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N-ETHYL-N-[1 - (m-TRIFLUOROMETHYLPHENYL)-PROPYL-(2)]-CARBAMIC ACID ETHYL ESTER

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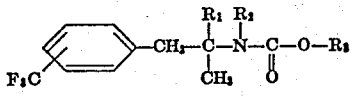
ABSTRACT OF THE DISCLOSURE

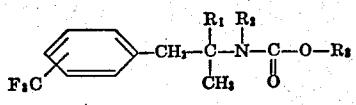
Appetite-inhibiting substituted N-(trifluoromethylphenylethyl)-carbamic acid esters having the general formula



(I)

wherein R_1 and R_2 are hydrogen or lower alkyl with the proviso that when R_1 is hydrogen, R_2 is alkyl and R_3 is alkyl.

This invention relates to new substituted N-(trifluoromethylphenylethyl)-carbamic acid esters of the general formula



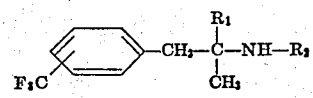
(I)

wherein the trifluoromethyl group may occupy the ortho, meta or para positions on the phenyl ring, R_1 is hydrogen or a lower alkyl radical with up to 3 carbon atoms, R_2 is hydrogen or a lower alkyl radical with up to 3 carbon atoms with the proviso that if R_1 is hydrogen, R_2 is an alkyl radical, and R_3 represents an alkyl radical with 1 to 4 carbon atoms.

In the animal test, the compounds according to the invention exhibit a very good appetite-inhibiting effectiveness, which approximately corresponds to that of compounds presently used for this purpose in human medicine. However, contrary to a number of compounds available on the market, they do not show any stimulating and motility-increasing effect even in sublethal dosage and are characterized in particular by good compatibility and low toxicity. Thus, for instance, N-ethyl-N-[1-(m-trifluoromethylphenyl)-propyl-(2)]-carbamic acid ethyl ester, an LD_{50} of 1,000 mg./kg. was determined with a single oral application on a rat, whereas the compound N-ethyl - 1-(m-trifluoromethylphenyl)-propylamine-(2) used in human medicine and which is chemically closest thereto has an LD_{50} of 170 mg./kg. (D. Lorenz, Mitt. Arch. Pharmaz, 36, vol. 12 (1966). Cf. also J. C. Le Douarec, H. Schmitt and M. Laubic, Arch. int. Pharmacodyn., 161, p. 211 (1966).

N - [2-methyl-1-(p-trifluoromethylphenyl)-propyl-(2)]-carbamic acid ethyl ester also has an LD_{50} of only approximately 2,000 mg./kg. Thus the compounds according to the invention are about five to ten times less toxic than N - ethyl-1-(m-trifluoromethylphenyl)-propylamine-(2). Their appetite-inhibiting effect is, however, only about two to three times less so that their therapeutic range is two to three times larger. They can, therefore, be handled with considerably greater safety in human medicine than the preparations used thus far for this purpose.

The compounds according to the invention of the general Formula I can be made by known methods from amines of the general formula



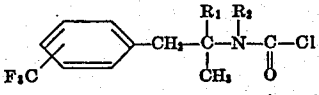
(II)

wherein R_1 and R_2 have the above-mentioned meaning, by

(a) Reacting a Formula II amine with chloroformic acid esters of the general formula $ClCOOR_3$, wherein R_3 has the above-mentioned meaning, or

(b) Reacting a Formula II amine with carbonic acid dialkyl esters of the general formula $R_3O—CO—OR_3$, wherein R_3 has the above-mentioned meaning, or

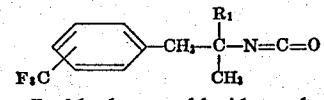
(c) Converting a Formula II amine with phosgene into carbamic acid chlorides of the general formula



(III)

and reacting Formula III compounds with alcohols of the general formula R_3OH, wherein R_3 has the above-mentioned meaning, or

(d) In the case where R_2 is hydrogen, converting the carbamic acid chlorides (III) into the corresponding isocyanates of the general formula



(IV)

with splitting off of hydrogen chloride, and reacting same with R_3OH. In the above Formula II, III and IV, R_1, R_2, and R_3 are defined previously.

The invention will be illustrated further by the following examples:

EXAMPLE 1

Part 1

0.03 mole of 1-(m-trifluoromethylphenyl)-propylamine-(2) is dissolved in glacial acetic acid and mixed with a 25% excess of acetic anhydride while cooling. The reaction mixture was maintained at 50° C. for 30 minutes, then broken up with ice water and dissolved in ether. The ethereal solution is shaken out with 1/10 N hydrochloric acid, dried with sodium sulfate, evaporated and the residue is dissolved in warm ligroin. Through strong cooling N - [1 - (m - trifluoromethylphenyl) - propyl - (2)] - acetamide having a melting point of 59–62° C. crystallizes out.

Part 2

0.02 mole of N-[1-(m-trifluoromethylphenyl)-propyl-(2)]-acetamide from Part 1 is dissolved in anhydrous ether and added drop by drop to a suspension of 0.07 lithium aluminum hydride in absolute ether in the absence of oxygen and moisture. After boiling for five hours, the reaction mixture is broken up with water and 20% solution of caustic soda and filtered. The filtrate is mixed with ethereal hydrochloric acid and evaporated. N-ethyl-1-(m-trifluoromethylphenyl) - propylamine - (2) - hydrochloride having a melting point of 166° C. is obtained. By dissolving this product in water and mixing with a solution of caustic soda the base is obtained, which then is separated by absorption in ether and is dried with sodium sulfate. After evaporating the ether and distilling the residue, N - ethyl - 1 - (m - trifluoromethylphenyl) - propylamine-(2) having a boiling point of 98 to 100° C./10 mm. Hg and a refractive index of n_D^{20} 1.4545 is obtained.

Part 3

1.0 mole of N-ethyl-1-(m-trifluoromethylphenyl)-propylamine-(2) from Part 2 in 96% alcohol is added drop by drop at approximately 0° C. to a solution of 1.1 moles of chloroformic acid ethyl ester in 96% alcohol while stirring and cooling and then, in the course of 20 minutes, it is mixed with an aqueous saturated potassium hydrogen carbonate solution. After stirring for three hours, the alcohol is distilled off, the residue absorbed in ether, dried with sodium sulfate and freed of the ether. After distilling in high vacuum, N-ethyl-N-[1-(m-trifluoromethylphenyl)-propyl-(2)]-carbamic acid ethyl ester having a boiling point of 83–85° C./5·10^{-4} mm. Hg is obtained.

EXAMPLE 2

6 grams of 2-methyl-1-(p-trifluoromethylphenyl)-propylamine-(2) are dissolved in ethylene chloride and mixed with a solution of 3.1 g. of chloroformic acid ethyl ester in ethylene chloride while stirring. Subsequently an aqueous solution of 2.9 g. of potassium hydrogen carbonate is added drop by drop at 4–6° C. and the reaction mixture is stirred for several hours at 20° C. The separated ethylene chloride phase is washed with water, filtered and freed of the solvent in a vacuum. The residue is recrystallized in petroleum ether. N-[2-methyl-1-(p-trifluoromethylphenyl)-propyl-(2)]-carbamic acid ethyl ester is obtained in a yield of 90% of the theoretical value. Melting point: 72 to 73° C.

EXAMPLE 3

2.17 g. (0.01 mole) of 2-methyl-1-(m-trifluoromethylphenyl)-propylamine-(2) are dissolved in a small amount of ethanol and heated with 1.18 g. (0.01 mole) of diethyl carbonate for 5 hours on a water bath. After removal of the solvent, the resultant N-[2-methyl-1-(m-trifluoromethylphenyl)-propyl-(2)]-carbamic acid ethyl ester is distilled off under vacuum. The yield is 1.85 g. (66% of the theoretical).

EXAMPLE 4

2.31 g. (0.01 mole) of N-ethyl-1-(m-trifluoromethylphenyl)-propylamine-(2) are dissolved in benzene. Phosgene is introduced in the presence of some pyridine while

slowly increasing the temperature to 80° C. After having separated the resultant precipitate of pyridine hydrochloride and removed the solvent, the formed N-ethyl-N-[1-(m-trifluoromethylphenyl)-propyl-(2)]carbamic acid chloride is first taken up in ether and then mixed with ethanol. After shaking with water, drying over sodium sulfate and removal of the solvent and recrystallization in petroleum ether, 2.45 g. (80.7% of the theoretical yield) of N-ethyl-N-[1-(m-trifluoromethylphenyl)propyl-(2)]carbamic acid ethyl ester which is identical with the compound obtained in Example 1 are obtained.

EXAMPLE 5

Phosgene is slowly introduced for 4 hours while stirring at 125° C. into a solution of 3.63 g. (0.015 mole) of 2-methyl-1-(p-trifluoromethylphenyl)-propylamine-(2)-hydrochloride in a small amount of toluene. The solvent is distilled off and the resultant N-[2-methyl-1-(p-trifluoromethylphenyl)-propyl-(2)]isocyanate immediately mixed with excess ethanol. Recrystallization in ether gives 3.13 g. (77.8% of the theoretical yield) of N-[2-methyl-1-(p-trifluoromethylphenyl)-propyl-(2)]carbamic acid ethyl ester having a melting point of 72–74° C.

What is claimed is:

1. N-ethyl-N-[1-(m-trifluoromethylphenyl)-propyl-(2)]-carbamic acid ethyl ester.

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