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3,090,725

PHOSPHORYLATED QUATERNARY AMMONIUM COMPOUNDS OF IMPROVED ORAL ABSORPTION

Frederick Charles Copp, Arthur McCoubrey, and John Evelyn Warner Billingham, London, England, assignors to Burroughs Wellcome & Co. (U.S.A.) Inc., Tuckahoe, N.Y., a corporation of New York
 No Drawing. Filed Feb. 14, 1961, Ser. No. 39,126
 Claims priority, application Great Britain Feb. 29, 1960
 6 Claims. (Cl. 167—55)

The present invention relates to pharmaceutical formulations, to the method by which the formulations are prepared, and to pharmaceutical compositions containing the formulations.

A limiting factor in the pharmaceutical application of quaternary ammonium compounds which have a potent systemic pharmacological or chemotherapeutic action upon parenteral administration to man or animals or both and whose cations contain a hydroxyalkyl group is that these compounds are poorly and erratically absorbed from the gastro-intestinal tract, and are therefore not particularly suitable for oral administration. This limitation has resulted in the potent therapeutic value of these compounds not being fully realized in medical practice.

It has been found that pharmaceutical formulations having a high degree of absorption upon oral administration are obtained by phosphorylation of the said quaternary ammonium compounds. It has also been found that pharmaceutical formulations having a high degree of regular absorption upon oral administration, and thereby giving a high degree of uniform medication, are obtained by phosphorylation of the said quaternary ammonium compounds.

According to the present invention in one aspect, there is provided a method of improving the absorption upon oral administration of a quaternary ammonium compound which is poorly absorbed from the gastro-intestinal tract but has a potent systemic pharmacological or chemotherapeutic action upon parenteral administration and whose cation contains one or more hydroxyalkyl groups, which method comprises the phosphorylation of the compound to its phosphate ester.

According to the present invention in another aspect, there are provided the phosphate esters of quaternary ammonium compounds, which are poorly absorbed from the gastro-intestinal tract but have a potent systemic pharmacological or chemotherapeutic action upon parenteral administration and whose cations contain one or more hydroxyalkyl groups.

The preferred phosphate esters are those of quaternary ammonium compounds whose cations contain one or more 2-hydroxyethyl groups. Further, the preferred phosphate esters contain one phosphate group, but esters which contain two or more phosphate groups are also within the scope of the present invention.

It will be understood that the phosphate esters exist as internal salts. Further, it will be understood that the mono-phosphate esters contain one cation equivalent and the poly-phosphate esters contain an appropriate number of cation equivalent, for example, a di-phosphate ester contains three cation equivalents; and that each of these cation equivalents is preferably pharmaceutically and therapeutically acceptable, for example is a hydrogen or alkali metal atom, or an equivalent of a calcium or magnesium atom, or an ammonia group.

As used in this specification the term "potent systemic pharmacological or chemotherapeutic action" is to be understood as meaning a level of systemic therapeutic activity which is of value in medical practice. Thus, "a quaternary ammonium compound which has a potent systemic pharmacological or chemotherapeutic action

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upon parenteral administration" is one which it would be valuable to administer in medical practice. Examples of such quaternary ammonium compounds are those which have a systemic anti-adrenergic (that is, adrenergic neurone blocking or specific sympatholytic), ganglion blocking or spasmolytic action.

(i) Anti-adrenergic compounds have a specific sympatholytic action due to depression of the adrenergic nerve mechanism and not due to a direct antagonism of adrenaline and its congeners; they are therefore useful in the treatment of hypertension. Examples of quaternary ammonium compounds which have a systemic anti-adrenergic action are described in the complete specifications of British patent applications Nos. 12,354/58, 18,963/58, now Patent No. 881,265, 21,117/58, 4,082/60 and 4,850/60, and in the provisional specification of British patent application No. 22,144/60. Specific examples of cations of such quaternary ammonium compounds are:

N-benzyl-N-2-hydroxyethyl-N,N-dimethylammonium;
 N-benzyl-N-ethyl-N-2-hydroxyethyl-N-methylammonium;
 N-benzyl - N,N-di-(2-hydroxyethyl) - N-methylammonium;
 N-o-bromobenzyl - N,N-di-(2-hydroxyethyl) - N-methylammonium;
 N-o-bromobenzyl - N-2-hydroxyethyl-N,N-dimethyl - ammonium;
 N-o-chlorobenzyl-N,N-di-(2-hydroxyethyl)-N-methylammonium;
 N-o-chlorobenzyl - N-2-hydroxyethyl - N,N - dimethylammonium;
 N-o-fluorobenzyl - N,N-di-(2-hydroxyethyl)-N-methylammonium;
 N-o-fluorobenzyl-N-2 - hydroxyethyl-N,N-dimethylammonium;
 N-o-iodobenzyl - N-2-hydroxyethyl - N,N-dimethylammonium;
 N-o-methylbenzyl - N,N-di-(2-hydroxyethyl) - N-methylammonium;
 N-o-methylbenzyl - N-2-hydroxyethyl - N,N-dimethylammonium;
 N-o-nitrobenzyl - N,N-di-(2-hydroxyethyl)-N-methylammonium;
 N-o-bromobenzyl-N-2-hydroxyethylpyrrolidinium;
 N-cyclohexylmethyl - N-2-hydroxyethyl-N,N-dimethylammonium;
 N-(bicyclo - (2,2,1)-hept-2-yl)methyl - N-2-hydroxyethyl-N,N-dimethylammonium;
 N-2-hydroxyethyl - N-methyl-1',2',3',4'-tetrahydroisoquinolinium;
 N-2-hydroxyethyl-N - methyl-8-bromo - 1',2',3',4'-tetrahydroisoquinolinium;
 N - 2-(4 - benzoyl - 2,6 - dimethylphenoxy)ethyl - N,N-di-(2-hydroxyethyl)-N-methylammonium;
 N-2-(4-benzoyl-2,6-dimethylphenoxy)ethyl-N-2-hydroxyethyl-N,N-dimethylammonium; and
 N-2-(2-bromo-4-methoxyphenoxy)ethyl - N - 2 - hydroxyethyl-N,N-dimethylammonium.

The preferred quaternary ammonium compounds which have a systemic anti-adrenergic action contain a benzylammonium cation, optionally carrying an ortho-substituent.

(ii) Ganglion blocking compounds block transmission in the ganglia of the autonomic nervous system, resulting in a lowering of vasomotor tone and a consequent fall in blood pressure; they are therefore useful in the treatment of hypertension. Specific examples of cations of quaternary ammonium compounds which have a ganglion blocking action are: Hexamethylene-1,6-bis-(N-2-hydroxyethyl-N,N-dimethylammonium) and 3-hydroxypentamethylene-1,5-bis-(N-methylpyrrolidinium).

(iii) Spasmolytic compounds relieve the spasms of smooth muscles caused, for example, by exaggerated impulses from the parasympathetic nervous system, and by

stimulation from chemical changes in the surrounding tissues; they are therefore of therapeutic value. Specific examples of cations of quaternary ammonium compounds which have a spasmolytic action are: N'-(o-chlorobenzhydryl) - N - methyl-N-2-hydroxyethylpiperazinium and N - (3-cyclohexyl-3-hydroxy-3-phenylpropyl)-N-(2-hydroxyethyl)-pyrrolidinium.

According to the present invention in a further aspect, the phosphate esters of quaternary ammonium compounds which are poorly absorbed from the gastro-intestinal tract but have a potent systemic pharmacological or chemotherapeutic action upon parenteral administration and whose cations contain one or more hydroxyalkyl groups, are prepared by the hydrolysis or hydrogenolysis of an O,O-X¹,X²-phosphate ester of the quaternary ammonium cation, wherein X¹ and X² are each a labile group, such as a phenyl, benzyl, allyl, 1-alkoxyvinyl or 2-cyanoethyl group. The hydrolysis is carried out under mild conditions, and the hydrogenolysis in the presence of a catalyst such as platinum oxide or palladium. The O,O-X¹,X²-phosphate esters are prepared by phosphorylation of the quaternary ammonium cation with a phosphoryl halide such as phosphorochloridate, or by quaternisation of a tertiary amine containing the groups desired in the quaternary ammonium cation, other than the desired hydroxyalkyl group, with an O,O-X¹,X²-O-Y-phosphate, wherein X¹ and X² are as defined above and Y is an alkyl group containing a reactive atom or group.

According to the present invention in a yet further aspect, the phosphate esters of quaternary ammonium compounds which are poorly absorbed from the gastro-intestinal tract but have a potent systemic pharmacological or chemotherapeutic action upon parenteral administration and whose cations contain one or more hydroxyalkyl groups, are prepared by the reaction of the quaternary ammonium compound with concentrated phosphoric acid and phosphoric pentoxide. The acid is preferably in excess, and the reaction mixture is preferably warmed and under a partial vacuum.

The phosphate esters prepared by the above described methods of preparation may be converted by double decomposition, for example in solution or on an ion exchange column, into esters containing different cation groups. This may be particularly desirable if an ester which is not therapeutically acceptable, for example one wherein barium is the cation, is first prepared.

According to the present invention in two yet further aspects, there are provided a pharmaceutical composition which comprises a phosphate ester of a quaternary ammonium compound which is poorly absorbed from the gastro-intestinal tract but has a potent systemic pharmacological or chemotherapeutic action upon parenteral administration and whose cation contains one or more hydroxyalkyl groups, and a pharmaceutically acceptable carrier therefor; and the method of making the pharmaceutical composition by inclusion of the phosphate ester with the acceptable carrier. The pharmaceutical composition is preferably administered orally, but a composition which is administered parenterally also falls within the scope of the term "pharmaceutical composition." For oral administration, fine powders or granules of the ester may contain diluents and dispersing and surface active agents, and may be presented in a draft in water or in a syrup; in capsules or cachets in the dry state or in a non-aqueous suspension, when a suspending agent may be included; in tablets, when binders and lubricants may be included; or in a suspension in water or a syrup or an oil, or in a water/oil emulsion, when flavouring, preserving, suspending, thickening and emulsifying agents may be included; the granules or the tablets may be coated. For parenteral administration, the ester may be presented in aqueous injection solutions which may contain antioxidants, buffers, bacteriostats, agents which solubilise a relatively insoluble ester, and solutes which render the ester isotonic with the blood; or in solutions or suspen-

sions, which are non-aqueous if the ester is affected by water; extemporaneous injection solutions may be prepared from sterile pills, granules or tablets which may contain diluents, dispersing and surface active agents, binder and lubricants; the injection solutions or suspensions may be presented in unit dose ampoules or multi-dose containers. The preferred form of pharmaceutical composition is tablets.

The effective dose range of the phosphate ester to be administered depends on a number of variable factors. Thus, it will depend on the toxicity and the mode and frequency of administration of the particular ester. In particular, however, it will depend on the activity of the quaternary ammonium compound which is poorly absorbed from the gastro-intestinal tract but has a potent systemic pharmacological or chemotherapeutic action upon parenteral administration and whose cation contains one or more hydroxyalkyl groups, because the therapeutic activity resides in the quaternary ammonium cation and the phosphorylation only improves the absorption of the quaternary ammonium compound upon oral administration.

According to the present invention in a yet further aspect, there is provided a process for the treatment of hypertension which comprises the administration of a phosphate ester of a quaternary ammonium compound which is poorly absorbed from the gastro-intestinal tract but has a potent systemic anti-adrenergic or ganglion blocking action upon parenteral administration and whose cation contains one or more hydroxyalkyl groups.

According to the present invention in a yet further aspect, there is provided a process for the treatment of spasms of smooth muscle which comprises the administration of a phosphate ester of a quaternary ammonium compound which is poorly absorbed from the gastro-intestinal tract but has a potent systemic spasmolytic action upon parenteral administration and whose cation contains one or more hydroxyalkyl groups.

The invention, whose scope is in no way limited thereby but is fully described herein, will now be described by reference to the following examples, in which all temperatures are given in degrees centigrade.

Example 1

N-o-chlorobenzyl-N,N-dimethyl - N - 2 - hydroxyethyl-ammonium iodide (5 g.) was suspended in 90% phosphoric acid (15 g.) and heated at 70° for 3 hours under reduced pressure with an air leak to remove hydrogen iodide. Phosphorus pentoxide (4 g.) was added in small portions with cooling, and the heating then continued under reduced pressure for 2½ hours. The mixture was poured into water (50 ml.) and a hot concentrated solution of barium hydroxide added with cooling until the mixture was just alkaline. The barium phosphate was filtered off and washed. The filtrate was made slightly acid by 5 N-sulphuric acid and the barium sulphate centrifuged down. The supernatant was evaporated under reduced pressure and the residue dissolved in alcohol, blacked, filtered and evaporated to dryness. The residue was crystallised from alcohol to give N-o-chlorobenzyl-N,N-dimethyl - N - 2 - phosphatoethylammonium betaine, melting point 221°.

Example 2

N-o-bromobenzyl-N,N-dimethyl - N - 2 - hydroxyethyl-ammonium iodide was converted to N-o-bromobenzyl-N,N-dimethyl-N-2-phosphatoethyl ammonium betaine, melting point 209-210°, by methods analogous to those described in Example 1 and crystallised from acetone-alcohol.

Example 3

N-o-methylbenzyl-N,N-dimethyl - N - 2 - hydroxyethyl-ammonium iodide was converted to N-o-methylbenzyl-N,N-dimethyl-N-2-phosphatoethylammonium betaine, melt-

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ing point 209°, by methods analogous to those in Example 1 and crystallised from acetone-alcohol.

Example 4

N - o - chlorobenzyl - N - methyl-N,N-di-(2-hydroxyethyl)ammonium chloride was converted to N-o-chlorobenzyl - N - methyl-N,N-di-(2-phosphatoethyl)ammonium betaine, melting point 218–219°, by methods analogous to those described in Example 1 and crystallised from ethanol.

Example 5

N - o - bromobenzyl - N - 2 - hydroxyethylpyrrolidinium bromide was converted to N - o - bromobenzyl-N-2-phosphatoethylpyrrolidinium betaine by methods analogous to those described in Example 1. The phosphobetaine was an extremely deliquescent solid and its melting point was not obtained.

Example 6

A mixture of N-2-(4-benzoyl-2,6-dimethylphenoxy)ethyl-N-2'-hydroxyethyl-N,N-dimethylammonium iodide (5 g.) and syrupy phosphoric acid (90%; 12 g.) was heated at 100° in vacuo for 8 hours, a current of air being drawn continuously through the mixture. Phosphorus pentoxide (6 g.) was then added and the mixture heated in vacuo for a further 12 hours. The resulting viscous solution was mixed with water (200 ml.) and a boiling saturated solution of barium hydroxide added, with stirring, until the pH of the resulting suspension reached about 8.5. After standing overnight at 0°, the precipitated barium phosphate was filtered off and 2 N-sulphuric acid was added slowly to the filtrate until no more precipitate formed. The resulting barium sulphate was filtered off and the filtrate evaporated in vacuo. The crystalline residue was treated with boiling acetone, filtered off and dried in vacuo. It was then dissolved in methanol (50 ml.) and the resulting solution was percolated through a column of Amberlite (I.R. 45, OH⁻ form), the column being finally washed with fresh methanol until a test spot of the eluate on filter paper showed no absorption in U.V. light. The crystalline residue obtained from evaporation of the combined washings was recrystallised from a mixture of ethanol and propan-2-ol (1:1) to give N-2-(4-benzoyl-2,6-dimethylphenoxy)ethyl - N,N - dimethyl-N - 2' - phosphatoethylammonium betaine monohydrate, melting point 206–207°.

Example 7

N-2-(2 - bromo - 4 - methoxyphenoxy)ethyl-N-2'-hydroxyethyl - N,N - dimethylammonium bromide was converted to N-2-(2-bromo-4-methoxyphenoxy)-ethyl-N,N-dimethyl - N - 2 - phosphatoethylammonium betaine trihydrate, melting point 49–51°, by methods analogous to those described in Example 6.

Example 8

N-2-hydroxyethyl-N-methyl - 1',2',3',4' - tetrahydroisoquinolinium bromide was converted to N-methyl-N-2-phosphatoethyl-1',2',3',4'-tetrahydroisoquinolinium betaine, melting point 237–238°, by methods analogous to those described in Example 6.

Example 9

Tablets (0.555 g.) of N-2-(2-bromo-4-methoxyphenoxy)ethyl-N,N-dimethyl-N-2-phosphatoethyl ammonium betaine were made by mixing the ester (0.25 g.) in a fine powder with lactose (0.25 g.) and starch (0.05 g.) granulating the mixture with alcohol or alcoholic polyvinyl pyrrolidone or a mixture of equal parts of alcohol and water, drying the granules at 40°, adding magnesium stearate (0.005 g.) as a lubricant and compressing the mixture.

Example 10

Tablets (0.505 g.) of N-2-(2-bromo-4-methoxyphenoxy)ethyl-N,N-dimethyl-N-2-phosphatoethyl ammonium

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betaine were made by granulating the ester (0.5 g.) in a fine powder with equal parts of alcohol and water. Magnesium stearate (0.005 g.) as a lubricant was added, and the mixture compressed directly.

Example 11

Injection solutions containing N-2-(2-bromo-4-methoxyphenoxyethyl)-N,N-dimethyl-N-2-phosphatoethyl ammonium betaine in water of injection (0.2 g. per ml.) were made by autoclaving the solution at 15 lb. steam pressure for 30 minutes in unit dose ampoules or multi-dose containers. For the latter, the water for injection contained benzyl alcohol (1.0%), phenol (0.5%) or chlorocresol (0.1%).

Example 12

Tablets and injection solutions containing N-o-chlorobenzyl-N,N-dimethyl - N - 2 - phosphatoethylammonium betaine or N-o-chlorobenzyl-N-methyl-N-di-(2-phosphatoethyl)ammonium betaine were made by methods analogous to those described in Examples 9, 10 and 11.

Example 13

N,N-di-(2-hydroxyethyl)-N-methylamine (1.2 g.) was added to a solution of o-fluorobenzyl bromide (2.1 g.) in acetone (3 ml.), when a spontaneous reaction ensued. After standing for 15 minutes, the resulting mixture was heated to reflux for 1 hour. The resulting N-o-fluorobenzyl - N,N - di - (2 - hydroxyethyl) - N - methylammonium bromide was filtered off and recrystallised from propan-2-ol, melting point 99–100°.

Example 14

N,N-di-(2-hydroxyethyl)-N-methylamine was reacted with o-nitrobenzyl bromide by methods analogous to those described in Example 13. The resulting N,N-di-(2 - hydroxyethyl)-N-methyl-N-o-nitrobenzylammonium bromide was recrystallised from methanol, melting point 153–154°.

Example 15

A solution of 1-cyclohexyl-1-phenyl-3-(1-pyrrolidinyl)-propan-1-ol (2.9 g.) and 1-bromo-2-hydroxyethane (1.9 g.) in acetone (15 ml.) was boiled under reflux for 24 hours. The reaction mixture was cooled and filtered to give N-(3-cyclohexyl-3-hydroxy-3-phenyl-propyl)-N-(2-hydroxyethyl)pyrrolidinium bromide, melting point 168–169°.

Example 16

o-Chlorobenzhydrol (44 g.) was reacted with hydrogen chloride in benzene, and the resulting o-chlorobenzhydride reacted with anhydrous piperazine (70 g.) in toluene (375 ml.) at 70–80° for 12 hours. The solution was washed with water until the washings were neutral, and extracted with dilute hydrochloric acid (5%). N-o-chlorobenzhydride piperazine was liberated from the acid extracts, taken into ether, dried over potassium carbonate, and distilled at 1.3 mm., boiling point 140–142°.

N-o-chlorobenzhydride piperazine (7.1 g.) was dissolved in acetonitrile (25 ml.). 2-bromoethanol (3.7 g.) and anhydrous N,N,N-triethylamine (15 ml.) were added to the solution. The reaction mixture was refluxed for 10 hours, cooled, and diluted with anhydrous ether (250 ml.). The precipitated triethylamine hydrobromide was filtered off, and the filtrate concentrated in vacuo on a steam-bath. The residual oil was dissolved in ether, washed three times with water, and dried over potassium carbonate. Etheral hydrogen chloride was added in excess to the dried etheral solution to give N-o-chlorobenzhydride-N' - 2 - hydroxyethyl piperazine dihydrochloride, melting point 255°.

The piperazine base was liberated from this dihydrochloride (8 g.), and dissolved in benzene. The solution (125 ml.) was dried over potassium carbonate, and acetone (50 ml.) and methyl iodide (4.5 g.) added succes-

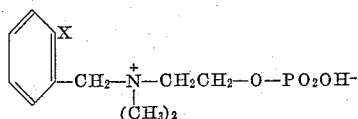
sively. The solution was allowed to stand for 24 hours, and the precipitated N'-o-chlorobenzhydryl-N-methyl-N-2-hydroxyethylpiperazinium iodide collected; it had a melting point of 213-214°. It was dissolved in acetone (200 ml.), and anhydrous ether (100 ml.) was added; the precipitated pure iodide had a melting point of 215-216°.

Example 17

A mixture of N,N,N',N'-tetramethylhexamethylenediamine (1.7 g.), o-2-bromoethyl-O,O-diphenylphosphate (8.0 g.) and anhydrous sodium carbonate (5.0 g.) in ethanol (25 ml.) was boiled under a reflux condenser for 16 hours. The reaction mixture was filtered, and the filtrate evaporated. The residual gum was shaken with a mixture of water (50 ml.) and ether (50 ml.). A hot concentrated aqueous solution of barium hydroxide (10 g.) was added to the aqueous extract, and the solution boiled in a nitrogen atmosphere under a reflux condenser for 24 hours. The reaction mixture was filtered and the white solid washed with hot water to give the dibarium salt of N,N'-di-(2-phosphatoethyl)N,N,N',N'-tetramethylhexamethylenediammonium dibetaine, melting point greater than 300°.

We claim:

1. A therapeutically acceptable phosphate ester of a quaternary ammonium compound which contains a benzylammonium cation having the formula



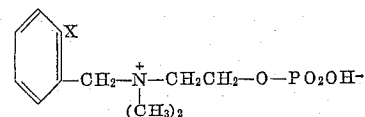
wherein X is selected from the class consisting of hydrogen, chlorine, bromine, methyl and nitro, and a pharmaceutically acceptable non-toxic carrier.

2. A therapeutically acceptable N-o-bromobenzyl-N,N-dimethyl-N-2-phosphatoethylammonium betaine.

3. A therapeutically acceptable N-o-chlorobenzyl-N-methyl-N,N-di-(2-phosphatoethyl)ammonium betaine.

4. A therapeutically acceptable N-o-chlorobenzyl-N,N-dimethyl-N-2-phosphatoethylammonium betaine.

5. A process for the treatment of hypertension which comprises the administration of a therapeutically acceptable phosphate ester of a compound whose cation has the formula



wherein X is selected from the class consisting of hydrogen, chlorine, bromine, methyl and nitro, said ester being administered with a pharmaceutically acceptable non-toxic carrier.

6. A method for improving the absorption upon oral administration of a β -hydroxyethyl quaternary ammonium compound which is poorly absorbed from the gastrointestinal tract but has a potent systemic therapeutic action upon parenteral administration which comprises the phosphorylation of said β -hydroxyethyl quaternary ammonium compound to its phosphate ester.

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