THE PRESENT COMPOSITION

The dosages of the present invention which are smaller than the maximum diuretically active dose, e.g. at dosages of between 20 and 40 milligrams per day, provide com-

pletely unexpected interference with catecholamine dependent functions which makes the present composition in unit dosage form outstandingly useful for the treatment of hypertension in which there is a benefit from the control of sodium chloride diuresis within narrow limits.

The salidiuretic activity of N-[2',6'-dimethyl-piperidyl-(1')]-3-sulfamyl-4-chloro-benzoic acid amide is much greater than that of each of the following:

(a) N-[pyrrolidiny-(1')]-3-sulfamyl-4-chloro-benzoic acid amide

(b) N-[morpholinyl-(4')]-3-sulfamyl-4-chloro-benzoic acid amide

(c) N-[piperidyl-(1')]-3-sulfamyl-4-chloro-benzoic acid amide

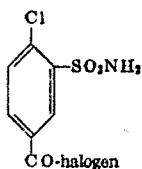
(d) 4-chloro-3-sulfamoyl-benzoic acid hydrazide

(e) 4-chloro-3-sulfamoylbenzoic acid N²,N²-dimethyl hydrazide.

The present active ingredient, N-[2',6'-dimethyl-piperidyl-(1')]-3-sulfamyl-4-chloro-benzoic acid amide has shown an unexpectedly high antagonistic activity in reserpine hydrothermia which is effective, remarkably, in doses smaller than the maximally diuretic active dose. In contrast, compounds (a), (b), (c), (d) and (e) above are inactive in this respect (reserpine hypothermia) when administered in dosages throughout each of their effective diuretic ranges and even up to the maximally diuretic active dose. In the case of rats the ED₅₀ value of the compound of the present invention for the inhibition of reserpine hypothermia over 3 hours was found to be 0.05 mg./kg.

The action of N-[pyrrolidiny-(1')]-3-sulfamyl-4-chloro-benzoic acid amide appears to be explained by assuming an interference with the catecholamine metabolism of the body. This assumption is substantiated by the fact that continuous treatment of animals with the present active ingredient also increases the sensitivity of their vascular walls to noradrenaline, just as happens with continuous treatment of animals with reserpine. In the light of the present understanding of the patho-physiology of essential hypertension and in view of the present significance attributed to the catecholamines in hypertension, this interfering property appears to provide an unexpected advantage in the application of N-[2',6'-dimethyl-piperidyl-(1')]-3-sulfamyl-4-chloro-benzoic acid amide for the treatment of hypertensive diseases. In short, the sympathetic involvement in hypertension is unexpectedly influenced by the present active compound thereby permitting its use where no other compound can be successful.

A process for the preparation of the new compound is characterized in that a 3-sulfamyl-4-chloro-benzoyl-halide of the Formula II,



in which halogen signifies a chlorine and bromine atom, is reacted in the liquid phase with 1-amino-2,6-dimethyl-piperidine, or a salt thereof. The liquid phase in the process may be homogeneous or not homogeneous and may be achieved by an excess of 1-amino-2,6-dimethyl-piperidine when this is liquid under the reaction conditions otherwise, the presence of an inert organic solvent, e.g. a halogenated hydrocarbon such as chloroform, is necessary. It is advantageous to add a proton acceptor, for example, a tertiary organic base, to the reaction mixture to take up the hydrogen halide produced during the reaction, but this is not essential.

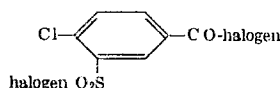
The following is a method of carrying out the process: Triethylamine is added to a suspension of 1-amino-2,6-dimethyl-piperidine or a salt thereof in chloroform. A

3-sulfamyl-4-chloro-benzoyl-halide is then added to the solution and the mixture is stirred at room temperature for 1 to 4 days. The mixture is then evaporated to dryness, the residue taken up with a water immiscible solvent, e.g. ethyl acetate, and washed with water.

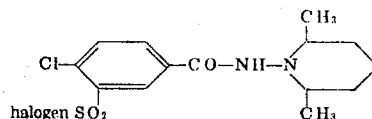
After drying the solution and evaporating the solvent preferably at reduced pressure, N-[2',6'-dimethyl-piperidyl-(1')]-3-sulfamyl-4-chloro-benzoic acid amide, obtained as a residue, is purified in accordance with known methods.

As suitable 3-sulfamyl-4-chloro-benzoyl-halides may be mentioned 3-sulfamyl-4-chloro-benzoyl chloride or bromide.

Another process for the preparation of the new compound is characterized in that a 3-halogeno-sulfonyl-4-chloro-benzoyl halogenide of general Formula III,



wherein halogen has the above significance, is reacted with a 1-amino-2,6-dimethyl piperidine and the resulting compound of general Formula IV,



wherein halogen has the above significance, is treated with ammonia to give the N-[2',6'-dimethyl-piperidyl-(1')]-3-sulfamyl-4-chloro-benzoic acid amide. The 1-amino-2,6-dimethyl piperidine can be reacted with a compound of general Formula III, as well as in the form of a free base as in the form of a salt. The process mentioned above can be effected as follows:

The suspension or solution of a 3-halogeno-sulfonyl-4-chloro-benzoyl halogenide of general Formula III is reacted with 1-amino-2,6-dimethyl piperidine in an indifferent solvent, e.g. acetone, chloroform or chlorobenzene, and heated for several hours. After the cooling down of the reaction mixture, the eventually crystallized reaction product is either sucked off or the solution is evaporated to dryness, the residue is dissolved in an indifferent organic solvent, e.g. chloroform, and treated with ammonia. The ammonia can be added as an aqueous solution, in the form of liquid ammonia, as ammonia gas in chloroform or diluted in alcohol. The solution is then left to stand at room temperature, evaporated to dryness after all of the ammonia has volatilized and the resulting N-[2',6'-dimethyl-piperidyl-(1')]-3-sulfamyl-4-chloro-benzoic acid amide is then purified in a manner known per se, e.g. crystallization or chromatography over aluminium oxide.

Suitable 3-halogeno-sulfonyl-4-chloro-benzoyl-halogenides are, for example, the 3-chloro-sulfonyl-4-chloro-benzoyl-chloride, the 3-bromo-sulfonyl-4-chloro-benzoyl chloride, the 3-chloro-sulfonyl-4-chloro-benzoyl bromide, the 3-bromo-sulfonyl-4-chloro-benzoyl bromide. Of these compounds, the acid chlorides have been found to be the most suitable, but the acid bromides can also be used. The 3-chloro-sulfonyl-4-chloro-benzoyl chloride is preferably produced by heating a mixture of 3-chloro-sulfonyl-4-chloro-benzoic acid and thionyl chloride to 100° C. It can also be obtained by reacting equimolecular quantities of 3-chloro-sulfonyl-4-chloro-benzoic acid and thionyl chloride in the presence of a little dimethyl formamide and using chlorobenzene as a solvent.

In the following non-limiting examples, all temperatures are indicated in degrees centigrade and are corrected.

Example 1.—N-[2',6'-dimethyl-piperidyl-(1')]-3-sulfamyl-4-chloro-benzoic acid amide

7.6 g. of 3-sulfamyl-4-chloro-benzoyl chloride are added to a solution of 3.8 g. of 1-amino-2,6-dimethyl-piperidine

and 3.0 g. of triethylamine in 150 cc. of chloroform within 20 minutes while stirring at 20–25° and the yellow reaction solution is then stirred for another 48 hours at room temperature. The mixture is then evaporated to dryness in a vacuum, the residue taken up in 200 cc. of ethyl acetate and washed with a total of 200 cc. of water. After drying over magnesium sulfate, the ethyl acetate is distilled off in a vacuum and the residue chromatographed on aluminum oxide, the N-[2',6'-dimethyl-piperidyl-(1')]-3-sulfamyl-4-chloro-benzoic acid amide being eluted with a solvent mixture of chloroform/methanol (9:1). After recrystallization from methanol/diisopropyl ether, the hydrazine derivative melts at 233–235°.

Example 2.—N-[2',6'-dimethyl-piperidyl-(1')]-3-sulfamyl-4-chloro-benzoic acid amide

(a) 3.3 g. of 1-amino-2,6-dimethyl-piperidine hydrochloride (M.P. 155–157°) are added portionwise to a solution of 5.5 g. of 3-chloro-sulfonyl-4-chloro-benzoyl chloride in 20 cc. of chlorobenzene with agitation at room temperature. Complete dissolution is obtained. The solution is then heated at reflux for 8 hours to 100–105° and, after cooling down to room temperature, the crystalline precipitated N-[2',6'-dimethyl-piperidyl-(1')]-3-chloro-sulfonyl-4-chloro-benzoic acid amide is filtered off. After drying in a vacuum at 100°, the sulfochloride is suspended in 15 cc. of chloroform and added carefully to 60 cc. of liquid ammonia. The reaction mixture is left to stand at room temperature until the excess ammonia has volatilized and it is then evaporated to dryness in a vacuum. The residue is chromatographed on aluminum oxide, the N-[2',6'-dimethyl-piperidyl-(1')]-3-sulfamyl-4-chloro-benzoic acid amide being eluted with a mixture of the solvents chloroform/methanol (9:1). After recrystallization from methanol/ether, the benzoic acid derivative melts at 235–237°.

(b) 3.3 g. of 1-amino-2,6-dimethyl-piperidine-hydrochloride are added portionwise to a solution of 5.5 g. of 3-chloro-sulfonyl-4-chloro-benzoyl chloride in 20 cc. of benzene while agitating at room temperature. The suspension is then boiled at reflux for 12 hours. The crystalline portion, i.e. the N-[2',6'-dimethyl-piperidyl-(1')]-3-chloro-sulfonyl-4-chloro-benzoic acid amide, is filtered off and the filtrate evaporated to dryness in a vacuum. After drying for a short time, the sulfochloride is carefully added to 60 cc. of liquid ammonia. Complete dissolution is obtained. The reaction mixture is left to stand at room temperature until the excess ammonia has volatilized. The solid residue is then suspended in a solvent mixture of 125 cc. of water and 250 cc. of ethyl acetate and shaken thoroughly. After filtering and separating the aqueous phase, the ethyl acetate solution is dried over magnesium sulfate and the ethyl acetate is evaporated in a vacuum. The residue and the residue which had been filtered off are united and recrystallized from methanol/ether. The N-[2,6-dimethyl-piperidyl-(1')]-3-sulfamyl-4-chloro-benzoic acid amide.

(c) 3.3 g. of 1-amino-2,6-dimethyl-piperidine hydrochloride are added portionwise to a solution of 5.5 g. of 3-chloro-sulfonyl-4-benzoyl chloride in 20 cc. of chlorobenzene while agitating at room temperature. The reaction mixture is then refluxed for 2½ hours and evaporated to dryness in a vacuum. The residue is suspended in 15 cc. of chloroform and added carefully to 60 cc. of liquid ammonia. The reaction mixture is allowed to stand at room temperature until the excess ammonia has volatilized and is then evaporated to dryness in a vacuum. The residue is chromatographed on aluminum oxide, the N-[2',6'-dimethyl-piperidyl-(1')]-3-sulfamyl-4-chloro-benzoic acid amide being eluted with a solvent mixture of chloroform/methanol (9:1). After

recrystallization from methanol-ether, the benzoic acid derivative melts at 235–236°.

(d) 3.3 g. of 1-amino-2,6-dimethyl-piperidine-hydrochloride are added portionwise to a solution of 5.5 g. of 3-chloro-sulfonyl-4-chloro-benzoyl chloride in 20 cc. of absolute benzene while agitating at room temperature. The suspension is then boiled at reflux for 24 hours. The crystalline portion, i.e. the N-[2',6'-dimethyl-piperidyl-(1')]-3-chloro-sulfonyl-4-chloro-benzoic acid amide is filtered off and the filtrate evaporated to dryness in a vacuum. The filter residue is suspended in 10 cc. of chloroform and added carefully to 60 cc. of liquid ammonia. The reaction mixture is allowed to stand at room temperature until the excess ammonia has volatilized. The chloroform is removed in a vacuum, the solid residue suspended in a solvent mixture of 100 cc. of water and 250 cc. of ethyl acetate and shaken thoroughly. The ethyl acetate solution is separated, dried over magnesium sulfate and evaporated to dryness in a vacuum. After recrystallization from methanol-ether, the solid residue, i.e. the N-[2,6-dimethyl-piperidyl-(1')]-3-sulfamyl-4-chloro-benzoic acid amide, melts at 232–234°.

(e) A solution of 2.58 g. of 1-amino-2,6-dimethyl-piperidine in 5 cc. of benzene is added dropwise to a solution of 5.5 g. of 3-chloro-sulfonyl-4-chloro-benzoyl chloride in 15 cc. of benzene at room temperature while agitating, a reddening of the reaction solution with slightly increasing temperature being obtained. After boiling for 12 hours at reflux, the crystalline portion, i.e. the N-[2,6-dimethyl-piperidyl-(1')]-3-chloro-sulfonyl-4-chloro-benzoic acid amide is filtered off, suspended in 10 cc. of chloroform and slowly added to 60 cc. of liquid ammonia. Complete dissolution is obtained. The reaction solution is allowed to stand at room temperature until the excess ammonia has volatilized and then evaporated to dryness in a vacuum. The residue is suspended in a solvent mixture of 100 cc. of water and 200 cc. of ethyl acetate and thoroughly shaken. After filtering off and separating the aqueous phase, the ethyl acetate solution is dried over magnesium sulfate and the solvent is evaporated in a vacuum. The residue and the undissolved part are united and recrystallized from methanol-ether. The N-[2,6-dimethyl-piperidyl-(1')]-3-sulfamyl-4-chloro-benzoic acid amide melts at 234–235°.

(f) Analogously, N-[2',6'-dimethyl-piperidyl-(1')]-3-sulfamyl-4-chloro-benzoic acid amide can also be obtained from 3-chloro-sulfonyl-4-chloro-benzoyl chloride and 1-amino-2,6-dimethyl-piperidine-hydrochloride using acetone as a solvent.

At room temperature N-[2',6'-dimethyl-piperidyl-(1')]-3-sulfamyl-4-chloro-benzoic acid amide is a crystalline compound useful as a pharmaceutical or as an intermediate for the production of other compounds. The exemplified compound is administered in therapeutic dosages of 2–100 mg. per day, preferably 20–40 mg. per day, in conventional pharmaceutical acceptable vehicles as well as in the form of tablets. The dosage of the present invention is effective upon enteral and parenteral administration. In order to produce such medicinal preparations, the compounds of the invention are worked up with organic or inorganic adjuvants which are physiologically acceptable and inert. Examples of such adjuvants or carriers for various medicinal preparations are as follows:

Tablets and dragées.—Lactose, starch, talc, magnesium stearate, gellative and stearic acid,

Syrups.—Solutions of cane sugar invert sugar and glucose,

Injectable solutions.—Water, physiologically acceptable alcohols, glycerine and physiologically acceptable vegetable fats,

Suppositories.—Physiologically acceptable, natural or hardened oils and waxes,

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Ointments, suspensions and emulsions.—Inorganic and organic, lipophilic or hydrophilic compounds, paraffin, alginates, cellulose derivatives, polyoxyethylene derivatives, bentonite and petroleum jelly.

The preparations may contain suitable preserving, stabilizing or wetting agents, solubilizers, sweetening and colouring substances or flavourings, with the proviso that they must be physiologically acceptable.

What is claimed is:

1. N - [2',6' - dimethyl - piperidyl - (1')] - 3 - sul- 10 famyl - 4 - chloro-benzoic acid amide.

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References Cited

UNITED STATES PATENTS

3,043,874	7/1962	De Wald et al.	260—293.47
3,337,547	8/1967	Jucker et al.	260—293.47

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