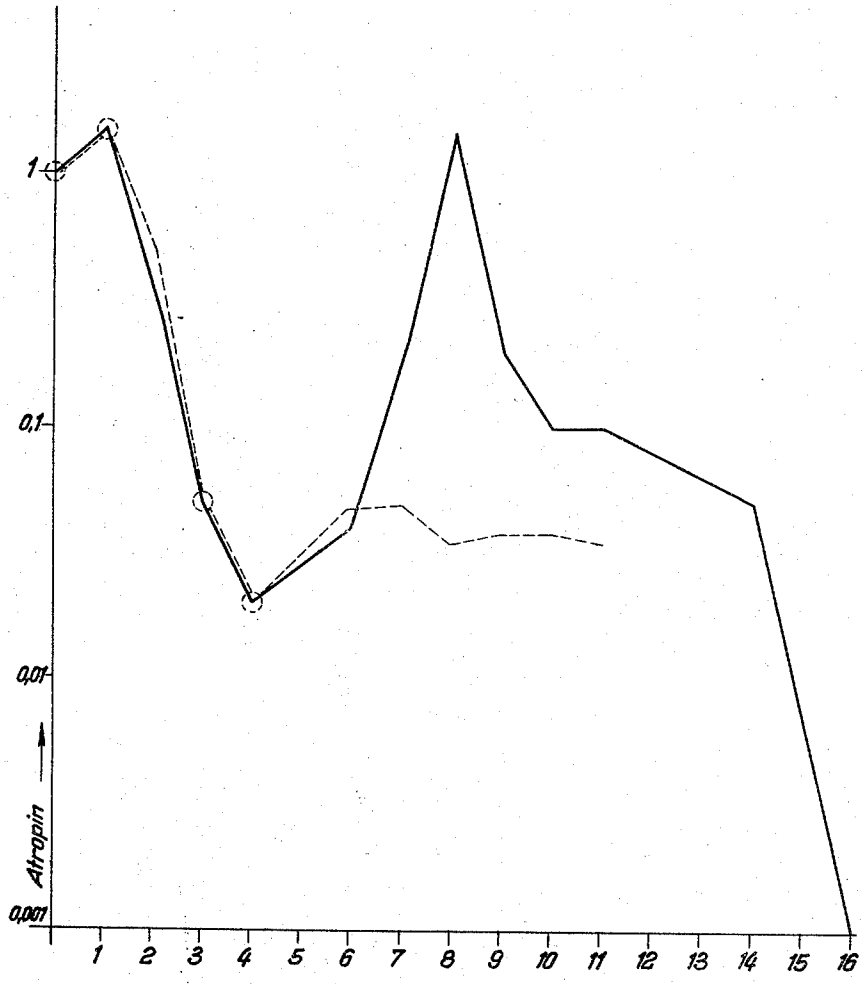
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QUATERNARY TROPEINE COMPOUNDS AND A PROCESS OF MAKING SAME

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QUATERNARY TROPEINE COMPOUNDS AND A PROCESS OF MAKING SAME

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The present invention relates to new tropeine compounds and more particularly to new quaternary tropeine compounds and to a process of making same.

Atropine is employed in medicine for its valuable antispasmodic activity which is due to its excellent spasmolytic properties as well as to its low toxicity. Atropine, however, has also considerable disadvantages. It causes undesired side effects which are encountered even when given in small doses. Atropine, for instance, inhibits secretion of the salivary glands, causes mydriasis, and has an accelerating effect on the heart beat. The medical profession, therefore, has been seeking a spasmolytic agent having a more favorable ratio between desired principal pharmacological effect and undesired side effects than atropine.

Such an agent is, for instance, scopolamine bromo butylate, a quaternary ammonium compound the spasmolytic activity of which, especially with respect to the gastro-intestinal tract, is similar to that of atropine. This compound, however, has only 1/500 of the mydriatic activity of atropine, 1/30 of its pulse accelerating effect, and 1/50 of its inhibiting effect on saliva secretion. Furthermore, said spasmolytic agent has the desired capacity of blocking the ganglia and especially the ganglia of the vagal nervous system. It is, however, rather difficult to provide scopolamine in sufficient amounts and its price is very high.

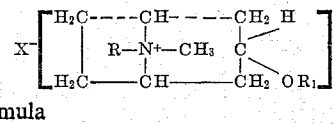
Therefore, attempts have been made to produce, in an economical manner, compounds having the same favorable effects as scopolamine bromo butylate by quaternizing more readily available tropeine compounds. Thereby, it was found that, for instance, quaternary alkyl compounds of the tropeine series with increasing length of the alkyl chain initially exhibit a considerably reduced spasmolytic activity. For instance, atropine bromo butylate corresponding to scopolamine bromo butylate is practically ineffective as spasmolytic agent.

It is one object of the present invention to provide quaternary alkyl derivatives of the tropeine series having an increased spasmolytic activity which surpasses even that of atropine, said new compounds, however, exhibiting undesired side-effects only to a far less extent than atropine.

Another object of the present invention is to provide a simple and effective process of producing such new and valuable quaternary alkyl derivatives of the tropeine series.

Other objects of the present invention and advantageous features thereof will become apparent as the description proceeds.

In principle, the present invention consists in providing quaternary alkyl derivatives of the tropeine series wherein the alkyl radical contains 7 to 11 carbon atoms. Such compounds correspond to the following formula



In said formula

R indicates an alkyl radical with 7 to 11 carbon atoms, said alkyl radical being a straight chain or a branched chain saturated or unsaturated alkyl radical;

R_1 indicates an acid radical containing an aromatic ring system, for instance, the radical of benzoic acid, mandelic acid, tropic acid, benzilic acid, and other aromatic acids; and

X indicates halogen and especially bromine.

The new compounds according to the present invention can be prepared according to various methods. For instance, tropine can be quaternized by means of a compound of the formula RX, and is then esterified by means of the acid R_1OH or a reactive derivative of said acid to the desired tropeine compound. One may also first esterify tropine with the acid R_1OH or a reactive derivative thereof and then subject the resulting ester to quaternization. It is, of course, also possible to start with naturally occurring tropeine compounds and to quaternize such compounds.

Another method of producing the new and valuable quaternary alkyl derivatives of the tropeine series consists in first synthesizing nortropine by reacting succinaldehyde, acetone dicarboxylic acid, and ammonia and then converting the resulting nortropine into the corresponding alkyl nortropine having 7 to 11 carbon atoms by means of alkyl halogenide and thereafter quaternizing said alkyl nortropine by means of a compound of the formula CH_3X to form the corresponding tropinium compound the hydroxyl group of which is finally esterified by means of an acid of the formula R_1OH. Such alkyl nortropine compound can also be obtained by reacting succinaldehyde, acetone dicarboxylic acid, and an alkylamine having 7 to 11 carbon atoms which is subsequently quaternized and esterified. The order in which quaternization and esterification takes place may be reversed, i. e. the alkyl nortropine compound may first be esterified and thereafter quaternized. During all these reactions the formation of compounds being nitrogen-stereoisomers is possible.

The reaction conditions during quaternization are dependent on the nature of the compound RX used as the one reaction component and among others on the length of its alkyl chain. Quaternization is preferably effected while gently heating the reaction mixture for a prolonged period of time. For instance, the reaction mixture can be heated to about 60° C. for several hours up to two weeks or it can be allowed to stand at room temperature (20° C.) for several days up to several months. Preferably quaternization is carried out in a solvent and most advantageously in a solvent having a strongly polar character such as acetonitrile or formamide. An excess of the alkyl halogenide used for quaternization may be employed as solvent. If the acid R_1OH contains hydroxyl groups, such groups can also be etherified or esterified.

The new compounds produced by the process according to the present invention are soluble in water and crystallize from organic solvents such as alcohols, acetonitrile, acetone, and others.

As has been stated hereinbefore, the new compounds produced according to the present invention are excellent spasmolytic agents wherein the undesired side-effects observed, for instance, with atropine, completely recede. Furthermore, the new compounds according to the present invention are distinguished over known compounds of this series by their ability of counteracting the action of ganglia-stimulating compounds. Octyl atropinium bromide obtained, for instance, according to the present invention, surpasses by 20 to 30 times the action of tetraethyl ammonium which is generally considered as the standard compound of this type of compounds. The toxicity of said compound obtained according to the pres-

ent invention is very low. The L. $D._{50}$ of said compound, determined on white mice, is 335 mg. per kg. on subcutaneous injection and 410 mg. per kg. on oral administration.

As has been mentioned hereinbefore, the spasmolytic activity of compounds of this type is dependent upon the chain length of the alkyl radical present at their nitrogen atom. Fig. 1 of the attached drawings graphically illustrates the principal effects and the side-effects of such compounds in relationship to the chain length of their alkyl radical. The curves given therein show that, for instance, the spasmolytic effect of quaternary atropinium bromo alkylates initially decreases considerably up to an alkyl chain length of 6 carbon atoms. Compounds having an alkyl chain length of 7 to 9 carbon atoms exhibit a pronounced maximum of activity and with longer chain length the spasmolytic activity again is decreased to only fractions of that of atropine. The solid line in said Fig. 1 clearly illustrates this maximum of spasmolytic activity exhibited by compounds according to the present invention having an alkyl chain length between 7 and 11 carbon atoms.

The dotted line in said Fig. 1 illustrates the influence of the alkyl chain length upon mydriasis. While the mydriatic activity corresponds to the spasmolytic activity, in compounds having an alkyl chain length up to six carbon atoms, said side-effects are almost completely eliminated when increasing the side chain length to between 7 and 11 carbon atoms. This mydriasis-reducing effect due to an increase in alkyl chain length could not at all be expected and renders the new compounds especially valuable.

Heretofore, a number of low alkyl or aralkyl quaternary ammonium compounds of the tropeine series were known and have been investigated. These compounds however, in so far as they exhibit a spasmolytic effect, produce the same undesirable side-effects as those of atropine. Furthermore, the preparation of a series of compounds has been described, which although they exhibit a blocking effect upon the ganglia, have a spasmolytic activity which amounts only to a very small fraction of that of atropine. In contrast hereto the high spasmolytic activity of compounds produced according to the present invention is especially surprising and said new compounds, because of their pronounced spasmolytic activity and their very reduced side-effects as illustrated in the attached drawing, are of extraordinary value in therapy and for the medical profession.

The following examples serve to illustrate the present invention without, however, limiting the same thereto.

Example 1.—N-octyl atropinium bromide

58 g. of atropine (about 0.2 mol) and 105 g. of octyl bromide (about 0.6 mol), in a mixture of 100 cc. of acetonitrile and 100 cc. of methanol, are kept in an oil bath at 60° C. for about 1 week. The reaction mixture is evaporated to dryness on heating on a water bath in a vacuum. The residue is triturated with cold acetone and N-octyl atropinium bromide crystallizes. On repeated recrystallization from acetone, N-octyl atropinium bromide of analytical purity, melting at 139–140° C., is obtained. Said quaternary ammonium compound contains less than 0.4% of the salt of the tertiary base used as starting material. Further amounts of said new compound are obtained on working up the mother liquors. The total yield amounts to about 80% to 85% of the theoretical yield.

The same compound is obtained when allowing the reaction mixture to stand at 20° C. for several months. In place of the solvent mixture employed in the above given example, a larger excess of the alkyl halogenide can be used. In a similar manner the following compounds can be prepared by using the corresponding alkyl halogenides.

Alkyl halogenide	Quaternary atropinium halogenide	Recrystallized from—	M. P., ° C.	Yield
Heptyl bromide	N-heptyl atropinium bromide	Acetone	133–136	About 50%.
Nonyl bromide	N-nonyl atropinium bromide	do	128–131	50%.
Decyl bromide	N-decyl atropinium bromide	Dioxane [1]	109–112	32%.
Undecyl bromide	N-undecyl atr. br	Acetone	116–119	58%.
2-ethyl hexyl bromide	N-(2-ethyl hexyl) atropinium bromide	Isopropanol	166–170	About 50%.
Undecenyl bromide	N-undecenyl atropinium bromide	Acetone	105–106	About 30%.

[1] N-decyl atropinium bromide is purified by repeatedly dissolving said compound in ethanol and precipitating it with acetic acid ethyl ester followed by recrystallization from dioxane.

Example 2.—N-octyl homatropinium bromide

50 g. of homatropine base, obtained by esterifying synthetically produced tropine or tropine produced from atropine by esterification with mandelic acid, and 105 g. of octyl bromide (about 3 mols) are heated in a mixture of 100 cc. of acetonitrile and 100 cc. of methanol in an oil bath at 60° C. for one to two weeks. The residue remaining after distilling off the solvents and excess octyl bromide is twice recrystallized from isopropanol. 22 g. of octyl homatropinium bromide of analytical purity, having a melting point of 137–139° C., are obtained thereby. The compound is substantially free of homatropine hydrobromide. Further 15 g. of said compound are recovered from the mother liquors. The yield amounts to about 50% of the theoretical yield.

Example 3.—N-octyl benzoyl tropinium bromide

50 g. of tropine are dissolved in 325 cc. (80 mols) of benzoylchloride and the mixture is heated to boiling for ten minutes. The crystals filtered off after cooling said reaction mixture are washed with ether. The base is obtained therefrom by treating said crystals with sodium carbonate solution and extraction with ether. The ethereal solution is dried over sodium sulfate and the ether is removed by distillation. 40 g. of benzoyl tropine boiling at 185–187° C./5 mm. are obtained thereby.

50 g. of said benzoyl tropine are reacted and quaternized with octyl bromide in the same manner as described hereinabove in Example 2. The crude N-octyl benzoyl tropinium bromide is repeatedly recrystallized from isopropanol. The mother liquors are also worked up. The combined yield is 51 g. of N-octyl benzoyl tropinium bromide melting at 227° C. The yield amounts to about 60% of the theoretical yield.

Example 4.—N-octyl benzoyl tropinium bromide

70 g. of tropine (about 0.5 mol) are reacted and quaternized with 290 g. of octyl bromide (about 1.5 mol) as described in Examples 1 and 2. After repeated recrystallization from acetone, 130 g. of N-octyl tropinium bromide melting at 174–176° C. are obtained. The yield is 78% of the theoretical yield. Said compound is esterified by means of benzoyl bromide by heating the reaction mixture for a short period of time as described in Example 3 with respect to tropine. The excess acid bromide is removed by distillation in a vacuum and the residue is recrystallized from isopropanol. Melting point: 227° C. Yield: 43% of the theoretical yield.

Example 5.—N-octyl diphenyl hydroxy acetyl tropinium bromide

52 g. of benzilic acid ethyl ester (about 0.2 mol) are heated with 14.1 g. of tropine (0.1 mol) and 0.3 g. of metallic sodium in an oil bath at 125–130° C. at a vacuum of a water-jet vacuum pump for 30 hours. Thereby re-esterification takes place. After cooling, the reaction mixture is poured into dilute hydrochloric acid and is extracted several times with ether. The extracted hydrochloric acid solution is rendered alkaline by the addition of ammonia. Thereby, a light yellow oily mass precipitates which crystallizes when kept in a refrigerator. The crystals are filtered off, washed with water, dried, boiled with a small quantity of ether, and recrystallized from benzene with the addition of a small amount of decolorizing carbon. 29 g. of diphenyl hydroxy acetyl tropine melting at 144–148° C. are obtained. The yield amounts to 80% of the theoretical yield.

The resulting benzilic acid ester of tropine is quaternized by means of octyl bromide. 30 g. of said benzilic acid ester base (about 1/12 mol) and 45 g. of octyl bromide (about 1/4 mol) are heated in a mixture of 100 cc. of chloroform and 50 cc. of acetonitrile at 60° C. for 14 days. The oily crystalline mass amounting to 25 g. is repeatedly recrystallized from acetonitrile and from ethanol. The melting point of the recrystallized compound is 212–214° C.

Example 6.—N-octyl diphenyl ethoxy acetyl tropinium bromide

The benzilic acid ester of tropine obtained according to Example 5 is converted into diphenyl chloro acetyl tropine hydrochloride in the following manner: 26.5 g. of said benzilic acid ester base are gently heated in 270 cc. of absolute ethanol. The mixture is acidified with absolute ethanolic hydrochloric acid and is allowed to stand in a refrigerator, the mother liquor is concentrated by evaporation and the combined reaction products are worked up to yield 23 g. of the hydrochloride melting at 237–240° C. with decomposition. 16 cc. of thionylchloride are gradually added to 16 g. of said hydrochloride in 200 cc. of carbon tetrachloride. The mixture is heated to boiling under reflux for two hours. The solvent and excess of thionylchloride are removed by distillation, finally in a vacuum. The crystals are again triturated with a small amount of carbon tetrachloride. 15.3 g. of diphenyl chloro acetyl tropine hydrochloride, melting at 146° C. and sintering at 130° C., are obtained.

Said diphenyl chloro acetyl tropine hydrochloride can also be prepared without first having to prepare the hydrochloride of the benzilic acid ester. For this purpose, 100 g. of benzilic acid ester of tropine are boiled under reflux in 1500 cc. of carbon tetrachloride with 100 cc. of thionylchloride for two hours. On working up the reaction mixture, 117 g. of diphenyl chloro acetyl tropine hydrochloride melting at 142–146° C. are obtained.

The benzilic acid ethyl ether tropine ester is prepared by reacting said chloro acetyl compound with ethanol and calcium carbonate. For this purpose 117 g. of diphenyl chloro acetyl tropine hydrochloride are boiled under reflux in 1500 cc. of absolute ethanol with 60 g. of calcium carbonate for 24 hours. The reaction mixture is filtered, ethanol is removed by distillation, and the residue is distributed between sodium carbonate solution and ether. The ether solution is extracted by means of dilute hydrochloric acid until it becomes of acid reaction against Congo paper. The hydrochloric acid solution is evaporated to dryness on the water bath in a vacuum. 106 g. are obtained thereby. On recrystallization from acetone, 70 g. of diphenyl ethoxy acetyl tropine hydrochloride melting at 196–198° C. are obtained. The compound contains 1 mol of water of crystallization. Said water of crystallization can be removed by drying the compound in a drying pistol at 100° C. The resulting benzilic acid ethyl ether tropine ester hydrochloride is dissolved in ammonia and the ammoniacal solution is extracted with ether yielding the non-crystallizing base which is quaternized by means of octyl bromide. 17 g. of said base, 50 cc. of acetonitrile, and 26 g. of octyl bromide are allowed to stand at 20° C. for one month. 16 g. of a crude product are obtained. Said crude product is repeatedly recrystallized from acetonitrile and from acetone and yields pure N-octyl diphenyl ethoxy acetyl tropinium bromide melting at 216–218° C.

Example 7.—N-stereoisomer octyl atropinium bromide

28 g. of octyl nortropine base (about 0.1 mol) boiling at 168–172° C./0.8 mm., prepared synthetically by reacting nortropine with octyl bromide and liberating the free base, are converted into the corresponding hydrochloride. Said hydrochloride is heated on the water bath with 34 g. of acetyl tropic acid (about 1.5 mol) whereby moisture is carefully excluded. During said heating, the crystals dissolve and hydrochloric acid escapes. The reaction mixture is allowed to cool after heating for 50 minutes, ice water is added thereto, and the Congo-acid solution is exhaustively extracted with ether. The resulting reaction product is shaken for two days in dilute hydrochloric acid in order to split off the acetyl group. The mixture is again extracted with ether, treated with decolorizing carbon, and evaporated to dryness in a vacuum at room temperature. The brown crystals obtained thereby are repeatedly recrystallized from acetic acid ethyl ester. Octyl nortropine hydrochloride melting at 165–168° C. is obtained. The base produced therefrom is quaternized by means of methyl bromide and yields the N-stereoisomer octyl atropinium bromide melting at 185° C. The yield is 90% to 93% of the theoretical yield.

Example 8.—Xanthene-9-carboxylic acid ester of N-heptyl tropinium bromide

5 g. of xanthene carboxylic acid tropine ester hydrochloride (0.013 mol) are converted into the free base and are heated with 3.6 g. of heptyl bromide (0.02 mol) on the boiling water bath for 14 hours. The solid reaction product is triturated with ether, filtered off by suction, and recrystallized from isopropanol. Yield: 70% of the theoretical yield. Melting point: 216° C.

Using equimolecular amounts of other alkyl bromides in place of heptyl bromide and otherwise proceeding in the same manner as described hereinbefore in Example 8, yields the following compounds:

Alkyl bromide	Reaction product obtained	M. P., ° C.	Solvent
Octyl bromide	Xanthene-9-carboxylic acid ester of N-octyl tropinium bromide.	213	Isopropanol.
Nonyl bromide	Xanthene-9-carboxylic acid ester of N-nonyl tropinium bromide.	207	Acetone.
Decyl bromide	Xanthene-9-carboxylic acid ester of N-decyl tropinium bromide.	209	Acetone/ isopropanol.

In a similar manner as described hereinbefore in the examples there can be produced the following and other quaternary tropeine compounds exhibiting the desired physiological properties and representing valuable spasmolytic agents. Said compounds correspond to the formula given in column 1 of this specification and differ

from each other merely by the substituents R, R_1, and X as indicated hereinafter:

No.	Tropeine compound with substituents			M. P., ° C.	Recrystallized from—
	R	R_1	X		
9	Heptyl	Diphenyl acetyl	Br	209–210	Acetone.
10	β-cyclohexyl ethyl	Racemic tropic acid radical	Br	198–200	Isopropanol.
11	Heptyl	Racemic mandelic acid radical	Br	160–163	Isopropanol and ethanol.
12	Nonyl	do	Br	141–144	Acetone and ethanol.
13	Undecyl	do	Br	106–108	Acetone.
14	Heptyl	Benzoyl	Br	229	Isopropanol.
15	Nonyl	do	Br	230	Do.
16	Decyl	do	Br	224	Do.
17	Undecyl	do	Br	224–225	Do.
18	Octyl	Diphenyl acetyl	Br	216	Ethanol and ether.
19	Nonyl	do	Br	203–205	Acetone.
20	Decyl	do	Br	198–200	Do.
21	Undecyl	do	Br	218	Do.
22	Heptyl	Diphenyl hydroxy acetyl	Br	218–220	Isopropanol.
23	Nonyl	do	Br	196–198	Acetonitrile.
24	Decyl	do	Br	196–197	Isopropanol.
24a	Octyl	Phenyl-cinnamoyl	Br	223	Do.
25	do	Salicyl	Br	236–238	Do.
26	do	N-phenyl amino acetyl	Br	178	Do.
27	do	2-furoyl	Br	[1] 240–241	Acetonitrile.
28	do	Nicotinoyl	Br	232	Isopropanol.
29	do	Isonicotinoyl	Br	238	Do.
30	do	2,6-dichloro isonicotinoyl	Br	234	Ethanol.
31	do	Racemic tropic acid radical	Cl	120–122	Acetone+methanol.
32	do	do	I	143–145	Isopropanol.

[1] Decomp.

When proceeding according to Example 7 and quaternizing N-heptyl nortropine benzilic acid ester with methyl bromide, the N-stereoisomer compound corresponding to the compound No. 22 of the above given table is obtained. Said N-stereoisomer compound melts, after recrystallization from acetonitrile at 211° C. and has one mol of water of crystallization.

The term "alkyl radical with 7 to 11 carbon atoms" as used in the specification and in the claims annexed hereto comprises not only alkyl radicals, with an open chain but also cycloalkyl radicals as is evident from the examples given hereinbefore.

Acylation of the hydroxyl group of the tropeine compounds can be effected not only by means of the acid chlorides but also by means of other reactive acid compounds such as the acid anhydrides, esters and even the acids themselves.

Examples of such reactions are as follows:

(1) 39 g. (=0.33 mol) of isonicotinic acid ethylester are refluxed for 30 hours with 23 g. (=0.165 mol) tropine and 0.5 g. metallic sodium at 120–125° C. at 12 mm., whereby the alcohol produced is distilled off. The residue is dissolved in dilute hydrochloric acid and washed with ether.

The acid solution is made alkaline with caustic soda solution and extracted with chloroform. After evaporation of the chloroform the residue is distilled at 190–192° C./2 mm. 38.5 g. of isonicotinic acid ester of tropine are thereby obtained. The M. P. of the hydrochloride is 256° C.

In same manner are produced:

Furoic acid ester of tropine. B. P. 144–151° C./0.5 mm. Yield 78%.

α-Phenyl cinnamic acid tropine ester. Yield 48.5%. M. P. of the hydrochloride 248–250° C.

Nicotinic acid tropine ester, B. P. 155–158° C./1 mm. Yield 72%.

N-phenylaminoacetic acid tropine ester, B. P. 170° C./0.01 mm. Yield 47%.

(2) 0.1 mol (=2 g.) 2,6 dichlorisonicotinoyl chloride and 0.05 mol tropine are heated together for 15 minutes at 200° C. and after cooling shaken up with ether and diluted hydrochloric acid. The acid solution is made alkaline with ammonia. An oil separates which crystallises rapidly.

The crystals (3.4 g) are filtered off and recrystallized from acetone. Yield 3.1 g.—19.7% of theoretical yield. The dichlorisonicotinic acid ester of tropine melts at 97–98° C. M. P. of the hydrochloride=255° C.

It is understood that in place of the quaternizing agents used in the preceding examples, there can be employed equimolecular amounts of other quaternizing agents while the procedure otherwise is the same as described in said examples. Such other quaternizing agents are, for instance:

p-Toluene sulfonic acid octyl ester
p-Toluene sulfonic acid heptyl ester
p-Toluene sulfonic acid nonyl ester
p-Toluene sulfonic acid decyl ester
Di-heptyl sulfate
Di-octyl sulfate
2-methyl-3-methyl pentyl bromide
2-dimethyl pentyl bromide
2,2,4-trimethyl pentyl bromide
β-Δ_2-cyclohexenyl ethyl bromide
Δ_3-heptenyl bromide
4-ethyl-Δ_2-hexenyl bromide
4-ethenyl heptyl bromide
2-methyl-6-methyl octyl bromide (myrcene bromide)

In place of the aromatic and heterocyclic acids used for esterifying the hydroxyl group in the new tropeine compounds as mentioned in the preceding examples, there can be employed equimolecular amounts of other aromatic or heterocyclic acids while otherwise the procedure is the same as described in said examples. Acids which can be used for this purpose are, for instance, the following:

α-Phenoxy phenyl acetic acid
α-Thiophen phenyl acetic acid
α-Thiophen phenyl glycolic acid
α-Naphthyl acetic acid
Fluorene-9-carboxylic acid
o-Benzoyl benzoic acid
Cyclohexyl phenyl acetic acid
Cyclohexyl phenyl glycolic acid

Of course, many other changes in variations in the starting materials and the quaternizing and esterifying agents, the reaction conditions, reaction temperature and duration, the methods of working up the reaction products and of purifying the resulting quaternary tropeine compounds, and the like may be made by those skilled in the art in accordance with the principles set forth herein and in the claims annexed hereto.

The new quaternary tropeine compounds are administered orally, subcutaneously, intramuscularly, intravenously, or topically. The daily dose is between 3 mg. and about 10 mg. depending on the route of administration. The preferred single dose for adults is 10 mg. and

the maximum single dose 50 mg. when administered orally, and 3 mg. to 5 mg. when administered parenterally.

The new compounds according to the present invention are employed in therapy with great advantage in the treatment of stomach and duodenal ulcers, spasms of the stomach and intestine, of the biliary duct and urinary tract and of spasms of the uterus.

For oral administration the compounds are preferably employed in the form of tablets, pills, dragees, powders, capsules, solutions, emulsions, suspensions, dispersions, or in any other suitable form. They are preferably not used as such but are diluted with suitable diluting agents, thus allowing better and more economical use to be made thereof.

In the case of powders, intimate and uniform dispersion of the active compound throughout the diluting agent is of importance. Such a fine dispersion can be achieved, for instance, by mixing and milling the new compounds with a solid, pulverulent extending agent to the desired degree of fineness or by impregnating the already milled, finely powdered, solid carrier with a solution of the active compound in water or a water miscible solvent and then removing the water or solvent.

As solid carriers which are suitable for the manufacture of pulverulent preparations, various inert pulverulent distributing agents, as they are conventionally used in the pharmaceutical industry, may be employed.

When preparing tablets, pills, dragees, powders, and the like, the commonly used diluting agents, binders, lubricants, and the like, are employed, such as sugar, lactose, talcum, starch, pectin, and as binders, gelatin,

gum arabic, methyl cellulose, yeast extract, agar, tragacanth, and others.

Solutions for parenteral administration are obtained, for instance, by dissolving the new compounds in distilled water or physiological salt solution.

We claim:

1. N-octyl atropinium bromide.
2. N-octyl atropinium chloride.
3. N-octyl atropinium iodide.
4. N-alkyl atropinium bromide, its alkyl radical having 7 to 11 carbon atoms.
5. N-alkyl atropinium halogenide selected from the group consisting of the chloride, bromide, and iodide, its alkyl radical having 7 to 11 carbon atoms.
6. In a process of producing N-octyl atropinium bromide, the steps comprising heating atropine and an excess of octyl bromide in a mixture of acetonitrile and methanol at about 60° C. until quaternization is completed, evaporating the reaction mixture to dryness, and triturating the evaporation residue with acetone to cause N-octyl atropinium bromide to crystallize.

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