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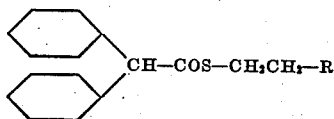
ANTISPASMODIC AGENTS

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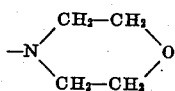
This invention relates to new compounds hav-
ing useful antispasmodic properties. The inven-
tion embraces di-N-substituted aminoethyl es-
ters of diphenylthioacetic acid of the formula



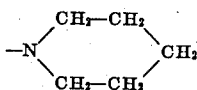
in which R represents a disubstituted amino radi-
cal of the group consisting of the diethylamino
group



the morpholino group



and the piperidino group



The creation of spasmolytic or antispasmodic
drugs by organic synthesis has been the subject
of much research in the past decade. The pur-
pose of a spasmolytic drug is to relieve spasms of
smooth muscles. Smooth muscles line most of
the visceral organs. The peristalsis and muscu-
lar activity of the stomach, intestines, gall blad-
der, urinary bladder, the uterus, and to a degree
the heart are all largely controlled by smooth
muscles. Smooth muscles are innervated by the
autonomic nervous system. The autonomic
nervous system consists of two antagonistic
branches—the sympathetic branch, and the
parasympathetic branch. On all visceral organs
except the heart the parasympathetic nerve im-
pulses increase the irritability and tension of the
smooth muscles; contrariwise, the sympathetic
nerve impulses increase the tension and irritability
of the muscles of the heart muscle and relax the
smooth muscles of the other visceral organs.

A spasm in a smooth muscle may be due to one
of two causes. Either the smooth muscle may be
receiving exaggerated impulses from the auto-
nomic nervous system which create violent con-
tractions in the muscle, or the muscle may be in-
trinsically stimulated into a spasm (most likely
from chemical changes in the surrounding tissue).
A spasm due to exaggerated impulses from the

parasympathetic branch of the autonomic ner-
vous system may often be corrected by adminis-
tering atropine (an active alkaloid of belladonna)
which serves to break a connection between the
parasympathetic nerve and the smooth muscle.
This ability and effect of atropine is called a
"neurotropic effect." A spasm intrinsic in the
smooth muscle itself may often be corrected by
papaverine (a derivative of opium which is classed
as a narcotic). Papaverine has an ability to de-
crease intrinsically the contractility of smooth
muscle; it has the ability to relax smooth muscles
directly. This ability and effect of papaverine is
called a "musculotropic effect."

In relieving spasms of smooth muscles gen-
erally, a musculotropic effect is acknowledged
to be superior to a neurotropic effect. A neuro-
tropic effect cannot relieve spasms intrinsic in
the smooth muscle itself, while a musculotropic
effect, by relaxing and decreasing the irritability
and responsiveness of smooth muscle to stimula-
tion from the autonomic nervous system, can help
to relieve a smooth muscle spasm even when it is
due to exaggerated impulses from the autonomic
nervous system.

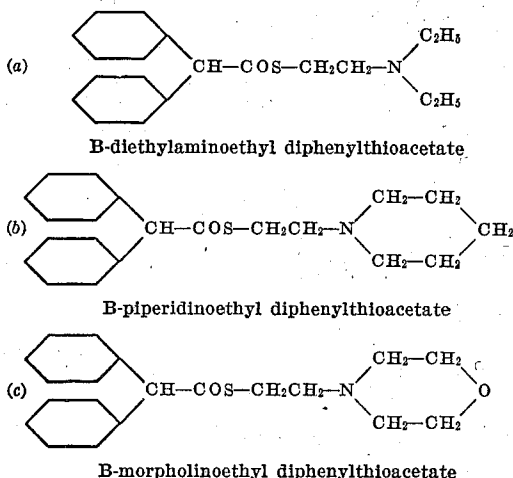
A clinical difficulty with atropine is that of
undesirable side-reactions. Atropine, when given
in effective doses, serves to break or partly break
all the parasympathetic nerve-smooth muscle
connections all over the body. Thus when atro-
pine is given in sufficient dosage to relieve a
spasm in a specific visceral organ, such as a
gastric or intestinal spasm (the spasm caused
by exaggerated nerve impulses from the para-
sympathetic nervous system) undesirable side-
actions due to the breaking of the parasympa-
thetic nerve-muscle connections elsewhere in
the body may occur. The most easily recognized
of these undesirable side reactions are dilation of
the pupil and dryness of the mouth, caused by the
breaking of the parasympathetic connections to
the oculomotor muscles and the saliva producing
mechanism respectively.

Atropine is acknowledged to have also a mus-
culotropic effect, but its neurotropic effect is so
strong that it cannot be given in greater than
minute doses ($1/60$ to $1/40$ grain) without encoun-
tering the undesirable side reactions. This dosage
is too small to permit a significant musculotropic
effect.

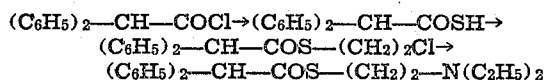
The philosophy and hope behind the creation of
the synthetic spasmolytic or antispasmodic drugs
is to remove from the atropine molecule much or
all of its neurotropic effect by chemical substitu-
tion and at the same time to preserve its musculo-

tropic effect. If successful, such substitution would permit the giving of the synthesized compound in much greater dosage before encountering the undesirable side reactions due to excessive neurotropic effect. The greater dosage would, of course, multiply the musculotropic effect preserved from the atropine molecule until it reached an intensity sufficient for therapeutic usefulness.

My invention is based upon my discovery that the thio analogs of certain disubstituted acetic acid esters of amino alcohols have desirable antispasmodic properties. I have prepared the following closely related specific compounds of this group and have found each of them to be useful as antispasmodics and superior to the corresponding compounds in which the acid group of the diphenyl acetic acid is a simple carboxyl group instead of the thio carboxylic acid group.



Example 1.—For the preparation of the B-diethylaminoethyl diphenylthioacetate I have found it convenient to start with diphenyl acetyl chloride which readily may be prepared, as is well known, by converting benzaldehyde to benzoin, benzoin to benzylic acid, benzylic acid to diphenylacetic acid, and the diphenylacetic acid to diphenylacetyl chloride. The diphenylacetyl chloride is converted into the B-diethylaminoethyl diphenylthioacetate by a sequence of steps represented by the following formulation—



The procedure followed to carry out the above reactions is as follows:

22.4 gm. of potassium hydroxide were dissolved in 400 cc. of ethanol contained in a 1-liter flask equipped with a mechanical stirrer. The flask was immersed in an ice-salt bath and the solution saturated with hydrogen sulfide. 46.1 gm. of diphenylacetyl chloride previously dissolved in benzene was then added slowly to the potassium hydrosulfide solution while stirring. Stirring was continued for thirty minutes. Then the mixture was filtered with suction and the filtrate evaporated slowly under reduced pressure. The residue was then dissolved in distilled water and dilute hydrochloric acid added slowly until precipitation was complete. The yellowish-white precipitate was collected on a filter, dissolved in dilute alkali and reprecipitated with dilute hydrochloric acid. The purified solid was filtered with suction, washed thoroughly with distilled water and dried by means of a vacuum pump and then by letting it stand in a desiccator over sodium

hydroxide. This product, diphenylthioacetic acid, is not stable to heat or oxygen and was used as soon as possible. Melting point: 55°–58° C.

In a three-neck flask equipped with a mechanical stirrer, condenser and dropping funnel was placed 5.6 gm. of potassium hydroxide dissolved in 100 cc. of ethanol. To this was added 22.8 gm. of diphenylthioacetic acid. When the acid had dissolved 20 gm. (excess) of ethylene chlorobromide was added dropwise while stirring. Stirring was continued for two hours while warming the mixture on a water bath, not over 40° C. The mixture was then filtered and the filtrate evaporated under reduced pressure. The residue, B-chloroethyl diphenylthioacetate, was recrystallized from a mixture of diethyl ether and petroleum ether. Melting point: 45°–47° C.

A mixture of 20 gm. of B-chloroethyl diphenylthioacetate and 20 gm. (excess) of diethylamine were heated in a sealed bottle for three days at 40° C. in a constant temperature oven. After cooling the reaction mixture was suspended in water and extracted by shaking with diethyl ether. The ether extract was dried over calcium chloride and the solvent evaporated. The B-diethylaminoethyl diphenylthioacetate thus obtained was dissolved in anhydrous ether and hydrogen chloride passed into the solution. Whereupon the ester hydrochloride precipitated. This was collected by filtration, and recrystallized from a mixture of alcohol and ether. Melting point: 82°–85° C.

The hydrochloride is preferred for use as a drug because of its greater water solubility than the basic ester.

Example 2.—A mixture of 0.1 mole of B-chloroethyl diphenylthioacetate prepared as described in Example 1, and 0.3 mole of morpholine were heated in a sealed bottle for three days at 40° C. in a constant temperature oven. After cooling the reaction mixture was suspended in water and extracted with ether. The ether extract was then evaporated and the residue purified by recrystallization from ethanol. The basic ester, B-morpholinoethyl diphenylthioacetate, thus obtained was dried, dissolved in anhydrous ether and treated with dry hydrogen chloride whereupon the ester hydrochloride precipitated. This was collected and recrystallized from a mixture of ethanol and ether. Melting point of the hydrochloride: 194°–196° C.

Example 3.—B-piperidinoethyl diphenylthioacetate hydrochloride was prepared in exactly the same way as the morpholino derivative from 0.1 mole of B-chloroethyl diphenylthioacetate and 0.3 mole of piperidine. Melting point of the hydrochloride: 210°–212° C.

It will be noted that the procedure described above in Examples 2 and 3 for the preparation of the morpholino and the piperidino compounds differs from the method for the preparation of the diethylamino compound described in Example 1 with respect to the recovery of the compounds from the reaction mixtures in which the B-chloroethyl diphenylthioacetate is combined with the morpholine, piperidine and diethylamine. This difference in the procedures is due to the fact that the morpholino and piperidino basic esters are crystalline solids whereas the diethylamino basic ester is a liquid and requires a different treatment for its recovery and purification.

Comparative pharmacological tests on the excised rat uterus, the excised rabbit intestine, and the excised human uterus have demonstrated

that the B-diethylaminoethyl diphenylthioacetate administered as the hydrochloride has a musculotropic action about twice that of the corresponding non-thio or simple acetate compound, that is, the same antispasmodic effect is obtained by the use of a concentration of the thioacetate compound equal to half of the concentration of the simple acetate compound required to give the specified antispasmodic effect.

The thioacetate compound presumably has some neurotropic action but it is so weak or small as to be of little or no consequence in the use of the drug and has not been accurately measured.

Tests made to determine the toxicity of the thioacetate compound indicate that its toxicity is very low and practically negligible. In tests made on white rats both young and mature, the minimum lethal doses of the thio and non-thio compounds are approximately the same. The minimum lethal dose was found to vary considerably with the age of the rats, being 1.5 grams per kilogram of body weight for rats 4 months old and only about 0.5 gram per kilogram body weight for rats 45 days old. This low toxicity of the thio compound was contrary to logical expectation.

The antispasmodic action of the morpholino and piperidino thioacetate compounds of Examples 2 and 3 was found to be approximately equal to that of the B-diethylaminoethyl diphenylthioacetate compound of Example 1 and their neurotropic action and toxicity well within the permissible range of tolerance for the use of the compounds as antispasmodic drugs.

The thio compounds have been found to have a distinct advantage over the non-thio compounds with respect to stability. This result, like the discovery of the low toxicity of the thio compounds, was contrary to logical expectation. This greater stability of the thio compounds appears as a factor in their preparation and use. For instance, in the preparation of B-diethylaminoethyl diphenylacetate it was found that the hydrochloride salt could not be made in the usual way by dissolving the basic ester in ether and passing hydrogen chloride into the solution

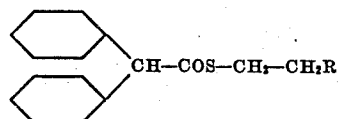
because hydrolysis of the ester occurs under these conditions. This customary procedure may, however, be applied for the production of the corresponding thio compound without hydrolysis.

Moreover, when it was attempted to purify the non-thio compound by recrystallization from alcohol hydrolysis occurred whereas the thio compound was stable under these conditions. The thio compound was found to be stable in aqueous solution for a period of at least two weeks.

So far as I am aware, the three compounds described in Examples 1, 2 and 3 are new and no one heretofore has suggested their use as drugs.

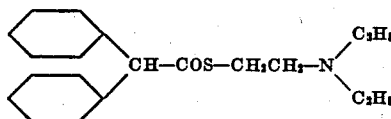
I claim:

1. A di-N-substituted aminoethyl ester of diphenylthioacetic acid of the formula

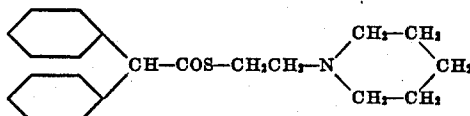


in which R represents a disubstituted amino radical of the group consisting of the diethylamino group, the morpholino group and the piperidino group.

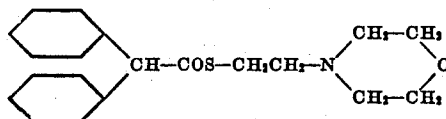
2. A compound of the formula



3. A compound of the formula



4. A compound of the formula



ANDREW G. RICHARDSON.