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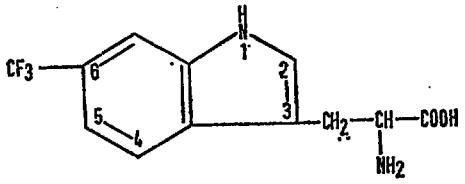
(54) 6-TRIFLUOROMETHYL-TRYPTOPHANE AND PROCESS FOR PRODUCING THE SAME

(71) We, ELI LILLEY & COMPANY, a Corporation organised and existing under the Laws of the State of Indiana, United States of America, of 307, East McCarty Street, City of 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 6-(trifluoromethyl)tryptophane, its non-toxic physiologically-acceptable salts and a process for producing the same and intermediates used in the process.

6-Trifluoromethyl-tryptophane and its above-mentioned salts are used as sweetening agents as is claimed and described in our parent application 17639/69 (Serial No. 1,269,851).

6-Trifluoromethyl-tryptophane has the formula I



The 6 - trifluoromethyl - tryptophane and its salts of 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 compound. 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 about 2, at a concentration of 0.1N. Suitable strong acids are hydrochloric, hydrobromic, hydriodic, and sulfuric.

The free amino compound of the present invention can be prepared readily by employing art-recognized procedures. Thus, for example, in one method of synthesis, 6-trifluoromethyl indole is caused to undergo a typical Mannich reaction with formaldehyde and diethylamine to yield 3 - (diethylaminomethyl) - 6 - trifluoromethyl indole which is then condensed with diethyl formamidomalonate according to the general procedure of Rydon et al., *J. Chem. Soc.*, 1955, 3499, to form diethyl (6 - trifluoromethyl - 3-indolylmethyl)formamidomalonate. Hydrolysis and decarboxylation of the foregoing intermediate produces the desired substituted tryptophane.

Alternatively, trifluoromethyl - 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.

The suitably substituted indole and phenylhydrazine which serve as intermediates in the foregoing syntheses are prepared by methods

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known in the art. The indole can be prepared either from the appropriately substituted *O*-nitrotoluene, by the method of Rydon et al., *J. Chem. Soc.*, 1955, 3499, or by cyclization of a suitably substituted phenylhydrazine. The latter can be prepared by the general procedure of Bullock et al., *J. Am. Chem. Soc.*, 78, 5854 (1956).

The compound 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 compound 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 1-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).

The preparation of the 6-(trifluoromethyl)-tryptophane and intermediates in its synthesis, is illustrated in the following Example I.

EXAMPLE 1

6-(Trifluoromethyl)tryptophane

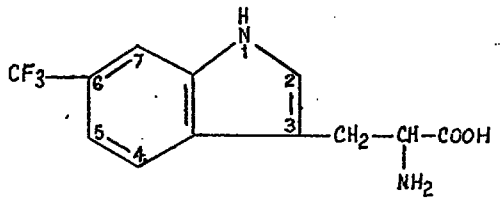
To a solution of 7.53 grams of diethylamine (0.15 mole) in 22.5 ml. of cold 60 percent acetic acid was added 8.25 ml. of 37 percent aqueous formaldehyde. 6-(Trifluoromethyl)-indole (19.0 grams; 0.10 mole) was then added, and the resulting mixture warmed to 60°C. After two hours at this temperature, the solution was poured into 360 ml. of 2N sodium hydroxide, and the desired 3 - (diethylaminomethyl) - 6 - (trifluoromethyl)-indole product extracted with ether. The extract was dried, and solvent removed by distillation to separate the product, which was an oil.

3 - (Diethylaminomethyl) - 6 - (trifluoromethyl)indole (12.5 grams; 0.046 mole), prepared as described in the foregoing example, and diethyl formamidomalonate (9.4 grams; 0.041 mole) were mixed in 31 ml. of toluene. Thereafter, 0.76 gram of powdered potassium hydroxide was added. The resulting mixture was refluxed, while bubbling in nitrogen, for 1.5 hours. It was then cooled, resulting in precipitation of the diethyl([6 - (trifluoromethyl) - 3 - indolyl]methyl) formamidomalonate product, which was separated by filtration and washed with water. A portion of the separated product was recrystallized from ethanol, and the recrystallized portion found to melt at 182—5°C.

A solution of diethyl ([6 - trifluoromethyl)-3 - indolyl]methyl)formamidomalonate (55.3 grams; 0.138 mole) in 330 ml. of 1.5N hydrochloric acid, 165 ml. of glacial acetic acid, and 50 ml. of ethanol was refluxed for 17 hours. The solution was then concentrated under vacuum, the residue neutralized with ammonium hydroxide, and the resulting 6 - (trifluoromethyl)tryptophane product separated by filtration. The separated product was washed with water and ethanol, and a sample thereof recrystallized from acetic acid. The recrystallized portion melted at 267—70°C. (dec.).

WHAT WE CLAIM IS:—

1. 6 - (Trifluoromethyl)tryptophane of the formula I



or its non-toxic physiologically acceptable salts.

2. A process for preparing the tryptophane compound of claim 1 comprising condensing 3 - (diethylaminomethyl) - 6 - (trifluoromethyl) - indole with diethyl formamidomalonate, and recovering the diethyl ([6-(trifluoromethyl) - 3 - indolyl] - methyl)-formamidomalonate, and then hydrolyzing and decarboxylating the diethyl ([6 - (trifluoromethyl) - 3 - indolyl] - methylformamidomalonate to prepare the 6-trifluoromethyl)tryptophane.

3. A process for preparing the compound of claim 1 substantially as here described in Example 1.

4. A compound according to claim 1 whenever prepared by a process as claimed in claim 2 or claim 3.

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The compound 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 compound 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).

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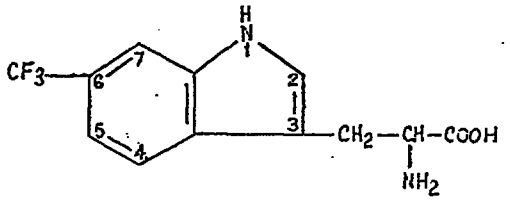

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