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NEW QUATERNARY SALTS

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The present invention concerns improvements in and relating to quaternary salts and solutions thereof. It is particularly concerned with novel quaternary salts of tropine esters and pseudo-tropine esters and with their preparation and use as hypotensive agents.

It is often most desirable in surgical operations to produce controlled hypotension. This can be done by the intravenous infusion of substances which are termed hypotensive agents, one example of which is hexamethonium dibromide.

It is an object of the present invention to produce new quaternary salts having hypotensive activity.

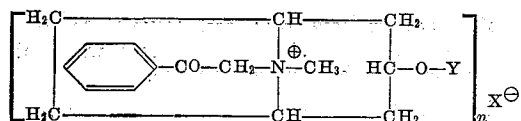
It is another object of the invention to produce solutions which can be administered to patients by intravenous infusion in order to reduce blood pressure during surgical operations.

It is a further object to provide quaternary salts of tropine esters and pseudo-tropine esters which have valuable therapeutic properties.

With these and other objects in view the present invention provides phenacyl quaternary salts of tropine esters. The invention further provides phenacyl quaternary salts of pseudo-tropine esters.

As is known, the phenacyl group is $-\text{CH}_2-\text{CO}-\text{C}_6\text{H}_5$, the benzene ring being otherwise unsubstituted.

These quaternary salts have the general formula:



wherein X represents the anion of an acid, especially an inorganic acid, n represents the valency of the anion X, and Y represents an organic carboxylic acyl group.

These quaternary salts may be termed phenacyl acyltropinium salts and phenacyl acylpseudo-tropinium salts, respectively.

As is known, tropine and pseudo-tropine are trans-cis-isomers and neither they nor their quaternary salts can be differentiated by plane formulae. Tropine is generally considered to be the trans form.

The preferred quaternary salts are halides, especially those in which the halogen has an atomic weight greater than 19, i. e. the chlorides, bromides and iodides.

The preferred tropine ester is homatropine, i. e. the ester of mandelic acid (phenylglycolic acid).

Phenacyl acyltropinium halides can be made by reacting phenacyl halides with organic carboxylic esters of tropine. Similarly, phenacyl acylpseudo-tropinium halides can be made by reacting phenacyl halides with organic carboxylic esters of pseudo-tropine. The reaction is most suitably carried out in an inert solvent, preferably with the aid of heat.

From the resulting phenacyl acyltropinium halides or phenacyl acylpseudo-tropinium halides, preferably the chlorides, quaternary salts of other acids can be made. A

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number of general methods are available for this, three of which are as follows:

(a) Double decomposition of an aqueous or aqueous alcoholic solution of a quaternary chloride with a soluble alkali metal salt such as sodium bromide or iodide.

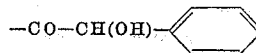
(b) Metathesis of a quaternary halide with, for example, a silver salt, preferably in alcohol.

(c) Reaction of an alcoholic solution of a quaternary halide with an acid in presence of an organic epoxide.

This method is described by O. Sackur in Bull. Soc. Chim., 1952, 796.

The quaternary salts of the present invention have useful therapeutic properties. When injected into the human blood stream they exhibit to a very useful degree the power to block transmission of nervous impulses across sympathetic ganglia and cause a fall in blood pressure. Some at least of the quaternary salts, especially phenacyl homatropinium halides, exhibit a hypotensive action which exceeds that of hexamethonium dibromide, and are in addition of low toxicity. The duration of action is much less than that of hexamethonium dibromide. The hypotension produced can readily be antagonised, when required, by adrenaline or methedrine. The quaternary salts are thus useful for producing controlled hypotension, for example during surgical operations.

As already stated, the preferred phenacyl quaternary salts are those of homatropine, wherein Y is



Phenacyl quaternary salts of other tropine and pseudo-tropine esters also have useful hypotensive action. Their potency in this respect can be compared by measuring the reduction in the extent of contraction of the nictitating membrane of the cat in response to the stimulation of the pre-ganglionic fibres of the cervical sympathetic nerve. When measured in this way the relative potencies of the phenacyl bromide quaternary salts of seven typical tropine esters were as follows:

Acyl radical=Y:	Potency
Mandelyl, $-\text{CO}-\text{CH}(\text{OH})\text{C}_6\text{H}_5$ -----	100
Phenylacetyl, $-\text{CO}-\text{CH}_2-\text{C}_6\text{H}_5$ -----	40
Benzoyl, $-\text{CO}-\text{C}_6\text{H}_5$ -----	30
Tropyl, $-\text{CO}-\text{CH}(\text{CH}_2\text{OH})\text{C}_6\text{H}_5$ -----	25
Acetyl, $-\text{CO}-\text{CH}_3$ -----	12
Diphenylacetyl, $-\text{CO}-\text{CH}(\text{C}_6\text{H}_5)_2$ -----	10
Diethylacetyl, $-\text{CO}-\text{CH}(\text{C}_2\text{H}_5)_2$ -----	30

By way of comparison the potency of hexamethonium dibromide was 10.

The phenacyl quaternary salts of pseudo-tropine esters appear, in general, to have a lower hypotensive action than the corresponding phenacyl quaternary salts of tropine esters. Nevertheless, many of them have a very useful potency when measured in the above way. The relative potencies of the phenacyl chloride quaternary salts of two typical pseudo-tropine esters and of the corresponding tropine esters were as follows:

Ester quaternised:	Potency
Phenylacetyl tropine -----	40
Phenylacetyl-pseudo-tropine -----	20
Isobutyryl tropine -----	14
Isobutyryl-pseudo-tropine -----	7

By way of comparison, the potency of hexamethonium dibromide was 10.

As regards the preferred quaternary salts, phenacyl homatropinium chloride, bromide and iodide, the potencies of these three salts are the same but their solubility

in water is very different. The solubility (weight by volume at 20° C. in water) is

Chloride -----	63.25
Bromide -----	1.59
Iodide -----	0.31

The chloride is therefore generally more convenient for use as a hypotensive agent in surgical operations.

In making the phenacyl acyltropinium halides and the phenacyl acyl-pseudo-tropinium halides, it is preferred to use inert solvents of a polar nature, such as ketones. Phenacyl halides are highly reactive and it is therefore not essential to heat the reaction mixture as a good yield may be obtained by allowing the mixture to stand for a sufficient period of time at room temperature. If the reaction is carried out at room temperature in the case of homatropine however it is advisable to use more inert solvent as otherwise there would be danger of some of the base crystallizing out before reacting. This difficulty does not arise when esters of tropine such as benzoyl or phenylacetyl tropines which are more soluble in cold inert solvents such as acetone are used. It is preferred, however, to heat the reactants as the formation of quaternary salts is then rapid.

The invention will be illustrated by, but is not limited to, the following examples.

Example 1.—Phenacyl homatropinium chloride

330 gm. (1.2 M) of homatropine were dissolved in 1 litre of dry methylethylketone and gently refluxed on a water-bath during the gradual addition of a solution of 204 gm. (1.32 M) re-distilled phenacyl chloride in 200 ml. of the same solvent. After 10–15 minutes 1 gm. of previously prepared homatropine phenacyl chloride was added to avoid formation of a supersaturated solution of the quaternary compound. Reflux was continued for 9 hours, then the thick suspension was allowed to cool, filtered and washed with 200 ml. methylethylketone to yield 490 gm. (95%) slightly creamy solid, M. P. 188–191° C.

For purification the crude quaternary salt was dissolved in hot ethyl alcohol (2 ml. per gm.) and warm dry acetone (8 ml. per gm.) was stirred into the clear filtrate. On cooling, 382 gm. (78% recovery) of a pure white powder, M. P. 195–197° C., were obtained, in which the ionisable chlorine assayed at 99.7% of the theoretical value.

By the procedure given in the foregoing example but substituting for the homatropine equivalent amounts of other tropine esters, corresponding phenacyl quaternary chlorides are obtained in good yield. The melting points of some of these are given below.

Ester employed:	M. P. of quaternary salt, °C.
Phenylacetyltropine -----	196
Atropine (tropyiltropine)-----	187–188
Acetyltropine -----	199–200
Isobutyryltropine -----	200

Example 2.—Phenacyl homatropinium bromide

30.0 gms. (0.109 M) of homatropine were dissolved in 150 mls. of warm, dry acetone. After cooling, a solution of 23.9 gms. (0.12 M) of phenacyl bromide in 150 mls. of dry acetone was added rapidly, and the reaction mixture was gently refluxed on a steam bath. A precipitate appeared after 10 minutes and had reached substantial proportions after 30 minutes' heating. After refluxing for 4 hours in all and standing overnight, the precipitate was filtered, washed with dry acetone and then ether, and finally dried at 100° C. for 1 hour. This gave a material melting at 193–5° C. (dec.) and weighing 45.7 gms. (88.8% theory).

Recrystallisation was easily carried out by suspending in 6 volumes of boiling ethyl alcohol and slowly adding sufficient water to give a clear solution. The purified material obtained on cooling consisted of a white micro-crystalline powder weighing 42.6 gms. (81% theory)

and melting at 198.5° C.–199.5° C. (uncorr.). As assay for ionic bromine gave a figure of 16.85% against 16.86% (calc.).

By the procedure given in the foregoing example but substituting for the homatropine equivalent amounts of other tropine esters, corresponding phenacyl quaternary bromides are obtained in good yield. The melting points of some of these are given below.

Ester employed:	M. P. of quaternary salt, °C.
Phenylacetyltropine -----	199–200
Benzoyltropine -----	218
Atropine (tropyiltropine)-----	185–186
Diphenylacetyltropine -----	209–210
Diethylacetyltropine -----	199–200

Example 3.—Phenacyl homatropinium iodide

Phenacyl homatropinium chloride (8.60 gm.) was dissolved in 30 ml. warm ethyl alcohol, and sodium iodide (3.00 gm.) in 20 ml. alcohol was added rapidly with shaking. After standing 10 minutes at room temperature 200 ml. water was added and the crystalline solid was filtered, washed with water and dried, giving 9.28 gm. (89% yield) of the quaternary iodide, M. P. 186–7° C. (dec.). Recrystallisation from ethanol/ethyl acetate gave an 80% recovery of solid M. P. 190° C. (dec.), with an iodide content 24.39% (found) as compared with 24.35% (calc.).

If the alcohol is omitted a sticky precipitate is obtained.

Phenacyl homatropinium iodide can also be made by the reaction of phenacyl iodide with homatropine according to the procedure of Examples 1 and 2.

Example 4.—Phenacyl homatropinium sulphate

Phenacyl homatropinium chloride (8.60 gm.; 0.02 M) dissolved in 70 ml. ethanol was stirred during the addition of concentrated sulphuric acid (0.98 gm.; 0.01 M). Then ethylene oxide (3.4 ml.; C. 0.1 M) was added dropwise with slight cooling to keep below 20°. The flask was then allowed to stand at room temperature until a few drops withdrawn and diluted with distilled water gave no reaction for chloride ion. This point was reached within an hour. The total product when precipitated with ether weighed 8.50 gm. and had M. P. 206–8° (96%). One recrystallisation from isopropanol and ethyl acetate gave 6.11 gm. (69%), M. P. 215 dec. Sulphur content 3.60% as compared with a theoretical 3.66% for the neutral sulphate.

Example 5.—Phenacyl homatropinium nitrate

Phenacyl homatropinium chloride (8.60 gm.; 0.02 M) was dissolved in 150 ml. alcohol and a solution of silver nitrate (3.40 gm.; 0.02 M) in 50 ml. ethanol and 4 ml. water was added with stirring. After standing a short time in the dark to allow coagulation the mixture was filtered. The volume of the filtrate was reduced to about one-third and hot ethyl acetate was added almost to the point of a permanent turbidity. After standing overnight only a small deposition of crystals had occurred. These were removed and used to seed the further amount of material obtained by stirring in about twice the bulk of ethyl acetate. Two crystallisations of the crude product from ethyl alcohol/ethyl acetate yielded material M. P. 140–2° in 50% yield and free from chloride ion.

Example 6.—Phenacyl phenylacetyl-pseudo-tropinium chloride

Phenylacetyl-pseudo-tropine (5.18 gm.; 0.02 M) was dissolved, together with phenacyl chloride (3.40 gm.; 0.022 M) in 20 ml. methyl ethyl ketone and refluxed for 6 hours. After then standing at room temperature for one day very little solid had appeared. A little dry ether was therefore added and the flask was well shaken. After a short interval further dry ether was added until no more crystalline solid separated. The yield of material at this stage was 4.63 gm. (56%). One crys-

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tallization from acetone/ether gave 3.56 gm. (44%) white crystalline quaternary, M. P. 174-5° C., chlorine content 8.38% against a theoretical value of 8.58%.

By the procedure given in the foregoing example but substituting for the phenylacetyl-pseudo-tropine equivalent amounts of other pseudo-tropine esters, corresponding phenacyl quaternary chlorides are obtained in good yield. The melting points of some of these are given below.

Ester employed:

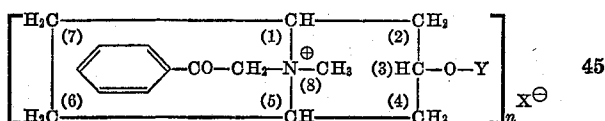
Benzoyl-pseudo-tropine	207
Isobutyryl-pseudo-tropine	173-174

It is convenient to employ the quaternary salts of the present invention as hypotensive agents in the form of simple aqueous solutions. It is desirable that these solutions should be kept out of strong daylight; for example, they should be contained in amber coloured ampoules and preferably stored in the dark. Phenacyl homatropinium chloride, for example, is conveniently supplied in ampoules containing a 5% weight by volume solution. This is intended to be diluted twenty to one hundred times for use in controlled intravenous infusion. The 5% solution is sensitive to direct sunlight, decomposition occurring with formation of a deposit. It is stable in the dark and does not readily decompose in diffused daylight.

In using phenacyl homatropinium chloride for reduction of blood pressure during a surgical operation an aqueous solution containing from 0.5 to 2.5 mg. per ml. is administered as an intravenous drip. Hypotension is achieved in a space of two to ten minutes depending on the rate of administration. The desired degree of hypotension can be maintained for prolonged periods by continued administration at a slow rate, and recovery is rapid. Operations have been carried out using total quantities varying from 50-500 mgms. The action can readily be reversed by the administration of, for example, Methedrine, 2 mgms.

We claim:

1. A quaternary salt of the general formula:



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wherein X represents the anion of an acid selected from the group consisting of hydrohalic acids in which the halogen has an atomic weight greater than 19, sulphuric acid and nitric acid, n represents the valency of the anion X, and Y represents the acyl radical of an organic carboxylic acid selected from the group consisting of mandelic, phenylacetic, benzoic, tropic, acetic, diphenylacetic, diethylacetic and isobutyric acids.

2. An N-phenacyl homatropinium halide of which the halogen has an atomic weight greater than 19.

3. N-phenacyl homatropinium chloride.

4. N-phenacyl homatropinium sulphate.

5. N-phenacyl homatropinium nitrate.

6. An N-phenacyl 3-benzoyl-pseudo-tropinium halide of which the halogen has an atomic weight greater than 19.

7. The process of preparing an N-phenacyl 3-acyl-tropinium halide which comprises reacting a phenacyl halide in which the halogen has an atomic weight greater than 19 with a tropine ester of an organic carboxylic acid selected from the group consisting of mandelic, phenylacetic, benzoic, tropic, acetic, diphenylacetic, diethylacetic and isobutyric acids.

8. The process as claimed in claim 7 carried out in presence of an inert solvent for the reagents.

9. The process as claimed in claim 7 carried out in presence of a polar solvent.

10. The process as claimed in claim 7 carried out in presence of a ketone as polar solvent.

11. The process as claimed in claim 7 in which heating is employed.

12. A liquid for intravenous infusion to produce hypotension consisting essentially of a solution in water of 0.5 to 2.5 mgms. per ml. of N-phenacyl homatropinium chloride.

No references cited.