

UNITED STATES PATENT OFFICE

2,432,049

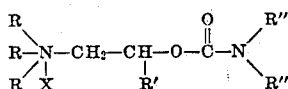
CHOLINELIKE COMPOUNDS

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G. White, Cranford, N. J.No Drawing. Application August 31, 1945,
Serial No. 613,964

8 Claims. (Cl. 260-482)

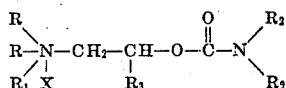
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This application is a continuation-in-part of our copending application Serial No. 497,858 filed August 7, 1943 (issued as U. S. Patent No. 2,408,893 on October 8, 1946), relating to a new class of carbamic acid esters of compounds of the choline type, which substances exhibit valuable pharmacological properties. The compounds of said copending application may be represented by the formula:



wherein R is selected from the group consisting of lower alkyl radicals; X is an anion; R' is selected from the group consisting of hydrogen and lower alkyl radicals; and R'' is selected from the group consisting of alkyl radicals having more than three carbon atoms, and aryl radicals.

The present application relates particularly to compounds of the above formula wherein two of the substituents R are similar lower alkyl groups and the third substituent R is a different lower alkyl group as well as to compounds having, instead of three alkyl substituents, two alkyl substituents and hydrogen. These compounds may be represented by the formula:



wherein the substituents R are the same and of the class consisting of lower alkyl radicals, R₁ is of the class consisting of H and lower alkyl radicals different from the substituents R, R₂ is of the class consisting of alkyl radicals of at least four carbon atoms and aryl radicals, R₃ is of the class consisting of H and lower alkyl radicals, and X is an anion.

We have found that, whereas other compounds of the choline series, such as acetylcholine chloride, and carbaminoyl choline chloride, and derivatives in which the hydrogens attached to the nitrogen of the carbamate group are re-

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placed by small polar groups, that is, radicals containing less than four carbon atoms, produce constriction of the pupil and contraction of the ciliary muscle when administered to individuals, the compounds of our invention, in which the hydrogens attached to the nitrogen of the carbamate group are replaced by large, non-polar groups, that is, radicals containing more than three carbon atoms, exhibit a reverse action in that they exhibit mydriatic and cycloplegic properties.

While we do not wish to commit ourselves to any definite theory as to the cause of the reversal of activity experienced with our new products, in which highly hydrophilic choline salts are combined by an ester linkage with highly hydrophobic groups, it appears that the unexpected properties exhibited by the compounds of our invention may be due to the fact that the elongated molecules which are predominantly hydrophilic at the choline end, and predominantly hydrophobic at the opposite end, are surface-active, and that such surface activity not only enables the compounds to penetrate the cornea of the eye more readily, but also causes the differences in pharmacological effects due to the differences in site of action on the cell.

The products of our invention are similar in action to atropine and homatropine. However, the compounds of our invention have advantages over both atropine and homatropine in that, while the degree of mydriasis and cycloplegia produced by our products is, generally speaking, of the same order as that of atropine and homatropine, we have found that where our products have been administered, cycloplegia, and particularly mydriasis, are markedly less prolonged, resulting in a shorter period of visual disability than is experienced in the case of atropine or homatropine. Further, the products of our invention do not produce the marked hyperemia and irritation of the conjunctiva which are incidental to the use of homatropine in many cases. The products of our invention have anti-septic properties.

Among the compounds which fall within the purview of our invention may be mentioned the following representative substances:

- N-di-n-butyl carbamyl choline chloride
M. P. 98-110° C.
- β -N-di-n-butyl carbamylethyl triethyl ammonium chloride
M. P. 68-89° C.
- N-diphenyl carbamyl choline chloride
M. P. 201-203° C.
- N-di-n-butyl carbamyl- β -methyl choline chloride
M. P. 85-105° C.
- N-di-n-amyl carbamyl choline chloride
M. P. 98-103° C.
- N-di-n-butyl carbamyl choline sulfate
M. P. 180-181° C.
- N-di-iso-butyl carbamyl choline chloride
M. P. 147-148° C.
- β -(Dimethyl ethyl ammonium sulfate)-ethyl-di-n-butyl carbamate
M. P. about 165-166° C. (dec.)
- β -(Dimethyl ethyl ammonium-ethyl-sulfate)-ethyl-di-n-butyl carbamate
M. P. 78-80.5° C.
- β -(Dimethyl ethyl ammonium iodide)-ethyl-di-n-butyl carbamate
M. P. 76-77° C.
- β -(Dimethyl ethyl ammonium bromide)-ethyl-di-n-butyl carbamate
M. P. 45-47° C.
- β -(Dimethyl ammonium chloride)-ethyl-di-n-butyl carbamate
M. P. 90-90.5° C.

In most instances, the compounds mentioned are extremely hygroscopic so that it is difficult to ascertain definite melting points therefor.

These new compounds are very valuable for clinical application in routine intraocular examination and cycloplegic refraction.

For example, we have found that two instillations of a 7.5% aqueous solution of N-di-n-butyl carbamyl choline sulfate into the conjunctival sac produce mydriasis and cycloplegia beginning within twenty minutes and becoming maximal in 60-90 minutes, the reactions of the intraocular muscles usually returning to normal in about 7-12 hours after administration of the substance.

In addition to being valuable mydriatic and cycloplegic drugs, the compounds of the present application have anti-spasmodic action on all types of smooth muscles in human beings. As anti-spasmodic drugs, these compounds have extremely low toxicity per unit of potency, thus making these compounds superior to anti-spasmodic drugs now in general use. For example, in relaxation of the ureter, compounds of the type listed above, and particularly compounds of the type of the last five listed, are more effective, and produce fewer side effects, than drugs normally employed for this relief. For optical application to produce mydriasis and cycloplegia, compounds which are salts of β -(dimethyl ethyl ammonium)-ethyl-di-n-butyl carbamate are preferred compounds, and the ammonium sulfate salt is the most suitable compound because of the extremely low conjunctival irritation produced.

The products of our invention may be obtained by several methods. One such method comprises reacting a tertiary aliphatic amine as, for instance, trimethylamine or tri-ethylamine, with β -chloro-ethyl-di-alkyl carbamate, the alkyl radicals of which contain more than three carbon

atoms, or with β -chloroethyldiaryl carbamate. The resulting product, a chloride, may be converted to other salts, or to the base, by known methods. Thus the chloride may be converted to other salts by reacting the same with a silver salt which is more soluble in water than silver chloride.

The following examples illustrate methods of carrying out the present invention, but it is to be understood that these examples are given by way of illustration and not of limitation.

Example I

50 gms. of β -chlor-ethyl-chlorcarbonate are dissolved in ether and cooled to 0° C. An ether solution containing 86.5 gms. of di-n-butylamine is added, and the mixture is stirred carefully to maintain the temperature at 0° C. Ether is used in sufficient volume to permit adequate mixing. Most of the di-n-butylamine hydrochloride precipitates, and is filtered off. The filtrate is extracted with dilute hydrochloric acid to remove any unreacted di-n-butylamine in the form of di-n-butylamine hydrochloride.

The ether and water fractions are separated, and the ether fraction is distilled at atmospheric pressure to remove ether. The residue is then distilled under reduced pressure and the fraction boiling at 151-152° C./18 mm. (uncorrected) is collected as one fraction. That fraction is pure β -chlor-ethyl-di-n-butyl-carbamate, a colorless liquid with a refraction index of 1.446-1.448 at 26° C.

21 gms. of β -chlorethyl-di-n-butyl-carbamate and 6 gms. of condensed trimethylamine are placed in a vessel, and the vessel is closed firmly and maintained at 85° C. A white, crystalline solid forms. After 18 hours, the vessel is opened and placed in vacuo to remove any unreacted trimethylamine. The final product is washed with anhydrous ether in a dry atmosphere to remove any unreacted β -chlorethyl-di-n-butyl-carbamate. N-di-n-butyl carbamyl choline chloride occurs as a highly hygroscopic, snow-white crystalline compound, melting at about 98-110° C. A 5% aqueous solution of the product has an air-water interfacial tension of approximately 41 dynes/cm. at 25° C. The pH of aqueous solutions thereof is approximately neutral.

Example II

8 gms. of β -chlorethyl-di-n-butyl carbamate are placed in a vessel with 4 gms. of triethylamine. An equal volume of absolute methyl alcohol is added to the mixture. The vessel is sealed and maintained at 120° C. for 12 hours, after which the tube is cooled to room temperature and opened. The solvent (methyl alcohol) and unreacted triethylamine are removed by evaporation under reduced pressure. After evaporation is completed, two volumes of acetone are added, which results in the precipitation of a pharmacologically inactive fraction which is removed by filtration. Acetone is evaporated from the filtrate under reduced pressure. Two volumes of ethyl ether are added to the acetone-free residue, and the active principle is extracted with distilled water. Unreacted β -chlorethyl ester of di-n-butyl carbamic acid remains in the ether fraction. When the water is evaporated under reduced pressure, the product, β -N-di-n-butyl carbamylethyl triethyl ammonium chloride remains in the form of white, hygroscopic crystals melting at about 68-89° C. A 7% aqueous solution of the product has an

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air-water interfacial tension of approximately 42.0 dynes/cm. at 39° C.

Example III

10 gms. of β -chloroethyl-chlorcarbonate are mixed with 22.2 gms. of diphenylamine, and refluxed for two hours on a water bath. The solid mixture is then refluxed with 150 cc. of 60-70° ligroin, and filtered hot to remove diphenylamine hydrochloride. The filtrate is cooled to 0° C., and β -chloroethyl-diphenyl-carbamate crystallizes out and is separated by filtration. It is then recrystallized from 60° ligroin. The product occurs in the form of white crystals melting at about 72° C.

14 gms. of β -chloroethyl-diphenyl-carbamate are placed in a container with 10 gms. of a 30% trimethylamine solution in absolute alcohol. The container is closed firmly and heated at 85° C. for 16 hours. The solution is then cooled to 0° C. and N-diphenyl-carbamylchlorine chloride is precipitated by the addition of acetone. The product is recrystallized from acetone. It occurs in the form of non-hygroscopic, snow-white crystals melting at about 204° C. (uncorrected). It is soluble in water and alcohol; slightly soluble in acetone.

Example IV

32 gms. of β -chlor-isopropyl-chlorcarbonate are dissolved in ethyl ether, and the solution is cooled to 0° C. An ethyl ether solution containing 50 gms. of di-n-butylamine is added, and the mixture is stirred carefully to maintain the temperature at 0° C. Most of the di-n-butylamine hydrochloride formed precipitates, and is filtered off; the filtrate is extracted with dilute hydrochloric acid to remove any unreacted di-n-butylamine in the form of di-n-butylamine hydrochloride. The ether and water fractions are separated, and the ether fraction is distilled at atmospheric pressure to remove ether. The residue is then distilled under reduced pressure, and the fraction boiling at 158-159° C./20 mm. (uncorrected) is collected as one fraction. That fraction is pure β -chlorisopropyl-di-n-butyl-carbamate, a colorless liquid with a refractive index of about 1.446 at 26° C.

21 gms. of β -chlor-isopropyl-di-n-butyl carbamate and 20 gms. of 30% (by weight) trimethylamine in absolute ethyl alcohol are placed in a vessel. The vessel is firmly closed, and maintained at 105° C. After 18 hours, the vessel is opened in a dry atmosphere and placed in vacuo to remove any unreacted trimethylamine. Ethyl ether is added to the residue, and the product is extracted with distilled water. After the water is removed in vacuo over P_2O_5 , the final product, N-di-n-butyl carbamyl- β -methylcholine chloride, remains as highly hygroscopic, snow-white crystals melting at about 85-105° C. A 7.5% solution of the product in water has an air-water interfacial tension of approximately 42.5 dynes/cm. at 29.5° C.

Example V

50 gms. of β -chloroethyl-chlorcarbonate are dissolved in ether, and the solution cooled to 0° C. An ether solution containing 105 gms. of di-n-amyl amine is added, and the mixture is stirred carefully to maintain the temperature at 0° C. Di-n-amyl amine hydrochloride is precipitated and filtered off; the filtrate is extracted with dilute hydrochloric acid to remove any unreacted

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di-n-amyl amine, in the form of di-n-amyl amine hydrochloride.

The ether and water fractions are separated, and the ether fraction is distilled at atmospheric pressure to remove ether. The residue is then distilled under reduced pressure, and the fraction boiling at about 178-180° C./20 mm. is collected as one fraction. The fraction is pure β -chloroethyl-di-n-amyl carbamate, a colorless liquid with a refraction index of 1.448-1.450 at 20° C.

24 gms. of β -chlor-ethyl-di-n-amyl-carbamate and 6 gms. of condensed trimethylamine are placed in a vessel, and the vessel is closed firmly and maintained at 85° C. A white crystalline solid forms. After 18 hours, the vessel is opened and placed in vacuo to remove any unreacted trimethylamine. The residue is washed with anhydrous ether in a dry atmosphere to remove any unreacted β -chloroethyl-di-n-amyl-carbamate. The final product, N-di-n-amyl carbamyl choline chloride, occurs in the form of highly hygroscopic, snow-white crystals, having a melting point of about 98-103° C. An aqueous solution containing 5% of the product has a surface tension of approximately 38.5 dynes/cm. at 29° C. Aqueous solutions thereof have approximately neutral pH.

Example VI

50 gms. of β -chloroethyl-chlorcarbonate are dissolved in ether, and the solution is cooled to 0° C. An ether solution containing 86.5 gms. of di-isobutylamine is added, and the mixture is stirred carefully to maintain the temperature at 0° C. Most of the di-isobutylamine hydrochloride precipitates, and is filtered off; the filtrate is extracted with dilute hydrochloric acid to remove any unreacted di-isobutylamine (in the form of di-isobutylamine hydrochloride).

The ether and water fractions are separated, and the ether fraction is distilled at atmospheric pressure to remove ether. The residue is then distilled under reduced pressure, and the fraction boiling at 144-146° C./20 mm. (uncorrected) is collected as one fraction. That fraction is pure β -chloroethyl-di-isobutyl-carbamate, a colorless liquid with a refraction index of 1.446-1.448 at 26° C.

21 gms. of β -chloroethyl-di-isobutyl-carbamate and 6 gms. of condensed trimethylamine are placed in a vessel, and the vessel is firmly closed and maintained at 85° C. A white, crystalline solid forms. After 18 hours, the vessel is opened, and placed in vacuo to remove any unreacted trimethylamine. The product is washed with anhydrous ether in a dry atmosphere to remove any unreacted β -chloroethyl-di-isobutyl carbamate. The final product, N-di-isobutyl carbamyl choline chloride, occurs in the form of highly hygroscopic, snow-white crystals, melting at about 147-148° C. A 5% aqueous solution of the product has an air-water interfacial tension of approximately 41.5 dynes/cm. at 29.5° C. Aqueous solutions thereof have approximately neutral pH.

Example VII

7 gms. of di-n-butyl-carbamylcholine chloride are dissolved in 50 cc. of distilled water, and 4 gms. of finely powdered silver sulfate are added. The vessel is sealed, and shaken at room temperature until a filtered sample does not yield a precipitate when silver nitrate is added. The mixture is then filtered to remove precipitated silver chloride. The filtrate is dried in vacuo, and the residue is extracted with anhydrous ethyl alcohol. N-di-n-butyl carbamyl choline sulfate is

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precipitated from the alcohol solution by addition of anhydrous ethyl ether. It occurs in the form of slightly hygroscopic, white crystals melting at about 198–200° C. A 7.5% aqueous solution thereof has an air-water interfacial tension of 39–40 dynes/cm. at 29° C.

Example VIII

About 21 gms. of β -chloroethyl-di-n-butyl-carbamate and about 8 gms. of dimethylethylamine are placed in a vessel, and the vessel is closed firmly and maintained at about 85° C. A white crystalline solid forms. After about 18 hours, the vessel is opened and placed under diminished pressure to remove any unreacted dimethylethylamine. The solid product is washed with anhydrous ether in a dry atmosphere to remove any unreacted β -chloroethyl-di-n-butyl-carbamate. The ethyl chloride salt of β -dimethylaminoethyl-di-n-butylcarbamate (i. e., β -(dimethyl ethyl ammonium chloride)-ethyl-di-n-butyl carbamate) thus obtained is a very highly hygroscopic white crystalline compound. A 5% aqueous solution of this product has an air-water interfacial tension of approximately 39 dynes/cm. at 25° C.

About 7 gms. of the β -(dimethyl ethyl ammonium chloride)-ethyl-di-n-butyl carbamate is dissolved in about 50 cc. of distilled water and about 4 gms. of finely powdered silver sulfate is added. The vessel is sealed and shaken at room temperature until a filtered sample does not yield a precipitate when silver nitrate is added. The mixture is then filtered to remove the precipitated silver chloride. The filtrate is dried under diminished pressure and the residue extracted with anhydrous ethyl alcohol. The β -(dimethyl ethyl ammonium sulfate)-ethyl-di-n-butyl carbamate is precipitated from the alcoholic solution by the addition of anhydrous ethyl ether. It occurs in the form of a very hygroscopic white crystalline substance having a melting point of about 166° C. with decomposition.

Example IX

About 55.5 gms. of β -chloroethyl-di-n-butyl-carbamate and about 22.6 gms. of dimethylamine are placed in a container, firmly sealed, and heated at about 95° C. for about 16 hours. To the resulting crude mixture is added ethyl ether and the mixture filtered to remove dimethylamine hydrochloride formed during the course of the reaction. The ethereal solution is then extracted with 12 N hydrochloric acid. Under a fresh layer of ether and at a temperature under 10° C. the aqueous acid extract is first neutralized with sodium carbonate and then made strongly alkaline with sodium hydroxide. The supernatant ethereal solution is then separated and dried over potassium hydroxide. The ethereal solution is finally concentrated and the residue obtained is fractionally distilled under vacuum. The β -dimethylaminoethyl-di-n-butyl-carbamate is found to distill undecomposed at about 128–130° C. under approximately 2 mm. pressure.

A mixture of about 100 gms. of β -dimethylaminoethyl-di-n-butyl-carbamate and about 188 cc. of ethyl iodide is held at about 25° C. for two hours. The temperature is kept about 25° C. by occasional cooling in an ice bath during the first half hour. About 1600 cc. of anhydrous ethyl ether is then added causing the precipitation of a dense white product. After standing for about 16 hours at 0° C. the product is filtered off, washed thoroughly with anhydrous ether, and dried under diminished pressure at room temperature over

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sulfuric acid. The β -(dimethyl ethyl ammonium iodide)-ethyl-di-n-butyl carbamate thus obtained is a white crystalline powder, slightly hygroscopic with a melting point of about 76–77° C.

By reacting β -chloroethyl-di-n-butyl carbamate with diethylamine and then reacting the intermediate β -diethylaminoethyl-di-n-butyl carbamate with methyl iodide, according to the foregoing procedure, β -(diethyl methyl ammonium iodide) ethyl di-n-butyl carbamate is obtained.

Example X

A quantity of β -dimethylamino ethyl di-n-butyl carbamate, prepared as in Example IX above, is dissolved in anhydrous ethyl ether, and dry hydrogen chloride gas in excess of that theoretically required to form the hydrochloride salt is passed through the mixture. Ether is then removed by evaporation and the residue is extracted with cold acetone by thorough trituration. The acetone extract is then filtered, partially evaporated, and the product, β -(dimethyl ammonium chloride)-ethyl-di-n-butyl carbamate is precipitated by addition of anhydrous ethyl ether.

Example XI

A mixture of about 150 gms. of β -(dimethyl ethyl ammonia iodide)-ethyl-di-n-butyl carbamate, 90 gms. of silver sulfate, 750 cc. of water and 750 cc. of ethanol is stirred at about 30° C. for approximately 45 minutes. The silver iodide formed is removed and the excess silver remaining in solution is removed by bubbling in hydrogen sulfide for five minutes followed by filtration to remove the precipitated silver sulfide. The filtrate is concentrated to a thick syrup under vacuum and about one liter of benzene is added which is distilled off with stirring at atmospheric pressure to remove the last traces of water. The residual benzene is removed under vacuum and the product granulated by stirring with one liter of anhydrous ether for two hours. The product is removed, washed with anhydrous ether, and dried under diminished pressure over phosphorous pentoxide at 25° C. The β -(dimethyl ethyl ammonium sulfate) ethyl-di-n-butyl carbamate thus obtained is a very hygroscopic white solid having a melting point of about 166° C. with decomposition.

Example XII

A mixture of about 10 gms. of β -dimethylaminoethyl-di-n-butyl-carbamate and about 18 cc. of ethyl bromide is refluxed for approximately four hours. To the resulting solution is added about 150 cc. of anhydrous ethyl ether, causing precipitation of the β -(dimethyl ethyl ammonium bromide) - ethyl-di-n-butyl carbamate which is removed by filtration. This product, purified by recrystallization from carbon tetrachloride, has a melting point of about 45–47° C.

Example XIII

A mixture of about 10 gms. of β -dimethylaminoethyl-di-n-butyl-carbamate, about 12.6 gms. of diethyl sulfate, and 50 cc. of anhydrous ethyl ether is refluxed overnight. The β -(dimethyl ethyl ammonium ethyl-sulfate)-ethyl-di-n-butyl carbamate precipitates on standing, is filtered, and washed with ethyl ether, and recrystallized from 50 cc. of carbon tetrachloride. The recrystallized material has a melting point of about 78–80.5° C.

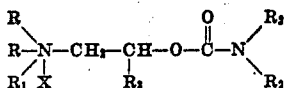
Example XIV

About 23.5 gms. of β -chloroethyl-di-n-butyl carbamate and about 14.6 gms. of diethylamine are placed in a container capable of being tightly closed and heated for about twelve hours, at 110° C. The container is then cooled and opened and the mixture is transferred into about 300 cc. of anhydrous ether. Dry hydrogen chloride gas in excess of that required to react with a 100% theoretical yield of tertiary amine is passed through the mixture. The ether is then removed by evaporation and the resulting mass is extracted with about 100 cc. of cold acetone by thorough trituration. After filtering off the acetone extract, the acetone is evaporated until a precipitate begins to form. Acetone, just sufficient for complete solution, is then added and to this solution is added anhydrous ethyl ether causing precipitation of β -(diethyl ammonium chloride) - ethyl-di-n-butyl carbamate. This product is obtained as fine, snow-white, slightly hygroscopic crystals melting at about 90-90.5° C.

Modifications may be made in carrying out the present invention without departing from the spirit and scope thereof, and the invention is to be limited only by the appended claims.

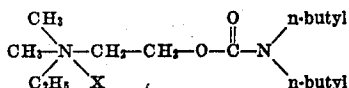
What is claimed is:

1. An essentially non-toxic surface-active compound of the formula



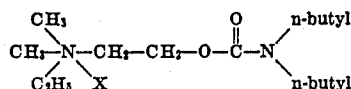
wherein the substituents R are the same and of the class consisting of methyl and ethyl radicals, R₁ is different from the substituents R and of the class consisting of H and methyl and ethyl radicals, R₂ is of the class consisting of alkyl radicals of at least four carbon atoms and the phenyl radical, R₃ is of the class consisting of H and methyl radicals and X is an anion.

2. An essentially non-toxic surface-active compound of the formula



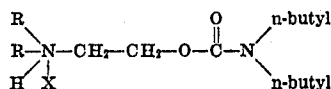
wherein X is an anion.

3. An essentially non-toxic surface-active compound of the formula



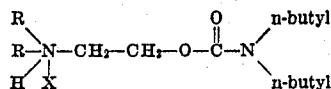
wherein X is halogen.

4. An essentially non-toxic surface-active compound of the formula



wherein R is of the class consisting of methyl and ethyl radicals and X is an anion.

5. An essentially non-toxic surface-active compound of the formula



wherein R is of the class consisting of methyl and ethyl radicals and X is halogen.

6. β -(Dimethyl ethyl ammonium iodide)-ethyl-di-n-butyl carbamate.

7. β -(Dimethyl ethyl ammonium sulfate)-ethyl-di-n-butyl carbamate.

8. β -(Diethyl ammonium chloride)-ethyl-di-n-butyl carbamate.

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