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3,485,825

CONESSINE DERIVATIVES

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Claims priority, application Netherlands, Feb. 26, 1965, 6502483

Int. Cl. C07c 173/00

U.S. Cl. 260—239.5

5 Claims

ABSTRACT OF THE DISCLOSURE

Certain mono- and bis-quaternary ammonium derivatives of conessine and its related compounds having a β -di-alkylamino substituent useful as muscular relaxing agents acting as competitive antagonists of acetylcholine, as well as therapeutic compositions containing them.

PRIOR APPLICATION

This application is a continuation in part of our co-pending U.S. patent application Ser. No. 529,202, filed Feb. 23, 1966, now abandoned.

THE PRIOR ART

For the induction of muscular relaxation, e.g. during surgical operations, a number of products are already known, which can be classified into four different types on the basis of their properties.

Type I comprises substances with depolarizing properties, such as succinylcholine. Cholinesterase inhibitors cannot antagonize their activity. The effect of succinylcholine is prolonged on the other hand by cholinesterase inhibition. Its breakdown normally takes place in the plasma under the influence of pseudocholinesterase.

Products of type II are competitive antagonists of acetylcholine. This type includes, inter alia, d-tubocurarine and gallamine. Their activity on the contrary can be antagonized by cholinesterase inhibitors.

Type III comprises non-competitively acting compounds, such as dioxahexadecanium bromide. Here again cholinesterase inhibitors are not antagonistically active.

Products of type IV inhibit the synthesis of acetylcholine, e.g., the hemicholinia. Cholinesterase inhibitors do have an antagonizing influence. Substances of type IV, however, can readily be distinguished from those of type II, inter alia through the difference in the rapidity with which the block sets in.

Finally, there are substances which have mixed properties, such as decamethonium, which has properties of types I and III.

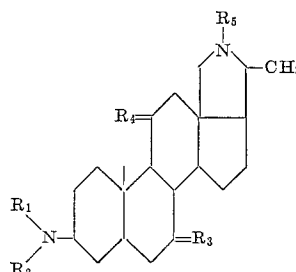
A peripherally acting muscular relaxing agent has to meet, inter alia, the following requirements. The block should rapidly be complete. If the effect does not rapidly disappear spontaneously, an antagonist should be available, in this case, a cholinesterase inhibitor. If possible, there should be an ample margin between the dose which just paralyzes the respiratory muscles and the smallest dose required to paralyze the other striated muscles completely. Finally, any objectionable side actions, such as muscular pains and an undesirable fall in blood pressure, should be absent.

None of the existing muscular relaxing agents meets all these requirements to the full.

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OBJECTS OF THE INVENTION

An object of the present invention is the obtention of a quaternary ammonium derivative of a compound of the formula

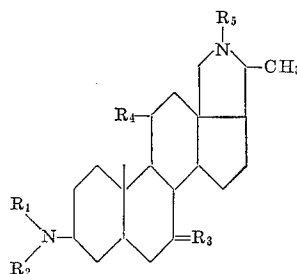


having double bonds in the positions selected from the group consisting of the 5,6-position and the 4,5- and 6,7-positions; wherein R_1 , R_2 and R_3 are alkyl having from 1 to 5 carbon atoms; and R_4 and R_5 are members selected from the group consisting of two hydrogens, one α -hydroxyl and one hydrogen, one β -hydroxyl and one hydrogen; with the proviso that when said double bonds are in the 4,5- and 6,7-positions, R_3 is one hydrogen; said quaternary ammonium derivative being selected from the group consisting of mono-quaternary compounds, bis-quaternary compounds and strong mineral acid addition salts of mono-quaternary compounds; said quaternary ammonium derivative being derived from esters of strong mineral acids with an alcohol selected from the group consisting of lower alkanol, lower alkenol, phenyl-lower-alkanol and cycloalkyl-lower-alkanol, with the proviso that when the double bond is in the 5,6-position, $R_1=R_2=R_3=CH_3$ and $R_4=R_5=H_2$, said alkanol has from 2 to 6 carbon atoms.

This and further objects of the present invention will become more apparent as the description thereof proceeds.

DESCRIPTION OF THE INVENTION

Now is was found that mono- and bis-quaternary ammonium derivatives of compound having the formula



which contain a double bond in the position 5, 6 or in the positions 4, 5 and 6,7, and in which R_1 , R_2 and R_3 each stand for an alkyl group with no more than 5 carbon atoms, while R_4 and R_5 each stand for two hydrogen atoms or one hydrogen atom and one α - or β -hydroxyl group, as well as acid addition salts of the mono-quaternary ammonium compounds, are eminently suitable for use as muscular relaxing agents.

The compound defined above are all type II muscular relaxing agents. They are, therefore, competitive antagonists of acetylcholine and their activity can be antagonized with cholinesterase inhibitors. The motor nerve end plate inhibition sets in very rapidly and the rate of its

spontaneous disappearance varies, dependent upon the substituents. The latter is of particular importance, for thus, the anaesthetist can make his choice for each individual case from a series of compositions with a very brief to a prolonged effect. Moreover, he can, if necessary, rapidly eliminate the effect by administering an antagonist. Finally, the margin between the dose which paralyzes the respiratory muscles and the dose which paralyzes the other muscles is relatively wide, while an influence on the blood pressure is completely or substantially absent.

Compositions of special importance are 11 α -hydroxy-3 β -dimethylamino- Δ^5 -conenine-bis-ethiodide, which has no undesirable influence on the blood pressure at dosages up to 5 times the therapeutic dosage and has an effect which sets in rapidly, while the rapidity with which the inhibition disappears is relatively low; 3 β -dimethylamino- Δ^5 -conenine-mono-ethiodide, which causes an increase in blood pressure of short duration, the blocking effect setting in very rapidly and disappearing very rapidly; and 3 β -dimethylamino- $\Delta^{4,6}$ -conadenine-mono-3N-ethiodide which differs from the other compounds of the invention in that it has no undesirable influence the blood pressure and the electrocardiogram (ECG) at dosages up to 10 times the therapeutic dosage, and hence is a very safe drug. At such dosages the compound causes only a slight and short-lasting rise of the blood pressure, but no dangerous lowering of the blood pressure occurs in this wide range of dosages.

The invention relates to the above-defined compounds with the exception of bis-metho-compounds of conessine. The last-mentioned compounds are excluded, as Heilbronn, Dictionary of Organic Compounds, vol. 2, p. 730, states the bis-metho-iodide and the bis-metho-sulfate of conessine, but without mention of any pharmacological activity. The bis-metho-compounds of conessine show a smaller margin between the dose which paralyzes the respiratory muscles and the dose which paralyzes the other muscles, than the other compounds of the invention.

The invention further relates to a process for preparing the above-defined compound. The compounds are prepared by reacting the corresponding non-quaternized compounds with a quaternizing agent.

Suitable quaternizing agents are the familiar esters of aliphatic and araliphatic alcohols derived from strong acids. Aliphatic and araliphatic esters of sulfuric acid, hydrohalogenic acids, such as hydrochloric acid, hydrobromic acid, or hydroiodic acid, may be mentioned as examples, in particular, the iodides and bromides. As alcohols, of particular importance are the lower alkanols, lower alkenols, phenyl-lower-alkanols and cycloalkyl-lower-alkanols. The quaternizing esters are preferably ethyl iodide, methyl iodide, ethyl bromide, methyl bromide, methyl sulfate, allyl bromide, benzyl bromide, cyclohexylmethyl bromide, etc.

The quaternizing reaction is carried out in the conventional way, for instance, by boiling the starting material, such as conessine or a conessine derivative, in a suitable solvent, such as acetonitrile, alcohols, mixtures of alcohols and water, benzene, or acetone with an alkyl or aralkyl halide.

By boiling in acetonitrile with a sufficient quantity of quaternizing agent, it is primarily the bis-quaternary ammonium compounds which are obtained, while in the other solvents mentioned it is generally mixtures of the mono- and the bis-quaternary compounds which are formed.

The mono-quaternary compounds are preferably obtained by boiling in anhydrous or 90% ethanol. In most cases compounds with a quaternized 3-dialkylamino group are thus obtained. A quaternization of the nitrogen of the pyrrolidine ring alone, however, is not precluded.

The invention also relates to pharmaceutical compositions containing the compounds according to the invention, as well as to processes for preparing such compositions. The pharmaceutical compositions can be prepared in a usual way. The compounds in question are preferably

dissolved in a physiological salt solution, may or may not be placed in particular doses in ampoules under an inert gas, and may subsequently be sterilized in the conventional way. The compositions can be used for human as well as veterinary practice.

EXAMPLE I

3 β -dimethylamino-11 α -hydroxy- Δ^5 -conenine-bis-ethiodide

1.5 gm. of 3 β -dimethylamino-11 α -hydroxy- Δ^5 -conenine and 15 ml. of ethyl iodide (freshly distilled) are boiled in 40 ml. of acetonitrile for 12 hours with reflux cooling.

The mixture is then cooled to room temperature, the crystallized product being sucked off, washed with acetonitrile, and dried under reduced pressure at 45° C. Yield=2.2 gm.; melting point=292.5–203.5° C. After recrystallization from methanol the melting point is 292 to 293° C.

Analysis.—Calculated: C, 49.12%; H, 7.31%; I, 37.13%. Found: C, 49.34%, 49.21%; H, 7.13%, 7.10%; I, 37.02%, 37.12%.

Infrared spectra (KBr): No absorptions for N—CH₃ or N+H.

The corresponding bis-methiodide is prepared in an analogous manner. It melts at 296 to 297° C.

EXAMPLE II

Conessine bis-ethiodide

5 gm. of conessine and 40 ml. of ethyl iodide (freshly distilled) are boiled in 100 ml. of acetonitrile with reflux cooling.

After 6½ hours the mixture is cooled to room temperature and the product is isolated and purified in the way described in Example I. Yield 5.4 gm.; melting point=288.5 to 289° C.

Analysis.—C₂₈H₅₀N₂I₂. Calculated: C, 50.30%; N, 4.19%; H, 7.49%; I, 38.02%. Found: C, 50.25%, 50.05%; N, 4.20%, 4.24%; H, 7.41%, 7.48%; I, 38.20%, 38.12%.

Infrared spectra (KBr): No absorption for N—CH₃ or N+H.

EXAMPLE III

Conessine monoethiodide hydroiodide

5 gm. of conessine and 12 ml. of ethyl iodide (freshly distilled) are boiled in 120 ml. of anhydrous ethanol with reflux cooling.

After three hours' boiling the reaction mixture is cooled to room temperature and then evaporated under reduced pressure. The residue is dissolved in 30 ml. of 50% methanol, basified with 2 ml. of 11 N sodium hydroxide solution, and shaken out with methyl isobutyl ketone. The extract is evaporated under reduced pressure. The remaining crude product (5.9 gm.) is dissolved in methanol and the solution is filtered. To the filtrate is added 1.2 ml. of hydroiodic acid (45%), after which the mixture is concentrated under reduced pressure to about 10 ml. The crystallized product is filtered off and washed with cold methanol. The product is then recrystallized once more from methanol. Yield 5.3 gm.; melting point=294.5 to 295.5° C.

Analysis.—C₂₆H₄₅N₂I.HI. Calculated: C, 48.75%; H, 7.19%; N, 4.38%; I, 39.69%. Found: C, 48.64%, 48.74%; H, 7.21%, 7.23%; N, 4.16%, 4.11%; I, 39.46%, 39.57%.

For I.R. and N.M.R. analyses, 1 gm. of the hydroiodide is converted into conessine mono-ethiodide (melting point=272 to 273° C.).

Analysis.—C₂₆H₄₅N₂I. Calculated: C, 60.94%; H, 8.79%; N, 5.48%; I, 24.80%. Found: C, 60.85%, 60.83%; H, 8.73%, 8.75%; N, 5.40%, 5.48%; I, 24.88%, 24.81%.

I.R. (KBr): 2775 cm.⁻¹ (N—CH₃).

N.M.R. (CDCl₃): δ =2.22 p.p.m. (3H from >N—CH₃).

EXAMPLE IV

Conessine bis-allyl bromide

10 gm. of conessine and 20 ml. of allyl bromide are boiled in 100 ml. of acetonitrile for 45 minutes with reflux cooling. The mixture is then cooled to 0° C., after which the crystallized product is sucked off and washed with cold acetonitrile.

The crude product is recrystallized several times from methanol-acetone. Yield 8.3 gm.; melting point=270 to 273° C.

Analysis.— $C_{30}H_{50}N_2Br_2$. Calculated: C, 60.20%; H, 8.36%; N, 4.68%; Br, 26.76%. Found: C, 59.90%, 59.96%; H, 8.41%, 8.44%; N, 4.61%, 4.66%; Br, 26.59%, 26.52%.

I.R. (KBr): 3080 cm^{-1} (CH_2 from $>C=CH_2$), 3014 cm^{-1} (CH from $>C=C<H$), 1665 cm^{-1} ($C=C$), 1649 cm^{-1} ($C=C$), no absorption for $N-CH_3$.

N.M.R. (D_2O): $\delta=2.92$ p.p.m. (3H; N^+-CH_3), $\delta=3.0$ p.p.m. (6H; $N^+(CH_3)_2$), $\delta=3.9-4.0$ p.p.m. (4H; multiplet; N^+-CH_2), $\delta=5.5-5.7$ p.p.m. (3H; $C=C<H$), $\delta=5.8$ p.p.m. (4H; $C=CH_2$).

EXAMPLE V

Conessine mono-allyl bromide hydrobromide

10 gm. of conessine and 4 ml. of allyl bromide are boiled in 150 ml. of 96% ethanol for 4 hours with reflux cooling. The mixture is then concentrated under reduced pressure to about 50 ml. To this quantity are added 50 ml. of water and 2.5 ml. of 11 N sodium hydroxide solution, and the mixture is extracted with methyl isobutyl ketone. The extract thus obtained is evaporated under reduced pressure and the residue is dissolved in a small quantity of methanol. To this solution hydrobromic acid (37%) is added until the pH is 3, and then acetone upon which the product is crystallizing.

The product is filtered off and washed with acetone. The crude product is recrystallized several times more from methanol-acetone. Yield 4.15 gm.; melting point =263 to 266° C.

Analysis.— $C_{27}H_{45}N_2Br \cdot HBr$. Calculated: C, 57.71%; H, 8.24%; N, 5.02%; Br, 28.67%. Found: C, 57.45%, 57.84%; H, 8.31%, 8.22%; N, 4.80%, 4.94%; Br, 28.72%, 28.30%.

For I.R. and N.M.R. analyses 300 mg. of the HBr salt is converted into conessine mono-allyl bromide.

I.R. (KBr): 3070 cm^{-1} (CH_2 from $>C=CH_2$), 3020 cm^{-1} (CH from $>C=C<H$), 2878 cm^{-1} ($N-CH_3$), 1665 cm^{-1} ($C=C$), 1640 cm^{-1} ($C=C$).

N.M.R. (D_2O): $\delta=2.19$ p.p.m. (3H; $>N-CH_3$), $\delta=3.2$ p.p.m. (6H; $N^+(CH_3)_2$), $\delta=5.67$ p.p.m. (1H; $>C=C<H$), $\delta=5.82$ p.p.m. (1H; $>C=C<H$), $\delta=6.2$ p.p.m. (2H; $>C=CH_2$).

EXAMPLE VI

Conessine bis-benzyl bromide

10 gm. of conessine and 25 ml. of benzyl bromide are boiled in 100 ml. of acetonitrile for 3½ hours with reflux cooling, after which the mixture is evaporated under reduced pressure. The residue is dissolved in dilute sulfuric acid (1 N) and the solution is shaken out with heptane to remove the excess of benzyl bromide. The solution is subsequently basified and extracted with methyl isobutyl ketone, non-converted conessine and any conessine monobenzyl bromide that may have formed being extracted. The aqueous layer is evaporated under reduced pressure and the residue (consisting of Na_2SO_4 and conessine bis-benzyl bromide) is stirred with anhydrous ethanol. The suspension thus obtained is filtered through a short aluminum oxide column. The column is washed with anhydrous ethanol until no more conessine bis-benzyl bromide is present in the filtrate. The filtrate is evaporated under reduced pressure and the residue is re-

crystallized several times from methanol-methyl isobutyl ketone. Yield 8.4 gm.; melting point=235 to 237° C.

Analysis.— $C_{38}H_{54}N_2Br_2$. Calculated: C, 65.33%; H, 7.74%; N, 4.01%; Br, 22.92%. Found: C, 65.36%, 65.15%; H, 7.69%, 7.79%; N, 3.93%, 4.02%; Br, 22.71%, 22.85%.

I.R. (KBr): No absorption for $N-CH_3$. 1700 cm^{-1} , 1620 cm^{-1} , 1580 cm^{-1} , 1450 cm^{-1} (phenyl absorption), 745 cm^{-1} and 705 cm^{-1} (mono-substituted benzene).

N.M.R. (D_2O): $\delta=2.99$ p.p.m. (9H; $N^+(CH_3)_2$ and N^+-CH_3), $\delta=7.54$ p.p.m., $\delta=7.60$ p.p.m.¹

¹ 10H; two phenyl groups.

EXAMPLE VII

Conessine monobenzyl bromide hydrobromide

10 gm. of conessine and 6 ml. of benzyl bromide are boiled in 150 ml. of 96% ethanol with reflux cooling.

After 6½ hours the reaction is broken off and the mixture is evaporated under reduced pressure. The residue is dissolved in 1 N sulfuric acid and the solution is shaken out with heptane to remove the excess of benzyl bromide. The acid solution is subsequently basified and extracted with methyl isobutyl ketone. The organic extract is evaporated under reduced pressure. The residue is dissolved in methanol; hydrobromic acid (37%) is added until the pH is 3, and then ether until the solution becomes turbid. The product is then allowed to crystallize at 0° C. The crystallized product is sucked off and washed with ether. Yield 8.6 gm. After another recrystallization from methanol-ether the melting point is 258–260° C.

Analysis.— $C_{31}H_{47}N_2Br \cdot HBr$. Calculated: C, 61.18%; H, 7.89%; N, 4.61%; Br, 26.32%. Found: C, 60.84%, 60.92%; H, 8.04%, 8.05%; N, 4.66%, 4.57%; Br, 25.95%, 26.14%.

I.R. (KBr): 3060 cm^{-1} , 3030 cm^{-1} , and 3015 cm^{-1} ($C-H$ from phenyl), 2620 cm^{-1} , 2549 cm^{-1} , and 2520 cm^{-1} (N^+H), 1583 cm^{-1} and 1450 cm^{-1} ($C=C$ from phenyl), 745 cm^{-1} and 703 cm^{-1} (mono-substituted benzene).

N.M.R. (D_2O): $\delta=2.86$ p.p.m. (3H; N^+-CH_3), $\delta=3.02$ p.p.m. (6H; $N^+(CH_3)_2$), $\delta=5.60$ p.p.m. (1H; $>C=C<H$), $\delta=7.58$ p.p.m. (5H; phenyl).

EXAMPLE VIII

Conessine monocyclohexyl methobromide

5 gm. of conessine and 80 ml. of cyclohexylmethyl bromide are boiled in 60 ml. of acetonitrile and 20 ml. of anhydrous ethanol with reflux cooling.

After 48 hours the reaction is broken off and the mixture is kept for several hours at 0° C.

The precipitate thus formed is subsequently filtered off and washed with acetonitrile. This precipitate consists substantially of conessine dihydrobromide.

Water is added to the filtrate, and after acidification to pH 3 the mixture is extracted several times with heptane.

The aqueous layer is subsequently made alkaline with sodium hydroxide solution to pH 10 and shaken out with methyl isobutyl ketone. The extract is evaporated under reduced pressure and the residue is purified with the aid of an aluminum oxide column.

Yield of conessine monocyclohexyl methobromide 1.3 gm.; melting point=265 to 267° C. After several recrystallizations from methanol-ether the compound melts at 270.5 to 273° C.

Analysis.— $C_{31}H_{53}N_2Br$. Calculated: C, 69.79%, H, 9.94%; N, 5.25%; Br, 15.00%. Found: C, 69.69%, 69.75%; H, 9.63%, 9.62%; N, 5.12%, 5.07%; Br 15.48%, 15.35%.

I.R. (KBr): 2775 cm^{-1} ($N-CH_3$).

N.M.R. (C_2D_6SO): $\delta=2.10$ p.p.m. (3H; $>N-CH_3$), $\delta=3.04$ p.p.m. (6H; $-N^+(CH_3)_2$).

EXAMPLE IX

3 β -dimethylamino-7 β -hydroxy- Δ^5 -conenine bis-methiodide

400 mg. of 3 β -dimethylamino-7 β -hydroxy- Δ^5 -conenine and 2 ml. of methyl iodide (freshly distilled) are boiled in 20 ml. of methanol with reflux cooling.

After 2 hours the reaction is broken off and the mixture is evaporated under reduced pressure. The residue is dissolved in water, basified with ammonia, and shaken out with methyl isobutyl ketone. The aqueous layer is subsequently evaporated under reduced pressure and the residue is recrystallized several times from methanol-methyl isobutyl ketone.

Yield of 3 β -dimethylamino-7 β -hydroxy- Δ^5 -conenine bis-methiodide 320 mg. Melting point=294 to 296° C.

Analysis.—C₂₆H₄₆N₂OI₂. Calculated: C, 47.56%; H, 7.01%; N, 4.26%; I, 38.71%. Found: C, 47.40%, 47.33%; H, 7.10%, 7.14%; N, 4.15%, 4.20%; I, 38.53%, 38.44%.

I.R. (KBr): No absorption for N—CH₃ or N⁽⁺⁾H.

The corresponding 7 α -hydroxy compound is prepared in an analogous manner (melting point approximately 230° C.).

EXAMPLE X

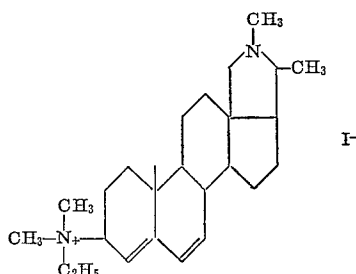
3 β -dimethylamino- $\Delta^{4,6}$ -conadienine bis-methiodide

400 mg. of 3 β -dimethylamino- $\Delta^{4,6}$ -conadienine (J. Chem. Soc., 1957, 4957) are reacted in the way described in Example IX with 2 ml. of methyl iodide. The product obtained is 474 mg. of 3 β -dimethylamino- $\Delta^{4,6}$ -conadienine bis-methiodide with a melting point of 214.5 to 215° C.

Analysis.—C₂₆H₄₄N₂I₂. Calculated: C, 48.90%; H, 6.90%; N, 4.39%; I, 39.81%. Found: C, 48.63%, 48.71%; H, 7.02%, 7.09%; N, 4.28%, 4.23%; I, 38.91%, 39.03%.

I.R. (KBr): No absorption for N—CH₃ or N⁽⁺⁾H.

EXAMPLE XI

3 β -dimethylamino- $\Delta^{4,6}$ -conadienine 3N-ethiodide of the formula

A solution of 110 g. of 3 β -dimethylamino- $\Delta^{4,6}$ -conadienine in 2.75 liters of hexane and 0.55 liters of ethyl iodide was refluxed with stirring under a nitrogen atmosphere on a water bath maintained at 75° C. As far as possible the reaction was carried out in the dark. After a reaction time of 22 hours, thin-layer chromatography (Al₂O₃; CH₂Cl₂/CH₃OH, 25:1, vol./vol.) showed that about 80% of the starting material had been converted into the desired compound, and very little of the bis-quaternary derivative has been formed.

As far as possible, the isolation and purification steps were carried out in a nitrogen atmosphere. The reaction mixture was cooled and the crystals formed were filtered off with suction, and washed with hexane. The crystal mass was dissolved in 1 liter of CH₂Cl₂ and 3 liters of water. The mixture was shaken and the organic layer was separated. The aqueous layer was extracted three times with 0.5 liters of CH₂Cl₂. The combined methylene chloride extracts were washed four times with 100 ml. of water. The extract was concentrated in vacuo to a volume of about 1 liter. Subsequently, concentration was continued under slow addition of acetone to the mixture, until a thick crystal suspension was obtained. This suspension

was filtered with suction, washed with acetone, and dried in a vacuum dryer.

The yield was 71 g. of 3 β -dimethylamino- $\Delta^{4,6}$ -conadienine-3N-ethiodide. Melting point=268–270° C.; λ_{\max} (in methanol)=226, 232, and 238 m μ ;

$$E_{1\%}^{1\text{cm.}}=552, 562$$

and 546 respectively; $[\alpha]_D^{20}=+70^\circ$ (c.=0.5% in chloroform).

I.R.-spectrum (in chloroform): 2788, 1709, 1634, and 1600 cm.⁻¹.

N.M.R.-spectrum (in CDCl₃): 0.98, 1.04 (doublet), 1.50 (triplet), 1.92 (doublet), 2.23, 3.07 (doublet), 3.30, 3.75 (quadruplet), 4.6 (multiplet), 5.55, 5.9, and 6.1 (AB-spectrum) p.p.m.

Analysis.—C₂₆H₄₃N₂I; molecular weight=510. Calculated: C, 61.18%; H, 8.43%; N, 5.49%; I, 24.90%. Found: C, 60.61%; H, 8.50%; N, 5.40%; I, 25.49%.

The liquids used had been prepared as follows:

Hexane and ethyl iodide were filtered through Al₂O₃ and saturated with nitrogen gas.

CH₂Cl₂ and acetone were also saturated with nitrogen gas.

The water was boiled and saturated with nitrogen gas during cooling.

EXAMPLE XII

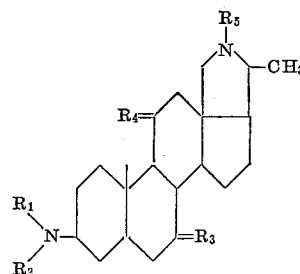
10 gm. of conessine monoethiodide hydroiodide is dissolved at room temperature in 1000 ml. of a pyrogen-free physiological salt solution.

The solution is introduced in the usual way under a nitrogen atmosphere into 2-ml. ampoules of actinic glass, which after being sealed are autoclaved for 20 minutes at 20° C.

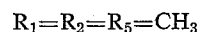
The preceding specific embodiments are illustrative of the invention. It is to be understood that other expedients known to those skilled in the art may be employed.

We claim:

1. A quaternary ammonium derivative of a compound of the formula:



having double bonds in the positions selected from the group consisting of the 5,6-position and the 4,5- and 6,7-positions; wherein R₁, R₂ and R₅ are alkyl having from 1 to 5 carbon atoms; and R₃ and R₄ are members selected from the group consisting of two hydrogens, one α -hydroxyl and one hydrogen, and one β -hydroxyl and one hydrogen, with the proviso that when said double bonds are in the 4,5- and 6,7-positions, R₃ is one hydrogen; said quaternary ammonium derivative being selected from the group consisting of mono-quaternary compounds, bis-quaternary compounds and strong mineral acid addition salts of mono-quaternary compounds; said quaternary ammonium derivative being derived from esters of strong mineral acids with an alcohol selected from the group consisting of lower alkanol, lower alkenol, phenyl-lower-alkanol and cycloalkyl-lower-alkanol, with the proviso that when the double bond is in the 5,6-position,



and $R_4=R_3=H_2$, said alkanol has from 2 to 6 carbon atoms.

2. The quaternary derivative of claim 1 wherein said quaternary ammonium derivative is derived from ethyl iodide.

3. 11 α - hydroxy -3 β - dimethylamino - Δ^5 - conenine- 5 bis-ethiodide.

4. Conessine-mono-ethiodide-hydroiodide.

5. 3 β -dimethylamino- $\Delta^{4,6}$ -conadienine-3N-ethiodide.

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HENRY A. FRENCH, Primary Examiner

U.S. Cl. X.R.

260—999