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2,774,787

POLYHYDROPHTHALAMIC ACID VISCERAL SMOOTH MUSCLE RELAXANTS

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5 Claims. (Cl. 260—514)

The present invention relates to therapeutic compounds and more particularly to compounds for relaxing spasm in smooth muscle.

This application is a continuation-in-part of application Serial No. 216,274, filed March 17, 1951, now abandoned.

Spasm of the smooth muscles has a number of disagreeable manifestations depending upon the particular smooth muscle involved. Asthma results from spasm of the bronchi; colitis, ulcer and constipation may result from spasm of the smooth muscle of the pyloric region and gastro-intestinal tract; and dysmenorrhea results from spasm of the smooth muscle of the uterus. In the blood vessels, spasm results in hyptertension and Raynaud's disease.

Many of these manifestations of smooth muscle spasm are also accompanied by hypersecretion, as is well known in the case of asthma, ulcer, colitis and hayfever.

It is known that smooth muscle spasm is caused by the presence of cholines in the system and one of the objects of the present invention is to provide a therapeutic compound which will neutralize or block the action of these cholines.

Another object is to provide a compound which will relax spasm in visceral smooth muscle.

Basically, choline includes a quaternary ammonium group and may also include hydroxy, carboxy, alkyl carboxy, acetyl and other groups. The composition of choline is known and frequently several types of choline are present in the system at the same time.

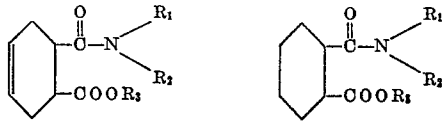
The antihistamines and local anesthetics usually contain a secondary amine group which replaces the quaternary ammonium group of the choline. The substitution of the secondary amine group for the quaternary ammonium group affords some relief from the effects of cholines but it does not block or counteract the effect of the quaternary ammonium group itself. Various efforts have been made to counteract or block the effect of the quaternary ammonium group but these efforts have been unsuccessful in that they have affected only the hypersecretion effect or because the effect was limited to the area of injection.

It has been found that when a cyclohexene or cyclohexane derivative of a secondary amine base is introduced into the system, complete relief from muscle spasm is obtained.

The secondary amine base may have the structure of



and is combined with the cyclohexene or cyclohexane ring in the form of the following compounds:



in which R_1 and R_2 may be methyl or ethyl and R_3 may be hydrogen, or magnesium.

These compounds have a relaxing effect on the visceral smooth muscles and are especially useful in the treatment of asthma, hayfever, ulcer, colitis and dysmenorrhea.

When R_3 is either magnesium or hydrogen the compounds are highly soluble in water while if R_3 were calcium the compounds would be only partially soluble in water and if R_3 were either methyl or ethyl, the compounds would be insoluble in water.

The compounds of the present invention may be prepared in various ways as shown by the following examples.

EXAMPLE I

N,N-diethyl-cis-Δ^4-tetrahydrophthalamic acid

In a 3 liter flask fitted with a dropping funnel, stirrer and reflux condenser was placed 1000 ml. of dry benzene and 304 g. of cis-Δ^4-tetrahydrophthalic anhydride. The stirrer was started and 146 g. of diethylamine dissolved in an equal volume of dry benzene was slowly dropped in. The reaction flask was cooled to moderate the reaction. After all the amine had been added, the mixture was refluxed for 15 minutes. The reaction mixture was allowed to cool and two-thirds of the benzene stripped off. On cooling, the residue set to a crystalline mass. The crystals after filtering and recrystallizing from benzene melted at 104–106° C.

EXAMPLE II

Magnesium N,N-diethyl-cis-Δ^4-tetrahydrophthalamate

The N,N-diethyl-cis-Δ^4-tetrahydrophthalamic acid prepared above was reacted in a 50% alcohol water solvent mixture with a 10% excess of magnesium carbonate. After the evolution of gas had subsided the reaction mixture was boiled half an hour to complete the reaction. The mixture was filtered from the excess magnesium carbonate. The filtrate was concentrated to dryness in vacuum to yield the salt as a white, free flowing, water soluble powder.

EXAMPLE III

N-diethyl hexahydrophthalamic acid

This compound was made as outlined in Example I, using 308 g. of hexahydrophthalic acid. The product melts at 111–113°.

The compounds described above have various therapeutic uses as described above and may also be used as a bronchial dilation, antispasmatic and cardiac stimulant.

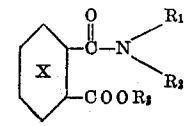
The compounds may be administered orally in capsule or tablet form and 50 to 300 milligrams may be administered three or four times daily. Over dosage should be avoided as it may irritate the bronchi and cause coughing.

That compounds may also be administered in aqueous solution. Dosages of 100 to 300 milligrams in water solution may be injected intramuscularly and dosages of 100 to 500 milligrams in water solution may be injected intravenously. Ordinarily, only one injection a day is given.

From the foregoing it is apparent that we have attained the objects of our invention and have provided a new therapeutic compound having an anticholine effect. Various changes may be made without departing from the spirit of our invention or the scope of the appended claims.

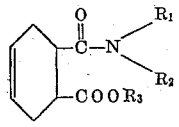
What is claimed and desired to be secured by United States Letters Patent is:

1. A new composition of matter having the formula



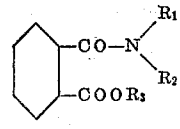
in which the ring X is selected from the group consisting of cyclohexene and cyclohexane, R_1 is selected from the group consisting of methyl and ethyl groups, R_2 is selected from the group consisting of methyl and ethyl groups, and R_3 is selected from the group consisting of hydrogen and magnesium.

2. A new composition of matter comprising a compound having the formula



in which R_1 is selected from the group consisting of methyl and ethyl, R_2 is selected from the group consisting of methyl and ethyl, and R_3 is selected from the group consisting of magnesium and hydrogen.

3. A new composition of matter comprising a compound having the formula



in which R_1 is selected from the group consisting of methyl and ethyl, R_2 is selected from the group consisting of methyl and ethyl, and R_3 is selected from the group consisting of magnesium and hydrogen.

4. As a new composition of matter N,N-diethyl-cis-Δ^4-tetrahydrophthalamic acid.

5. As a new composition of matter magnesium N,N-diethyl-cis-Δ^4-tetrahydrophthalamate.

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