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2,780,577

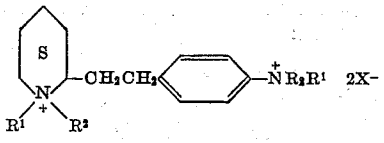
INHIBITING POLYMETHYLENE DIQUATERNARY CURARIFORM ACTIVITY BY α-STILBAZOLINE DERIVATIVES

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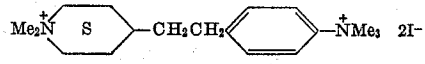
4 Claims. (Cl. 167—65)

The present invention relates to a new class of derivatives having the property of inhibiting the action of certain curariform drugs. These compounds comprise a family of diquaternary salts having the formula:



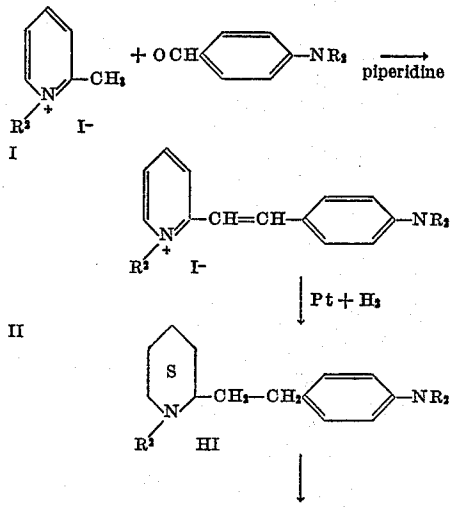
wherein R and R^2 are radicals selected from the class consisting of the methyl and ethyl radicals and R^1 is a lower alkyl radical of not over four carbon atoms, and X^- is the anion of a non-toxic acid.

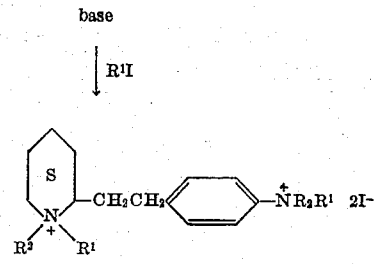
The inhibiting action of these compounds which are derived from alpha-stilbazoline is entirely unexpected in view of the very potent curare-like activity of the closely related diquaternary salts of the γ-stilbazoline system such as



While the present derivatives show only very minor curare-like activity, they possess the surprising property of inhibiting the action of their γ-analogs. This inhibitory action, however, does not extend to natural d-tubocurarine chloride but it does affect the powerful polymethylene diquaternary salts of which the best known is decamethylene bis-trimethylammonium bromide (Decamethonium Bromide, "Syncurine," Ceeten, C-10). Since these latter compounds which are already in clinical use suffer from the disadvantage of having no direct antidote, the protective utility of our α-stilbazoline diquaternary salts in medicine is considerable.

The compounds of the present invention are conveniently prepared by a sequence of reactions parallel to that shown in our co-pending patent application No. 218,279, now Pat. No. 2,655,503, on the γ-stilbazoline diquaternary salts.





Steps I and II have already been described (Phillips, J. Org. Chem., 12, 333 (1947), and J. Amer. Chem. Soc., 72, 1850 (1950)), wherefore the present application discloses only those processes involved in the third step and the preparation of certain intermediates not specifically reported before.

In the general formula of these diquaternary salts the nature of the alkyl groups (R, R^1 and R^2) appears not to be especially critical; however, the simplest compound in which all are methyl groups is at least as active as any of the others. Further, with increasing size of the alkyl groups the respiration is affected unfavorably and the synthetic operations become more difficult so that the given limits cover the substances that are believed to be of practical utility. The compounds having R^1=*n*-propyl and *n*-butyl with R=R^2=methyl were not obtained in crystalline form though analytically pure. In part this may be due to the general tendency of larger alkyl groups to lower melting points; however, other influences may be at work. When all alkyl groups are the same these substances have one asymmetric atom and exist as racemic mixtures, but when R^1 and R^2 are different a second point of asymmetry is created at the piperidino nitrogen. Such substances can exist in four stereo-isomeric forms or as two different racemic modifications. It is very likely that the lower and unsharp melting points correspond to the presence of such isomeric mixtures. Further separation of isomers will doubtless reveal variations in physiological activity, but it is not believed that such separation will be of commercial value.

According to the given scheme of synthesis X^- is I^-. However, other anions can be present such as Br^-, $SO_4^=$ etc. through the use of other alkylating agents in place of methyl or ethyl iodide. Furthermore, the iodides can readily be converted into other salts by conventional methods. In the doses to be used in practice the nature of the anion is of no consequence and therefore we consider all anions of acids possessing low inherent toxicity to be equivalent and comprehended in our invention.

EXAMPLE 1

1 - methyl - 2 - (4' - dimethylaminophenethyl) piperidine bis methiodide (compound 49–204)

The base obtained from 12.5 g. (0.033 mole) of 1 - methyl - 2 - (4' - dimethylaminophenethyl) piperidine hydroiodide (or 1 - methyl - 4' - dimethylamino - α - stilbazoline hydroiodide) was taken up in ether and dried over potassium carbonate. The solution was filtered from the desiccant and evaporated. The residual base (8.3 g.) was dissolved in methanol, 8 cc. of methyliodide was added, and the solution was refluxed 8 hours on the steam bath. The solvent and excess methyliodide were then evaporated and the diquaternary salt was crystallized from a methanol ethyl acetate mixture, M. P., 188–189° C. Conversion to the chloride was accomplished by shaking with silver chloride in aqueous solution.

EXAMPLE 2

N - methyl - 2 - (4' - dimethylaminophenethyl) piperidine bis ethiodide (compound 49–241)

By the method of Example 1, 1 - methyl - 2 - (4' - dimethylaminophenethyl) piperidine was converted to its bis-ethiodide which melts at 205–6°.

The corresponding bis *n*-propiodide and bis *n*-butiodide were also prepared by the same procedure. Although they could not be obtained crystalline, they were precipitated a number of times as oils which hardened on rubbing with ether to apparent solids. These gave correct analysis for carbon, hydrogen, and iodine and may be regarded as analytically pure. They may be mixtures of stereoisomers. These solids softened over the ranges of 145–150°, and 115–120° C. respectively

EXAMPLE 3

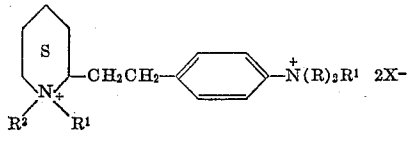
1 - methyl - 2 - (4' - diethylaminophenethyl) piperidine bismethiodide

The base was liberated from 6 g. (0.015 mole) of 1 - methyl - 2 - (4' - diethylaminophenethyl) piperidine, taken into ether and dried over potassium carbonate. After evaporation of the solvent ether the residue was dissolved in 15 cc. of methanol and the solution was divided into two equal portions. To one of these was added 5 cc. of methyl iodide and the solution was refluxed 18 hours. The solvent was evaporated and the residue was crystallized from ethanol-ether mixtures. The product (3.5 g.) melted with decomposition at 191–192° C.

The second portion of the solution of the precursor base was converted to the bis ethiodide. This, like the bis propiodide and bis butiodide of Example 2 could not be crystallized but was obtained as a pseudo solid of correct composition.

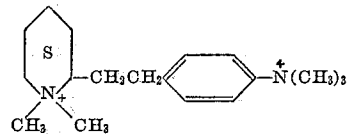
We claim:

1. A method of checking the curare-like activity of a polymethylene diquaternary curariform drug which comprises the administration to a human being of a compound of the formula

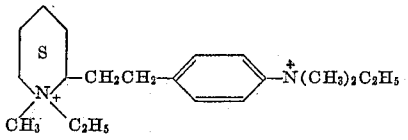


wherein R and R^2 are radicals selected from the class consisting of the methyl and ethyl radicals and R^1 is a lower alkyl radical having not over four carbon atoms and X^- is the anion of a non-toxic acid.

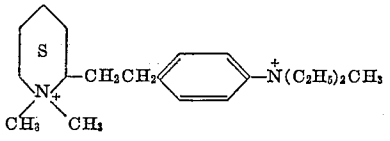
2. A method of checking the curare-like activity of a polymethylene diquaternary curariform drug which comprises the administration to a human being of a salt of the bivalent cation:



3. A method of checking the curare-like activity of a polymethylene diquaternary curariform drug which comprises the administration to a human being of a salt of the bivalent cation:



4. A method of checking the curare-like activity of a polymethylene diquaternary curariform drug which comprises the administration to a human being of a salt of the bivalent cation:



References Cited in the file of this patent

Phillips (I): J. Org. Chem., vol. 14, pp. 302–5 (1949).

Phillips (II): J. Am. Chem. Soc., vol. 72, pp. 1850–2, April 1950.