

PATENT SPECIFICATION

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(54) SWEETENED COMPOSITIONS

(71) We, ELI LILLY AND COMPANY, a Corporation of the State of Indiana, United States of America, of 307 East McCarty Street, Indianapolis, State of Indiana, 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:—

The present invention relates to sweetened compositions comprising as a non-nutritive sweetener the dextro enantiomorph of a substituted tryptophane.

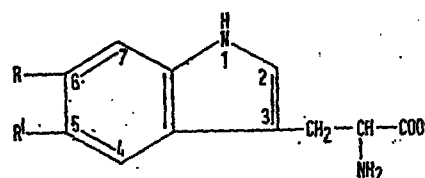
Numerous substances have been proposed and/or used as non-nutritive agents, affording the user thereof a sense of sweetness at least desirably comparable to that obtained with natural sugar, but without caloric effect. Such substances, while necessary for some persons in order to limit intake of the natural sugars and thus control various health conditions, including diabetes, still possess several disadvantages, including a bitter aftertaste and toxic side effects. At present, only two classes of non-nutritive sweetening substances are used to any great extent, saccharin-type compounds and cyclamate-type compounds, both of which classes show the typical disadvantage of bitter aftertaste; and in addition, the cyclamate-type compounds have only limited activity.

Among other chemicals evaluated for sweetening effect are the amino acids and enantiomorphs thereof as reported by Vuataz et. al., *Experientia*, Vol. 21, pages 692—694, inclusive (1965). The report shows that while a number of amino acids are sweet in the d-enantiomorphous form, this is not an absolute correlation. Furthermore, despite the sweet taste of the d-enantiomorph of a given amino acid, the l-enantiomorph of the same amino acid may be bitter. Resolution of the two enantiomorphs of a given amino acid is often difficult. For these various reasons,

despite the contribution of Vutaz et al., no amino acid is being used in the sweetening art.

Moreover, throughout the sweetening art, it is well known that there is no correlation between structure and activity, as even relatively small changes in chemical structure often destroy activity.

According to the present invention there is provided a sweetened composition which comprises the d-enantiomorph of a substituted tryptophane compound of the formula I



I

or a non-toxic physiologically acceptable salt thereof, wherein R represents halogen atom of an atomic weight of less than 85, lower alkyl, lower alkoxy, or trifluoromethyl radical; R' represents hydrogen atom, halogen atom of an atomic weight of less than 85, lower alkyl, or lower alkoxy radical, R' being hydrogen when R is trifluoromethyl, and a physiologically acceptable carrier. When used herein, the term "lower alkyl" and "lower alkoxy" means an alkyl or alkoxy group having from 1 to 4 carbon atoms. Preferably alkyl or alkoxy groups are methyl and methoxy.

The substituted tryptophanes used in the compositions of the present invention exhibit a sweet taste of a marked degree at rates below rates at which any undesirable side effect may be noted.

Included within the scope of the generic formula and valuable as non-nutritive

[Price 25p]

Price 33p

sweetening agents are tryptophanes known to the prior art as well as novel tryptophanes.

The compounds to be employed in accordance with the present invention are typically crystalline solid materials, with solubilities varying according to whether the compounds are the alkaline or acid addition salts, or the free amino compounds. As water solubility is desirable in the typical usage of a substance as a sweetening agent, the salts are generally preferred, especially for applications wherein the active agent is to be present in higher concentrations.

The type or identity of salt is not critical except that it be non-toxic and physiologically acceptable. Suitable alkaline salts are the ammonium, sodium, potassium, calcium, and magnesium salts, the sodium and calcium salts being preferred. Acid salt formation occurs at the amino nitrogen atom, the ring nitrogen atom being only weakly basic, making it necessary that the acid be a strong acid, having a pH of, numerically, below 2, at a concentration of 0.1 N. Suitable strong acids are hydrochloric, hydrobromic, hydriodic and sulfuric.

The free amino compounds of the present invention can be prepared readily by employing art-recognized procedures. Thus, for example, in one method of synthesis, an indole is caused to undergo a typical Mannich reaction with formaldehyde and diethylamine to yield a substituted 3 - (diethylamino-methyl) - indole which is then condensed with diethyl formamidomalonic acid according to the general procedure of Rydon et al., *J. Chem. Soc.*, 1955, 3499, to form the corresponding diethyl (3 - indolyl - methyl)-formamidomalonic acid. Hydrolysis and decarboxylation of the foregoing intermediate produces the desired substituted tryptophane.

Alternatively, an appropriately substituted phenylhydrazine is condensed with the adduct of acrolein and acetamidomalonic ester described by Moe et al., *J. Am. Chem. Soc.*, 70, 2765 (1948). Hydrolysis and decarboxylation affords the desired substituted tryptophane.

Suitably substituted indoles and phenylhydrazines which serve as intermediates in the foregoing synthesis are prepared by methods known in the art. The indoles can be prepared either from the appropriately substituted *o* - nitrotoluenes, by the method of Rydon et al., *J. Chem. Soc.*, 1955, 3499, or by cyclization of suitably substituted phenylhydrazines. The latter can be prepared by the general procedures of Bullock et al., *J. Am. Chem. Soc.*, 78, 5854 (1956).

The compounds obtained as described hereinabove can thereafter be reacted further with a stoichiometric amount of either a base or acid to procure the corresponding salt, the particular reaction to prepare the present salts being carried out in accordance with

procedures well known in the art for this type of reaction. Resolution of the compounds serving as active agent in accordance with the present invention is not necessary, the racemic mixture itself being quite active. However, since the d-enantiomorph is the active moiety, resolution may be preferred to lessen the amount of substance needed for the desired sweetening effect. Moreover, due to the fact that typically only the l-enantiomorph of amino acids is metabolized by the mammalian body, usage of the d-enantiomorph alone, may be preferred to preclude any opportunity for the mammalian body to incorporate the substance.

When it is desired to employ only the d-enantiomorph, resolution of the racemic mixture can be achieved in procedures known in the prior art for the resolution of unsubstituted tryptophane. Three such procedures are discussed and exemplified in detail in *Chemistry of the Amino Acids*, Greenstein et al., Vol. 3, page 2341 and following (John Wiley and Sons, Inc., New York, 1961); particular attention is directed to the first two of these (illustrative procedure 39—5 and illustrative procedure 39—6).

Representative compounds to be employed as active agent in accordance with the present invention include the following:

6-chlorotryptophane		
6-(trifluoromethyl)tryptophane		
6-bromotryptophane		
5-chloro-6-methyltryptophane	100	35
6-methyltryptophane		
6-fluorotryptophane		
6-ethyltryptophane		
5,6-dichlorotryptophane		
5-fluoro-6-methyltryptophane	105	40
5-chloro-6-bromotryptophane		
5-methyl-6-chlorotryptophane, sodium salt		
5-fluoro-6-chlorotryptophane		
5,6-dimethyltryptophane		
5-bromo-6-methyltryptophane	110	45
5-methyl-6-bromotryptophane		
5-bromo-6-chlorotryptophane		
6-chlorotryptophane, sodium salt		
5,6-dichlorotryptophane, sodium salt		
6-chlorotryptophane, potassium salt	115	50
5,6-dibromotryptophane		
6-(trifluoromethyl)tryptophane, ammonium salt		
6-n-propyltryptophane		
5,6-dimethyltryptophane, sodium salt	120	55
6-isopropyltryptophane		
5,6-dichlorotryptophane hydrochloride		
5,6-dimethyltryptophane nitrate		
6-methoxytryptophane		
5-methoxy-6-chlorotryptophane	125	60
6-ethoxytryptophane		
6-isopropoxytryptophane		
6-n-butoxytryptophane		
5,6-difluorotryptophane		

5,6-dimethoxytryptophane
 6-tert-butyltryptophane
 5-methyl-6-fluorotryptophane
 6-chlorotryptophane citrate
 5-fluoro-6-bromotryptophane
 6-chlorotryptophane hydrochloride
 5-bromo-6-fluorotryptophane
 6-bromotryptophane hydroiodide
 5,6-dimethyltryptophane hydrochloride
 5-chloro-6-fluorotryptophane

Mixtures of two or more compounds can also be employed. Any given compound can be employed either as the d-enantiomorph or as a mixture of the d- and l-enantiomorphs.

When referring to compositions of the present invention the term "physiologically acceptable carrier" means a substance or material which can safely be placed in the mouth, and, in appropriate cases, safely swallowed. Examples of such carriers are as follows:— chewing gum, toothpaste, lip cosmetics, mouthwash, mouthspray, substances used in dentistry for cleaning of teeth, denture treating substances, chewing tobacco and other tobacco products; pet toys, for example, rubber dog bones, as well as other mechanical devices temporarily retained within the mouth; glues and adhesives, as for use on stamps and envelopes; coffee, tea, fruitades such as lemonade, salad dressings, carbonated and non-carbonated beverages; baked goods such as bread, crackers, pretzels, pastries, or cake, cereal products; milk derived products, such as ice cream, ice milk, sherbets and custards; jelly and gelatin products; and processed vegetables and fruits, such as, for example, canned tomatoes and frozen vegetables; and nutritive solid foods, including meat products in which a sweetening substance is incorporated during processing, such as ham and bacon; prepared "mixes" such as mixes for puddings, cakes and pastries; and confectionary products, for example, popcorn, peanut candies, chocolate candies, jellybeans, gumdrops, candy cigarettes, toffee and licorice; natural sugar and glycine and other amino acids which are nutritive; a feed, such as a grain-type feed, silage, salt licks; attractant baits; fruit and vegetable juices; alcoholic beverages such as beer, wine, cocktails and cocktail mixes, milk beverages such as milkshakes, and egg-nogs; medicinal substances such as a tablet, capsule, powder, or lozenge, including cough drops, an elixir and a syrup.

The sweetener of the present invention can be combined with a flavouring agent. The flavouring agent can be one which is contained in, as an inherent part of, a natural food; or the flavouring agent can be one specifically added to a substance, as, for example, a flavoring agent added to a chewing gum. In this sense, "flavoring agent" is used to describe a substance which has a dis-

cernible and desirable flavor at a concentration in liquids of 250 ppm. by weight or less, even though in other specialized applications, such as chewing gum, and highly flavored baked goods, higher concentrations may be used.

Representatives of such flavoring agents include spices and herbs; the essential oils and their extracts; fruit-derived flavorings; plant extracts, as, for example, cola extract, caffeine; and synthetic flavorings, including those which simulate or duplicate the effective components of the flavoring agents of the previous categories.

The amount of the present non-nutritive sweetener to be employed is not critical either, it being necessary only that an effective amount is used, an effective amount being that amount which provides a sense of sweetness comparable to that afforded by sucrose at a given usage rate. The amount of the present active agent to be used will also depend upon such variables as the purpose of sweetening and other factors. For sucrose concentrations of from 6.5 percent to 45 percent, concentrations which occur in most foods and even many confectionary application, the present active agent, when substituted for sucrose, gives approximately equivalent sweetness at concentrations of from 0.05 to 30 percent, as the racemic mixture. Where the d-enantiomorph is employed alone, these rates can be reduced by a factor of about one-half. Higher or lower concentrations of the active agent of the present invention can be used where the degree of sweetness, by a sucrose standard, is greater or lesser. However, where a high degree of sweetness is desired, it is generally preferred to use a combination of the present active agent with one or more other known non-nutritive sweeteners, as is discussed further hereinbelow.

In an initial evaluation, dl - 6 - chlorotryptophane was administered orally to a group of mice at the rate of 2 grams of compound per kilogram of individual animal body weight. No toxic symptoms of any type were noted. The same results were obtained where the compound being evaluated was dl - 6 - methyltryptophane and where the compound being evaluated was dl - 6 - fluorotryptophane.

The compounds serving as the present active agent can be employed as sole agent; or, alternatively, such compound or compounds can be employed jointly with other known non-nutritive sweeteners. In particular, one or more of the compounds serving as active agent in accordance with the present invention can be combined with a saccharin-type sweetener; with a cyclamate-type sweetener; with a dihydrochalcone-type sweetener; or with 5 - (3 - hydroxyphenoxy) - 1H - tetrazole. As employed in the present

specification and claims, the term "saccharin-type sweetener" includes non-toxic physiologically acceptable salts, generally, the sodium or calcium salt.

- 5 As used in the present specification and claims, the term "cyclamate-type sweetener" means a compound having the essential structure of cyclamic acid, and includes non-toxic physiologically acceptable salts thereof,
10 generally, the sodium or calcium salt, although the magnesium salt has also been used for same purposes.

- 5 - (3 - Hydroxyphenoxy) - 1H - tetrazole can, in accordance with the present invention, be employed as one of its non-toxic physiologically acceptable salts. Suitable salts include the sodium, calcium, potassium, and ammonium salts.

- 20 The dihydrochalcone-type sweeteners include those of the genus disclosed and claimed in U.S. Patent 3,087,821, neohesperidin dihydrochalcone being a preferred compound. A publication by Krbechecks et al (*J. Ag. and Food Chem.*, Vol. 16, No. 1, page 108
25 [1968]) on this genus discloses other related compounds, notably higher alkoxy substituted compounds, which are even more sweet, and such related compounds are also dihydrochalcone-type sweeteners in accordance with
30 the present invention and can be employed jointly with the active agent of the present invention.

- When the active agent of the present invention is used in conjunction with another non-nutritive sweetener, the exact ratio of the components is not critical and can vary considerably, depending upon the particular use.

- Representative rates for the present active agent, when employed alone, are set forth hereinabove. When the active agent is combined with a saccharin-type sweetener, synergistic effects are obtained when combining the substances in a ratio ranging from 300 parts of present active agent to 1 part of
45 saccharin-type sweetener, to 1 part of present active agent to 300 parts of saccharin-type sweetener by weight, a generally preferred range of synergistic combination being that of a ratio ranging from 1:50 to 50:1, by weight.

- 50 In the combination of the present active agent with 5 - (3 - hydroxyphenoxy) - 1H - tetrazole, synergistic results are obtained at a ratio ranging from 1 part of present active

agent to 300 parts of the 5 - (3 - hydroxyphenoxy) - 1H - tetrazole by weight to 1
55 part of the 5 - (3 - hydroxyphenoxy) - 1H - tetrazole to 300 parts of the present active agent; a particularly preferred ratio of combination is a ratio of from 1:50 to 50:1, by weight.

Synergism with the dihydrochalcone-type of sweetener, synergism is likewise noted throughout the ratio ranging from 1 part of the present active agent to 30 parts of the dihydrochalcone-type sweetener, by weight, to
60 a ratio of 1 part of the dihydrochalcone-type sweetener to 30 parts of the present active agent, by weight. A preferred ratio is from 1:5 to 5:1 by weight.

Synergism with a cyclamate-type sweetener is noted in a ratio ranging from 1 part of cyclamate-type sweetener to 320 parts of the present active agent, by weight, to 1 part of the present active agent to 320 parts of the cyclamate-type sweetener, by weight. A preferred ratio ranges from 1:60 to 60:1, by weight.

It is also possible to combine the present active agent with sucrose or other nutritive sweeteners so as to obtain a sweetening substance of reduced caloric value. Such a mixture of nutritive sweetener and the present active agent can be formulated as a foam, in accordance with procedures known in the prior art for a combination of sucrose and sodium saccharin. Such manner of formulating results in a composition having both volume and sweetening effect equivalent to sucrose, alone, but with reduced caloric value.

The following Example 1 illustrates evaluations of compounds which may be used in the compositions of the present invention and Examples 2 to 6 illustrate the present invention and will enable those skilled in the art to practise the same.

EXAMPLE 1

An initial series of evaluations was carried out, each in essentially identical procedures. Each evaluation comprised the tasting of a small amount of the given compound, such amount being that which would adhere to a fingertip. Compounds so evaluated were rated for degree of sweetness, and after-taste, if any. The sweetness ratings were as follows:

Table I

	Compound Evaluated	Sweetness Rating
	dl-6-(trifluoromethyl)tryptophane	very sweet
	dl-6-bromotryptophane	sweet
110	dl-6-methyltryptophane	very sweet
	dl-6-chlorotryptophane	very sweet
	dl-6-chlorotryptophane hydrochloride	very sweet
	dl-6-fluorotryptophane	very sweet
	dl-5,6-dimethyltryptophane	sweet
115	dl-5,6-dichlorotryptophane	very sweet

dl-6-isopropyltryptophane hydrochloride sweet
 dl-6-methoxytryptophane sweet
 dl-6-chlorotryptophane, sodium salt very sweet

5 No aftertaste was observed with any of the compounds evaluated.

EXAMPLE 2

10 In further operations, dl-6-chlorotryptophane was evaluated in a carbonated beverage; the compound was dissolved at different concentrations in a number of solutions, each having the following composition:

	percent
sodium citrate	0.025
citric acid	0.22
15 alcoholic lemon-lime extract	0.125
sodium saccharin	0.01

20 the remainder being carbonated water. The various solutions were judged by a taste panel of five persons to determine which was comparable, in sweetness, to a standard solution. The standard solution contained sodium citrate, citric acid, and alcoholic lemon-lime extract in the same concentrations as above, but contained 0.1 percent of sodium cyclamate and 0.01 percent of sodium saccharin. This standard solution, therefore, was approximately equivalent to a commercially available carbonated beverage of this type sweetened with a known non-nutritive sweetener. The mixture containing the dl - 6 - chlorotryptophane in a concentration of 0.0125 percent was judged to be equivalent in sweetness to the standard. No off-flavor was noted in any of the solutions containing dl - 6 - chlorotryptophane.

EXAMPLE 3

40 In other operations, dl - 6 - chlorotryptophane was evaluated in hot cocoa. In these operations, the compound was dissolved in a number of mixtures, at varying concentrations, each such mixture comprising 1 cup of milk, a tablespoon of commercially available cocoa powder, 0.02 percent of sodium saccharin, and the dl - 6 - chlorotryptophane in a given amount. Each such mixture was heated to the boiling temperature and then permitted to cool somewhat. All mixtures were evaluated by a taste panel of five persons, to determine which of the mixtures afforded a degree of sweetness comparable to another mixture prepared as described but containing 1 cup of milk, 1 tablespoon of the same commercially prepared cocoa powder, and 0.2 percent of sodium cyclamate and 0.02 percent of sodium saccharin. The consensus of the taste panel was that the mixture containing 0.0125 percent of the dl - 6 - chlorotryptophane afforded a sense of sweetness comparable to

that of the standard control solution. No off-flavor was noted in any of the cocoa mixtures containing the dl - 6 - chlorotryptophane.

EXAMPLE 4

65 In another evaluation, dl - 6 - chlorotryptophane was evaluated in a vanilla-flavored dessert sauce. In the evaluation, the compound was dissolved in various mixtures, each such mixture comprising the following ingredients:

1 cup milk	70
1 tablespoon of cornstarch	
1/8 teaspoon of salt	
sodium saccharin, in a concentration of 0.08 percent dl-6-chlorotryptophane in a given amount.	75

80 The concentration of the dl - 6 - chlorotryptophane was varied among the several mixtures. Each such mixture was then cooked until gelatinized, and thereafter cooled and 2 tablespoons of butter and 1/4 teaspoon of vanilla added to each mixture. Another such mixture was prepared as a standard, as above, except that in place of the sodium saccharin and dl - 6 - chlorotryptophane, there was supplied sodium cyclamate in a concentration of 0.4 percent and sodium saccharin in a concentration of 0.04 percent. A taste panel of five persons then evaluated the various dessert sauces; the consensus of the panel was that the sauce containing 0.08 percent of sodium saccharin and 0.08 percent of dl - 6 - chlorotryptophane afforded a sense of sweetness approximately comparable to that of the standard. Some off-flavor was noted by some members of the taste panel in the sauces containing the dl - 6 - chlorotryptophane and sodium saccharin; this off-flavor was believed to be due to the sodium saccharin.

EXAMPLE 5

100 A liver-flavored dog food comprising dl - 6 - chlorotryptophane is prepared. The preparation consists of the mixing and blending of

meat and meat by-products, including liver,	105
soy grits,	
dried whey,	
propylene glycol,	
animal fat preserved with butylated hydroxyanisole and butylated hydroxy-	110
toluene,	
dicalcium phosphate,	
iodized salt,	
dried yeast,	

potassium sorbate,
garlic powder,
artificial coloring,
vitamin A and D oil,
vitamin B supplement,
vitamin E supplement,

as standard ingredients, and, in addition thereto, dl - 6 - chlorotryptophane, in an amount to provide 0.075 percent by weight of the ultimate dog food composition. The resulting mixture is compacted in standard procedures as small bite-size chunks. This composition serves as a complete dog food which is attractive to dogs without the caloric value of sucrose or other nutritive sweetener.

EXAMPLE 6

A dog treat composition is prepared comprising, as standard ingredients:

wheat flour,
corn meal,
soybean meal,
meat meal,
wheat germ meal,
poultry by-product meal,
animal fat preserved with butylated hydroxyanisole,
condensed fish soluble,
dried skimmed milk,
condenser fish soluble,
poultry fat stabilized with butylated hydroxyanisole,
dried meat soluble,
dried vegetable pomace,
dehydrated cheese,
animal liver and glandular meal,
steamed bone meal,
salt,
leavening,
titanium dioxide,
vitamin A oil,
irradiated yeast,
food colors,

and, as non-nutritive sweeteners, dl - 6 - (trifluoromethyl)tryptophane in an amount to constitute 0.0175 percent by weight of the total composition, and sodium saccharin in an amount to constitute 0.05 percent by weight of the total composition. The ingredients are mixed together and compacted in the form of bone-shaped snacks which have enhanced palatability without enhanced caloric content.

Unless otherwise indicated, percentages, wherever mentioned in the specification are percentages by weight.

The invention is not intended to be used in any way contrary to the provisions of "The Artificial Sweeteners in Food Regulations 1969".

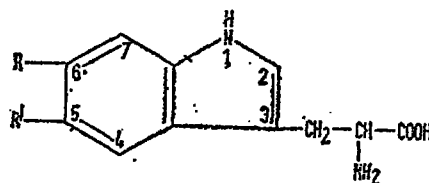
The Applicants' co-pending Application No. 9,658/71 (Serial No. 1269852), which is

a divisional of this application, is directed to the novel (6 - trifluoromethyl)tryptophane compound and its non-toxic physiologically acceptable salts.

The Applicants disclaim compositions consisting only of a common solvent and one or more of the known tryptophane compounds of formula I and also those compositions which have been used in the preparation, purification or isolation of the known tryptophane compounds of formula I. In addition the Applicants disclaim methods for preparing such compositions.

Subject to the foregoing, What we claim is:—

1. A sweetened composition which comprises the *d*-enantiomorph of a substituted tryptophane compound of the formula I



I

or a non-toxic physiologically acceptable salt thereof, wherein R represents halogen atom of an atomic weight of less than 85, lower alkyl, lower alkoxy, or trifluoromethyl radical; R' represents hydrogen atom, halogen atom of an atomic weight of less than 85, lower alkyl, or lower alkoxy radical, R' being hydrogen when R is trifluoromethyl, and a physiologically acceptable carrier.

2. A composition as claimed in claim 1 wherein the substituted tryptophane compound is 6 - chlorotryptophane, 6 - (trifluoromethyl)tryptophane or 6 - methyltryptophane.

3. A composition as claimed in claims 1 or 2 wherein it contains substances selected from saccharin-type sweetener, cyclamate-type sweetener, dihydrochalcone-type sweetener, 5 - (3 - hydroxyphenyl) - 1H - tetrazole or a nontoxic physiologically acceptable salt(s) thereof, and the *l*-enantiomorph of a substituted tryptophane of formula I.

4. A method of preparing a sweetened composition which comprises adding a compound of formula I to a physiologically acceptable carrier.

5. A composition according to claim 1 substantially as herein described.

6. A method of preparing a sweetened composition according to claim 4 substantially as herein described.

7. A composition according to any one of claims 1 to 3 wherein the compound of

- potassium sorbate,
garlic powder,
artificial coloring,
vitamin A and D oil,
5 vitamin B supplement,
vitamin E supplement,

- as standard ingredients, and, in addition thereto, dl - 6 - chlorotryptophane, in an amount to provide 0.075 percent by weight of the ultimate dog food composition. The resulting mixture is compacted in standard procedures as small bite-size chunks. This composition serves as a complete dog food which is attractive to dogs without the caloric value of sucrose or other nutritive sweetener.

EXAMPLE 6

A dog treat composition is prepared comprising, as standard ingredients:

- wheat flour,
corn meal,
soybean meal,
meat meal,
wheat germ meal,
poultry by-product meal,
25 animal fat preserved with butylated hydroxyanisole,
condensed fish soluble,
dried skimmed milk,
condenser fish soluble,
30 poultry fat stabilized with butylated hydroxyanisole,
dried meat soluble,
dried vegetable pomace,
dehydrated cheese,
35 animal liver and glandular meal,
steamed bone meal,
salt,
leavening,
titanium dioxide,
40 vitamin A oil,
irradiated yeast,
food colors,

- and, as non-nutritive sweeteners, dl - 6 - (trifluoromethyl)tryptophane in an amount to constitute 0.0175 percent by weight of the total composition, and sodium saccharin in an amount to constitute 0.05 percent by weight of the total composition. The ingredients are mixed together and compacted in the form of bone-shaped snacks which have enhanced palatability without enhanced caloric content.

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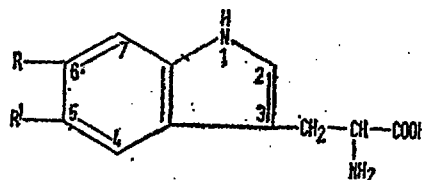
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a divisional of this application, is directed to the novel (6 - trifluoromethyl)tryptophane compound and its non-toxic physiologically acceptable salts.

The Applicants disclaim compositions consisting only of a common solvent and one or more of the known tryptophane compounds of formula I and also those compositions which have been used in the preparation, purification or isolation of the known tryptophane compounds of formula I. In addition the Applicants disclaim methods for preparing such compositions.

Subject to the foregoing, What we claim is:—

1. A sweetened composition which comprises the *d*-enantiomorph of a substituted tryptophane compound of the formula I



I

or a non-toxic physiologically acceptable salt thereof, wherein R represents halogen atom of an atomic weight of less than 85, lower alkyl, lower alkoxy, or trifluoromethyl radical; R' represents hydrogen atom, halogen atom of an atomic weight of less than 85, lower alkyl, or lower alkoxy radical, R' being hydrogen when R is trifluoromethyl, and a physiologically acceptable carrier.

2. A composition as claimed in claim 1 wherein the substituted tryptophane compound is 6 - chlorotryptophane, 6 - (trifluoromethyl)tryptophane or 6 - methyltryptophane.

3. A composition as claimed in claims 1 or 2 wherein it contains substances selected from saccharin-type sweetener, cyclamate-type sweetener, dihydrochalcone-type sweetener, 5 - (3 - hydroxyphenyl) - 1H - tetrazole or a nontoxic physiologically acceptable salt(s) thereof, and the *l*-enantiomorph of a substituted tryptophane of formula I.

4. A method of preparing a sweetened composition which comprises adding a compound of formula I to a physiologically acceptable carrier.

5. A composition according to claim 1 substantially as herein described.

6. A method of preparing a sweetened composition according to claim 4 substantially as herein described.

7. A composition according to any one of claims 1 to 3 wherein the compound of



formula I is present in an amount between 0.05 to 30% by weight.

8. A composition according to any one of claims 1 to 3 and 7 wherein the compound of formula I is present together with a saccharin-type sweetener, the ratio of parts by weight formula I compound to parts by weight saccharin-type sweetener lying within the range from 1/300 to 300/1.

9. A composition according to any one of claims 1 to 3 and 7 wherein the compound of formula I is present together with 5 - (3 - hydroxyphenyl) - 1H - tetrazole, the ratio of parts by weight formula I compound to parts by weight 5 - (3 - hydroxyphenyl) - 1H - tetrazole lying within the range from 1/300 to 300/1.

10. A composition according to any one of claims 1 to 3 and 7 wherein the compound of formula I is present together with a

dihydrochalcone-type sweetener, the ratio of parts by weight formula I compound to parts by weight dihydrochalcone-type sweetener lying within the range 1/30 to 30/1.

11. A composition according to any one of claims 1 to 3 and 7 wherein the compound of formula I is present together with a cyclamate-type sweetener, the ratio of parts by weight formula I compound to parts by weight cyclamate-type sweetener lying within the range 1/320 to 320/1.

12. A composition according to claim 1 substantially as described in any one of Examples 2 to 6.

BOULT, WADE & TENNANT,
Chartered Patent Agents,

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* C L M S *