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VASOCONSTRICTOR COMPOUNDS OF SACCHARIN AND PHARMACEUTICAL COMPOSITIONS PRODUCED THEREFROM

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16 Claims. (Cl. 167—65)

1

This invention relates generally to new chemical compounds, compositions containing the same and solutions thereof, and more particularly to those adapted for pharmaceutical uses. Especially, it involves the N-salts of saccharin with vasoconstrictors having salt-forming amine groups, including therapeutic compositions and solutions utilizing these salts.

It is an object of this invention to provide a single chemical compound which has a combined therapeutic effect of vasoconstriction, antibacterial activity, and local anesthesia. To illustrate one use of such a compound, in the preparation of nasal medicaments it is desirable to have a drug which will give the patient immediate relief by shrinking congested nasal mucosa, and which will at the same time have a marked corrective effect against the bacterial invaders which cause the congestion, as well as provide relief from neuralgic headaches by mild local anesthetic action. The N-salts of saccharin with vasoconstrictive amines, according to this invention, fully meet these requirements.

It is a further object of this invention to provide a pharmaceutical which may be used in small amounts and low concentrations and still achieve the desired therapeutic effects. This object is attained by my new salts, whose formation is evidenced by physiological synergism which is apparent clinically as well as bacteriologically.

A further object of the invention is to provide a single drug which is readily retained by the mucosa in intranasal therapy, which exerts a prolonged compound therapeutic effect locally, and which is not immediately or relatively soon eliminated by nasal discharge or secretions. Apparently, most nasal medication is soon eliminated from the nasal mucosa by the body fluids, and it is, therefore, an object of this invention to provide a drug which will be gradually eliminated over a period of six to twelve hours or more.

Another object of this invention is to provide a stable, clear therapeutic solution which may be sterilized by heat and which will keep indefinitely when stored under normal atmospheric conditions, without harmful deterioration or color change.

It is a further object of this invention to provide compounds which are relatively nontoxic, and which may be used topically as vasoconstrictive local anesthetic antiseptics.

Another object of this invention is to provide drugs for nasal or oral administration which are pleasing to the taste, and as even a small amount of free saccharin in solution has a sickeningly sweet taste to many persons, it was necessary to formulate therapeutic solutions so as to modify or substantially eliminate undesirable sweetness.

A further object of this invention is to provide a new series of salts of the vasoconstrictive

2

amines which potentiates the desirable vasoconstrictive effects of the amines and reduces the undesirable side reactions of the drugs, such as tachycardia, nervousness, sleeplessness and the like.

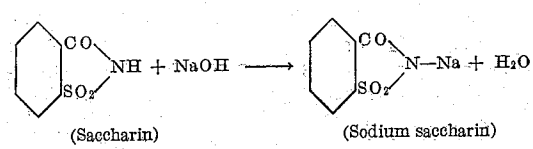
Ideally, nasal medicaments should be aqueous, isotonic or slightly hypertonic solutions which give rapid and prolonged vasoconstriction without untoward side effects, which are not irritating to the mucosa and which are relatively nontoxic systemically, which correct the bacterial flora of the upper respiratory tract by bactericidal or bacteriostatic action, and which provide relief from pain and headaches by promoting natural drainage and reducing congestion as well as by a mild local anesthetic effect. It is, therefore, an additional object of this invention to provide such aqueous solutions, and to provide the active drugs which cause such effects.

Most medicaments are unfortunately unpleasant for patients to take, and may cause nausea, vomiting or other undesirable reactions in individual cases. Consequently, it is another object of this invention to provide medicaments which may be dispensed in several flavors and which will thus be available to meet the individual tastes of sensitive patients, without changing the beneficial effects of the active drugs.

These and other objects and features of the invention will become apparent from the following detailed description of this invention.

In connection with my discovery of the N-salts of saccharin with salt-forming vasoconstrictive amines, I have not only found them to be highly desirable for yielding the above mentioned effects of vasoconstriction, antibacterial activity and local anesthesia, and for providing the desirable feature of accomplishing the necessary therapeutic effects with low concentrations and for relatively prolonged periods of time, but I have also found that they produce such results without objectionable effects as above indicated.

Saccharin itself, i. e., o-sulfobenzimide, is a stable, nontoxic acid of moderate strength which has been used as a sweetening agent for many years since its discovery in 1879 by Remsen and Fahlberg. There is apparently no case on record where human illness has been ascribed to the use of saccharin in normal amounts. In aqueous media, saccharin forms N-salts with alkaline materials. Thus:



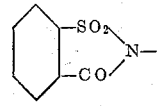
(Saccharin) (Sodium saccharin)

Because the sodium salt of saccharin is very soluble in water and because saccharin itself is not

very soluble, this salt is commonly called "soluble saccharin."

Many N-salts of saccharin are known, including those formed with sodium, potassium, ammonium, metallic ions, and the like. There are some data in the literature on amine salts of saccharin which form at room temperature and which are reported to cause cleavage of the imido ring when heated near the boiling point ("The Organic Chemistry of Sulfur," Suter, John Wiley & Sons Inc., N. Y., 1943). Of the many possibilities, the only commercially useful salts, aside from the sodium salt, of which I am aware are those formed with the phenylmercuric ions (U. S. Patents 2,087,959 and 2,135,533) which are antiseptics.

By the term "saccharin" I mean to include both o-sulfobenzimide and its relatively nontoxic, water-soluble derivatives which still contain the typical heterocyclic nucleus



It is obvious that hydrogens may be substituted in the benzene ring by nitro, bromo, iodo, carboxy, methoxy, or the like radicals without affecting the chemical equivalence of the nucleus, whose main reactivity is due to the heterocyclic ring nitrogen. For example, I may use p-methyl saccharin or 6-chloro-saccharin to form N-salts with vasoconstrictive amines, instead of saccharin itself.

By the term "vasoconstrictive amines" I mean to include all those amines which have a local vasoconstrictive effect and which are related to phenyl ethylamine, inter alia:

C-phenyl alkylamines such as phenyl ethylamine, amphetamine ("benzedrine") which is 1-phenyl-2-amino propane; and desoxyephedrine which is 1-phenyl-2-methylamino propane;

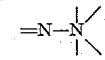
C-phenyl alkylolamines such as ephedrine which is 1-phenyl-2-methylamino propanol-1, and norephedrine ("propadrine") which is 1-phenyl-2-amino propanol-1;

C-hydroxyphenyl alkylamines such as tyramine which is p-hydroxyphenyl ethylamine, "paredrine" which is β-aminopropyl-4-hydroxy benzene, and "kephrin" which is 1-(3,4 dihydroxy phenyl)-2-methylamino ethanone-1;

C-hydroxyphenyl alkylolamines such as "neosynephrine" which is α-hydroxy-β-methylamino ethyl-3-hydroxy benzene, "synephrine" which is α-hydroxy-β-methylamino ethyl-4-hydroxy benzene, "cobefrine" which is 1-(3,4 dihydroxyphenyl)-2-amino propanol-1, and epinephrine which is 1-(3,4 dihydroxyphenyl)-2-methylamino ethanol-1;

as well as those alkylamines, having the same vasoconstrictive characteristics, such as 2-amino heptane, di-n-heptyl amine, n-hexylamine, and cyclohexyl amine; and in addition the N-salt-forming nitrogen heterocyclic "privine" which is 2-(1-naphthylmethyl)-imidazoline, and which also possesses the same vasoconstrictive characteristics. In other words, the term "vasoconstrictive amines" is intended to embrace those "sympathomimetic" or "pressor" drugs having salt forming amine groups and pronounced local vasoconstrictive action, as is well understood pharmacologically, and having therapeutic value, at least when combined as constituents in the new compounds of this invention. Other amines included are substances such as: epinine, hordenine, mescaline, arterenol, paredrinol, suprifen and veritol.

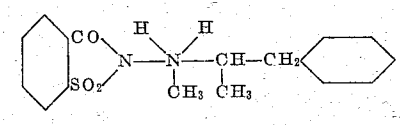
I have discovered that any vasoconstrictive amine having a salt-forming amine group will react with saccharin to form a complex N-salt in which the imido nitrogen is trivalent and the amino nitrogen is pentavalent. The pharmacodynamic grouping characteristic of all of these compounds is



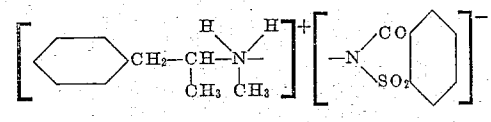
and as long as this linkage is maintained the compounds have a high degree of physiological activity. It is also to be noted that the N-saccharin salts given herein as having physiological activity, have in the amine radical at least four carbon atoms of which at least three are in a series carbon to carbon linkage attached at one end to the amino nitrogen.

The salts of saccharin of this invention may be prepared by the simple addition of equimolar quantities of saccharin to the amine, at room temperature, when the amine is liquid; by mixing equimolar quantities of saccharin sodium and the acid salt of the amine with water to form an aqueous solution which contains the amine salt of saccharin and the sodium salt of the acid from the amine; or by mixing equimolar proportions of the amine and saccharin in water, or some other suitable solvent. Other temperatures than room temperature may be employed up to about 100° C. in most cases, since the agents used are in most cases stable to at least 100° C.

In the present invention, the structure of the compounds is well indicated by the salt desoxyephedronium o-sulfobenzimide:



which, being the substituted ammonium salt formed between the acidic saccharin and the basic amine, may also be termed phenylisopropyl methyl ammonium o-sulfobenzimide. The ionic structure of the salt formed between desoxyephedrine and saccharin may be indicated conventionally:



and the meaning of this formula is identical to and merely clarifies the structure outlined in the preceding paragraph.

The salts formed between saccharin and the vasoconstrictive amines are new compositions of matter. They have new and different properties as compared with the reactants themselves. In general, they are very soluble in water in comparison with the sparing solubility of saccharin or the amine. In general, the amines are limpid liquids or solids and the saccharin a crystalline solid, whereas the salts are viscous liquids, crystals or transparent gums or resins depending upon the amine used in the reaction. pH titration curves between the amines and the saccharin indicate that at equimolar proportions the end point of the reaction is reached, and the pH of the salt formed is either approximately neutral or

slightly on the acid side, depending upon the basicity of the amine selected for reaction.

The physiological properties of the salts are entirely different from those of the reactants. Using *Staphylococcus aureus* and making agar plate cultures of these organisms, a filter disc 12.5 mm. in diameter saturated with 0.15 ml. of a 10% solution of the material to be tested will show a ring of inhibition after standing 24 hours in an incubator at 100° F. if the material is potent against the bacterial growth under these conditions. Some results obtained by conducting these tests are tabulated as follows:

Compound tested, 10% aqueous Solution	Clear area Diameter	Hazy area Diameter
Sodium Saccharin	Practically oil	Nil.
Ammonium Saccharin	Nil	Nil.
2-amino heptane sulfate	Trace	
Desoxyephedrine hydrochloride	Very slight trace	
2-heptylammonium saccharin	20 mm	28 mm.
Desoxyephedronium saccharin	16.5 mm	

It is readily seen that in these tests neither sodium saccharin, ammonium saccharin, desoxyephedrine hydrochloride, or 2-aminoheptane sulfate had any marked inhibitory effect on the growth of *S. aureus*, whereas under identical conditions the salt of desoxyephedrine with saccharin was moderately potent against the growth and the salt of 2-aminoheptane and saccharin was very potent in its growth inhibition. This "synergism" is due to the chemical compound formation between the amine and the saccharin.

A number of saccharin-amine salts were prepared and tested on agar plates under identical conditions, and the results below indicate that the above conclusion is a generality:

Compound of Saccharin with—	Concentration	Diameter of Area	
		Clear	Hazy
	Per cent	*mm.*	*mm.*
Phenylethyl amine	10	17	22
Phenylisopropyl amine	10	16	
Ephedrine	10	14	
Neosynephrine	10	14	
Tyramine	10	Faint	
Epinephrine	10	Sol'n decomposed.	
Propadrine	10	14	
m-Hydroxy Propadrine	10	14	
Isopropyl amine	10		16
n-Butyl amine	10		17
Di-n-butyl amine	10		16.5
Tri-n-Butyl amine	10		18
Amyl amine (mixed)	10	16.5	
Hexyl amine	10	19	
Dihexyl amine	10	17	
n-Heptyl amine	2.5	17	
Di-n-Heptyl amine	0.5	18	
n-octyl amine	0.5		16.5
Decyl amine	0.4	18.5	
Dodecyl amine	Sat'd	14	
Benzyl amine	10	17.5	
Cyclohexyl amine	10	15	26
Pyridine	10	15	
Octadecyl amine	Emulsified, could not test.		

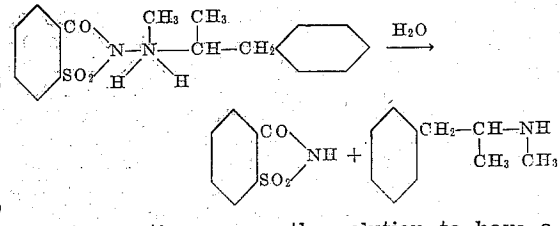
While the growth antagonism tests on agar plates are indicative of activity, they are not in themselves sufficient to base complete conclusions upon. Therefore, several series of tube cultures were made, in which the nutrient broth in test tubes was inoculated with *S. aureus*, and the desired concentrations of the materials to be tested were added. Growth after 24 hours' incubation was estimated by the cloudiness and amount of sediment in the cultures, and the concentration of the nutrient broth was in all cases adjusted to insure strictly comparable results. The following tabulation indicates the effect of various saccharin amine salts and mixtures in tube cultures:

Saccharin salt of—	Concentration	Growth Inhibition
	Per cent	
Desoxyephedrine	1	Good.
	0.5	Nil.
	0.1	Do.
2-Aminoheptane	1	Good.
	0.5	Poor.
	0.1	Nil.
Cyclohexyl amine	1	Good, not complete.
	0.5	Med.
	0.1	Poor.
Desoxyephedrine, Sodium Lauryl sulfate, 1:35	1	Good.
	0.5	Do.
	0.1	Excellent.
	0.05	Approx. 50%.
2-aminoheptane with Sodium Lauryl sulfate, 1:35	1	Excellent.
	0.5	Very good.
	0.1	Excellent.
	0.05	Do.
Neosynephrine with Sodium Lauryl sulfate, 1:35	0.5	Do.
	0.1	Excellent, 100%.
	0.05	Approx. 30%.

It is apparent that the salts are much more effective in tube cultures in lower concentrations than they are on the agar plates, and that in relatively small amounts they have pronounced growth antagonism characteristics.

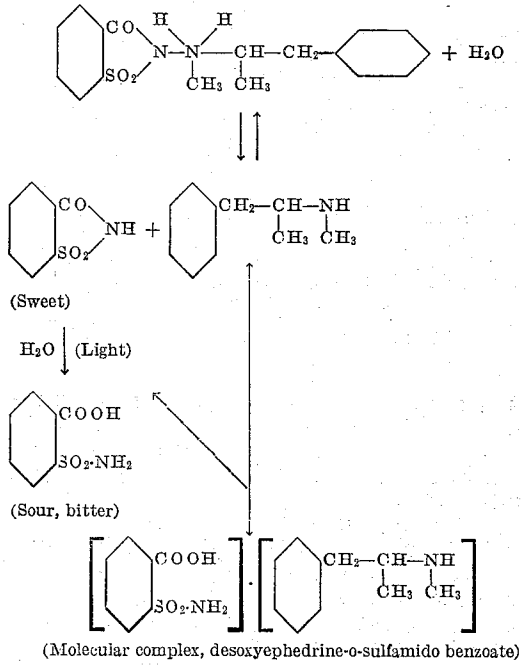
For clinical use, because of the pronounced vasoconstrictive properties of the salts, they can not be used in higher concentrations in nasal medicaments than approximately 0.5% without causing too much vasoconstriction in the nose, and the untoward effect of blanching the nasal mucosa. Therefore, it was necessary to add to the salts an ingredient increasing the antibacterial growth characteristic, and it was found that sodium lauryl sulfate, a wetting agent, would achieve this result in an unpredictable fashion. For example, in agar plate tests, sodium lauryl sulfate at 0.06% concentration gave a clear ring of inhibition of 15 mm. diameter; desoxyephedrine saccharin salt in 10% gave 16.5 mm. whereas the two together gave 23 mm. In contrast, sodium lauryl sulfate had no effect on the size of the inhibited areas of either 2-aminoheptane or cyclohexyl amine saccharin salts. Again, the salt of neosynephrine saccharin had little plate activity, but with the wetting agent in tube cultures it exhibits marked bactericidal activity in concentrations as low as 0.05%. In 0.10% solutions which showed excellent growth inhibition, no *S. aureus* grew in either culture or streak tests of liquid removed from the solution showing that the salt was actually bactericidal and the bacteria had been killed, whereas similar cultures from either the 2-aminoheptane or desoxyephedrine solutions showed growth, and these two salts were therefore bacteriostatic in their action.

In aqueous solutions the saccharin-amine salts hydrolyze to give some free saccharin and amine. Thus, for example:



This reaction causes the solution to have a very sweet flavor, and it is too sweet for many patients to take without unfavorable reactions. I have found that if the solution is exposed to air and sunlight and preferably warmed at the

same time, the sweet taste becomes so diminished as to be either hardly noticeable, or acceptable even to those sensitive to sweets. What happens might be expressed by the following equations, using the desoxyephedrine salt as an example:



Although I do not wish to be bound by this explanation, the free saccharin formed by hydrolysis of the amine salt hydrolyzes in the presence of light and air and is removed from the solution, being converted to o-sulfamidobenzoic acid. This acid then reacts with the free amine in solution to form a molecular complex of the indicated structure. The complex hydrolyzes reversibly to give the free amine and acid again, and by the law of mass action, the free amine shifts the saccharin salt hydrolysis equilibrium and greatly reduces the amount of free saccharin in solution, thus diminishing the sweet taste.

The ferric salt of o-sulfamidobenzoic acid is quite insoluble in water, but the ferric salt of saccharin is soluble, and no precipitation occurs when ferric chloride is added to desoxyephedrine hydrochloride. When ferric chloride is added to a freshly made solution of desoxyephedronium saccharin, no precipitate forms at first, but if the solution has been exposed to light and air, a precipitate is formed. This indicates that o-sulfamidobenzoic acid is formed in the solution, and the fact that the solution does not lose its clinical or antibacterial properties after ageing many months indicates that the reaction is slowed tremendously by the presence of excess amine ions.

The sweet taste of the saccharin-amine salts may be further camouflaged by the addition of flavors, such as menthol, lemon, clove or cinnamon. Care must be used in the selection of the flavor or the sweet taste may be accentuated. Because the solutions should be isotonic or slightly hypertonic for use as nasal medicaments, it is necessary to add an inert salt or buffer to the solutions. Sodium chloride may be used for this purpose, but magnesium sulfate has been found preferable because of its bitterness, which effectively offsets the mild residual sweetness characteristic of the imide-amine compounds. In addition to the mentioned neutral salts, sodium chloride and magnesium sulfate, other water soluble

nontoxic neutral salts may be used in appropriate proportions, such as magnesium chloride, potassium chloride, calcium chloride, sodium bicarbonate and sodium dihydrogen phosphate.

The following examples illustrate more specifically the nature of my invention:

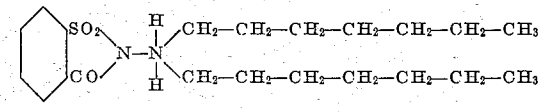
Example 1

The salt of saccharin with desoxyephedrine was prepared by mixing equimolar proportions of the two ingredients, stirring gently until all of the solid saccharin had disappeared. Thus, 1.831 parts of saccharin and 1.491 parts of desoxyephedrine (by weight) were stirred together. As the saccharin dissolved, the mass became more and more gummy, and finally stiff. It does not crystallize, and breaks with a conchoidal fracture.

The gum is water white, readily soluble in water giving an approximately neutral or slightly acid solution, readily soluble in ether, and poorly soluble in benzene. Chilling its concentrated aqueous solution results in the formation of a two phase liquid.

Example 2

Di-n-heptylammonium saccharin

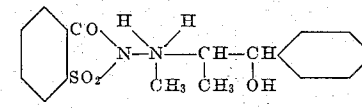


was prepared by adding 4.625 parts by weight of saccharin to 5.275 parts by weight of di-n-heptyl amine, and heating gently, stirring until a clear viscous liquid is obtained. Partial crystallization occurred when the liquid was chilled to 0° C.

The solid is viscous and gummy at room temperature; it is sparingly soluble in water (approximately 0.5%); it shows very pronounced vasoconstrictive and local anesthetic effects, particularly on mucous membrane, and effectively inhibits growth of *S. aureus*.

Example 3

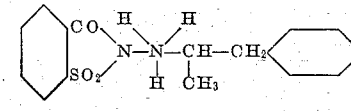
Ephedronium saccharin



was prepared as follows: 1.651 parts of ephedrine was melted with 1.831 parts of saccharin, stirring and heating gently. On cooling the mass became resinous, then gummy, and finally brittle. It did not crystallize, is very soluble in water (over 30%), and is deliquescent.

Example 4

Phenylisopropylammonium saccharin



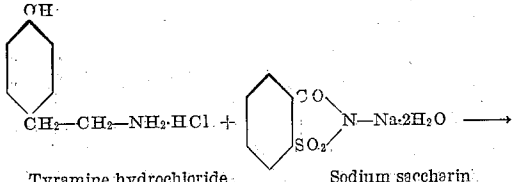
was made as follows: 1.34 parts of phenylisopropyl amine (amphetamine) was dissolved with 1.831 parts of saccharin in 2 parts of water, stirring. It was placed in a vacuum desiccator, and evacuated continuously for four hours. It became paste like, and water boiled from it, expanding the mass which finally became a porous solid. It was dried in vacuo, over magnesium perchlorate for three days. The material appeared dry, brittle and glassy.

Fragments of the mass, transferred rapidly to melting point tubes, became a viscous liquid at

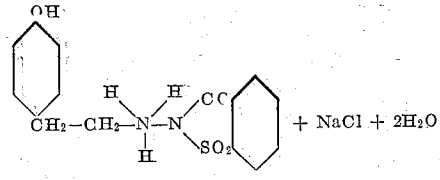
50–60° C. The material is deliquescent, rapidly becoming liquid in the moisture it removes from the air, and does not boil, but decomposes when heated to 290° C.

Example 5

Aqueous solutions can be made from any of the acid salts of the amines, by reacting them in water with the sodium salt of saccharin, in exactly equimolar quantities. The double decomposition which occurs results in the formation of the saccharin salt of the amine and the sodium salt of the acid which was coupled to the amine. The reaction, which is a general one, is illustrated by the reaction between tyramine hydrochloride and sodium saccharin. A ten percent solution of this material was needed for bacteriological testing, and was prepared as follows:



Tyramine hydrochloride (molecular weight 173.6) — Sodium saccharin (molecular weight 241.2)



Tyrammonium saccharin (molecular weight 320.2)

To make 0.5 part by weight of the compound:

$$\frac{320.2}{0.5}=\frac{241.2}{x}$$

x=0.376 part sodium saccharin required.

$$\frac{320.2}{0.5}=\frac{173.6}{y}$$

y=0.271 part tyramine hydrochloride required. The weighed amounts of sodium saccharin and tyramine hydrochloride were dissolved in 5 parts of water, and the resulting solution contained

10% tyrammonium saccharin.
1.8% sodium chloride.

Example 6

To prepare the pure salt of saccharin and a vasoconstrictive amine, by double decomposition, use may be made of the insolubility of inorganic salts formed in the double decomposition. The barium salt of saccharin is very soluble in water, whereas barium sulfate is insoluble. Barium saccharin reacts in aqueous solution with 2-aminoheptane sulfate to form 2-heptylammonium saccharin and barium sulfate. The insoluble barium sulfate may be filtered from the solution, and the filtrate evaporated in vacuo, to leave the residual 2-heptylammonium saccharin. Stoichiometric amounts of the various reactants are used, and the reaction goes to completion.

Example 7

Nasal medication should be isotonic or slightly hypertonic, and clinical tests have demonstrated that an 0.5% solution of desoxyephedronium saccharin gives adequate vasoconstriction, effective bacteriostasis, and relief from pressure and neuralgic headaches. A preferred embodiment of this invention in such a solution is prepared as follows:

To approximately 3 liters of water, add, with constant stirring at room temperature, 11.04 grams saccharin. Then, stirring continuously, add 9.76 ml. desoxyephedrine, and stir for at least one hour until the solution is entirely clear. Then add and dissolve 40.0 grams Epsom salts (magnesium sulfate heptahydrate), 1.00 gram "Duponol C" (60% sodium lauryl sulfate with 40% sodium sulfate), 4.0 ml. "lemon extract" (lemon dissolved in 85% ethanol), 0.020 gram menthol, and 2 ml. anise extract. Then add water, q. s. 4 liters.

The resultant cloudy solution is allowed to stand several days in strong light, and is then fine filtered and bottled in suitable container. The pH of the solution is 6.5–7.0; it is mildly sweet and has a pleasant mild licorice taste, will almost completely inhibit the growth of *S. aureus* even at a 5:1 dilution, permits ciliary activity to continue for reasonable period of time, is relatively nontoxic systemically, and in clinical tests on over one hundred patients it has not caused complaints of sleeplessness, nervousness, tachycardia, or other untoward side effects, but it has given outstanding symptomatic relief from pressure and neuralgic headaches. The solution is administered by jetting 0.15–0.2 ml. high into the nose, using 2–3 jets in each nostril every 2–3 hours.

Example 8

Solid, crystalline salt of neosynephrine-saccharin is prepared by dissolving 3.492 parts of neosynephrine hydrochloride and 3.756 parts of sodium saccharin (commercial salt containing 5% moisture) in 100 parts of absolute methanol by volume. After stirring until the solution is clear, 400 parts by volume of diethyl ether are added. The stoichiometric amount of precipitated sodium chloride is filtered from the reaction mixture, and the filtrate is vacuum evaporated at room temperature until the mass is gummy and there is no residual odor of methanol. Then, 25 parts of benzene is added, and the mixture is allowed to stand overnight at room temperature, after which the benzene and traces of ether, methonal, and moisture are removed by evaporation under high vacuum (0.3 micron of mercury or better). The colorless gum and white solid residue gradually crystallize after standing several weeks at room temperature. The crystals which form are very soluble in water, and melt sharply at about 103° C., and may be identified chemically as α-hydroxy-β-methylammoniumethyl -3-hydroxybenzene-N-o-sulfobenzimide.

Example 9

Crystalline n-hexylammonium-N-o-sulfobenzimide is prepared by purification by distilling commercial n-hexylamine and collecting that fraction condensed from the vapor when the temperature is between 128° C. and 128.5° C. and mixing 10.12 parts by weight of the distillate with 18.31 parts by weight of saccharin. The mass grows warm as heat is evolved by the reaction, and is stirred until it becomes a clear, water white, viscous liquid. It is then transferred to a dry, tightly capped container and stored at sub-freezing temperatures until crystallization commences. After crystals start to form, the container is stored at room temperature for several months until the entire mass has crystallized.

The n-hexylammonium-N-o-sulfobenzimide is a white, waxy or unctuous, crystalline solid which resembles paraffin wax, and which is deliquescent. It melts at 35° C. to 40° C. to form a clear, water white, viscous liquid.

Example 10

A preferred therapeutic solution of the salt of neosynephrine saccharin may be prepared as follows: In about 3 liters of water, dissolve, with constant stirring:

Neosynephrine hydrochloride	grams	3.492
Sodium saccharin (5% moisture content)	do	3.756
Sodium chloride	do	36.0
Duponol "C" (sodium lauryl sulfate 60%, sodium sulfate 40%)	do	0.300
Lemon extract (85% alcohol)	ml	1.60

Water, q.s. 4 liters.

The clear solution is filtered and bottled in suitable amber glass containers and is ready for use as nasal medication. The sodium chloride renders the solution isotonic, or slightly hypertonic, as would ordinarily be true of other solutions hereof as is well understood in this art.

This medication is very mildly lemon flavored, is salty and very slightly sweet to the taste, and has been found pleasing and effective by a very large number of patients. It gives adequate and prolonged vasoconstriction, relief from neuralgic and pressure headaches, and is well tolerated in doses of 2–5 ml. per day as required. It is bactericidal against *Staphylococcus aureus, Streptococcus hemolyticus* and *Streptococcus viridans.* Freedom from "side effects" has been outstanding.

The concentration of the active drug, which is α-hydroxy-β-methylammoniumethyl -3-hydroxybenzene-N-o-sulfobenzimide is 0.15%.

The foregoing examples are merely illustrative of suitable methods for preparing representative salts of saccharin with vasoconstrictors having a salt forming amine group, and pharmaceutical compositions embodying these salts for use as nasal medicaments. They are not intended to limit the scope of the invention, or preparations for other medicinal uses.

While the salts are in general soluble in water, some of the salts prepared from amines derived from the higher fatty acids are sparingly soluble, and my experiments indicate that they may find application for use as emulsifying agents, detergent compositions, topical application as simultaneous local anesthetics, vasoconstrictors, bacterial growth inhibitors, and the like.

I claim as my invention:

1. As a new chemical compound, an N-salt of saccharin and a vasoconstrictor amine in which the amine has at least four carbon atoms of which at least three are in a series carbon to carbon linkage attached at one end to the amino nitrogen.

2. As a new chemical compound, an N-salt of saccharin and a vasoconstrictor amine selected from the group consisting of C-phenyl alkylamines, C-phenyl alkylolamines, C-hydroxyphenyl alkylamines, C-hydroxyphenyl alkylolamines, alkylamines in which the amine has at least four carbon atoms of which at least three are in a series carbon to carbon linkage attached at one end to the amino nitrogen, and 2-(1-naphthylmethyl)-imidazoline.

3. As a new chemical compound, an N-salt of saccharin and a vasoconstrictor alkylamine in which the amine has at least four carbon atoms of which at least three are in a series carbon to carbon linkage attached at one end to the amino nitrogen.

4. As a new chemical compound, an N-salt of saccharin and a vasoconstrictor C-phenyl alkylamine.

5. As a new chemical compound, an N-salt of saccharin and a vasoconstrictor C-phenyl alkylolamine.

6. As a new chemical compound, an N-salt of saccharin and a vasoconstrictor C-hydroxyphenyl alkylamine.

7. As a new chemical compound, an N-salt of saccharin and a vasoconstrictor C-hydroxyphenyl alkylolamine.

8. As a new chemical compound, an N-saccharin salt of 1-phenyl-2-methylamino propane.

9. As a new chemical compound, an N-saccharin salt of dodecylamine.

10. As a new chemical compound, an N-saccharin salt of α-hydroxy-β-methylamino ethyl-3-hydroxy benzene.

11. As a new chemical compound, an N-saccharin salt of 1-phenyl-2-amino propane.

12. As a new chemical compound, an N-saccharin salt of 1-phenyl-2-methylamino propanol-1.

13. A pharmaceutical preparation comprising, an aqueous solution of an N-salt of saccharin and a vasoconstrictor amine in which the amine has at least four carbon atoms of which at least three are in a series carbon to carbon linkage attached at one end to the amino nitrogen.

14. A pharmaceutical preparation as defined in claim 13 in which sodium chloride is also present in said solution.

15. A pharmaceutical preparation as defined in claim 14 which also contains a cationic wetting agent having a dodecyl carbon chain in said solution.

16. A pharmaceutical preparation which comprises, an aqueous solution of the N-salt of saccharin and 1-phenyl-2-methylamino propane, said solution also containing sodium chloride and a cationic wetting agent having a dodecyl carbon chain.

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