

UNITED STATES PATENT OFFICE

2,670,360

QUATERNARY AMMONIUM SALTS OF BASIC DERIVATIVES OF SUBSTITUTED CINNAMIC ACIDS AND METHODS OF PRODUCING SAME

William A. Lott, Maplewood, N. J., assignor to Mathieson Chemical Corporation, New York, N. Y., a corporation of Virginia

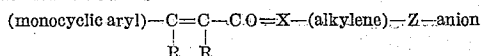
No Drawing. Application November 30, 1951,
Serial No. 259,303

8 Claims. (Cl. 260-404)

1

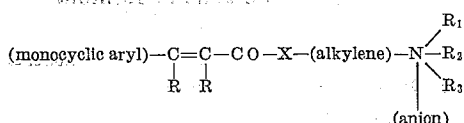
This invention relates to, and has for its object the provision of, certain quaternary ammonium salts of cinnamic acid derivatives.

The compounds embraced by this invention comprise quaternary ammonium salts of the general formula (I)



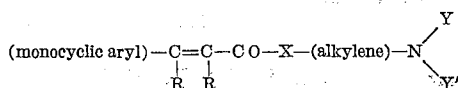
wherein one R represents a member of the class consisting of alkyl and aryl groups and the other R represents hydrogen, X represents a member of the class consisting of O, NH, and N(alkyl) groups, and —Z— represents a quaternary ammonium nitrogen. (The "monocyclic aryl" group may be unsubstituted or may be substituted with a halo, alkyl, alkoxy, alkylene-dioxy, and dialkyl-amino group.)

The compounds of this invention possess valuable therapeutic properties, especially ganglionic blocking activity. In addition, those compounds of the general formula (II):



[wherein one R represents an aryl group and the other R represents hydrogen, R₁ and R₂ each represent a member of the class consisting of alkyl, aryl, and aralkyl groups, and R₃ represents a member of the class consisting of alkyl, alkenyl, aryl and aralkyl groups] possess acetyl choline antagonizing activity. Compounds of general Formula II in which the R substituent is a higher alkyl group are not only effective ganglionic blocking agents but also possess cationic-detergent and bactericidal properties.

The compounds of this invention are prepared by the method which essentially comprises interacting a tertiary amine III of the general formula



wherein



is an amino group, with a quaternizing agent.

Tertiary amines III which are utilizable for the purposes of the invention include, inter alia:

β-diethylaminoethyl α-ethylcinnamate
β-diethylaminoethyl α-isopropylcinnamate
β-diethylaminoethyl β-amylocinnamate
N-(β-diethylaminoethyl)-α-ethylcinnamamide
N-(β-diethylaminoethyl)-β-butylcinnamamide

2

- β-diethylaminoethyl α-phenyl-o-chlorocinnamate
β-diethylaminoethyl α-ethyl-p-dimethylaminocinnamate
5 β-dimethylaminoethyl α-ethyl-3,4-dimethoxycinnamate
γ-dimethylaminopropyl α-ethyl-methylenedioxy-3,4-cinnamate
β-(amyl-ethyl-amino)-ethyl β-phenylcinnamate
10 β-(benzyl-ethyl-amino)-ethyl α-hexylcinnamate
β,β-dimethyl-γ-diethylaminopropyl α-phenylcinnamate
15 β-diethylaminoethyl β-decylcinnamate
β-diethylaminoethyl β-propylcinnamate
β-diethylaminoethyl β-phenyl-p-methoxycinnamate
N-ethyl-N-diethylaminoethyl-α-methylcinnamamide
20 N-(γ-diethylaminopropyl)-α-phenyl-p-methylcinnamamide
β-dimethylaminopropyl β-phenylcinnamate
N-(β-diethylaminoethyl)-β-decylcinnamamide
25 N-(β-diethylaminoethyl)-α-phenyl-p-dimethylaminocinnamamide
N-(β-diethylaminoethyl)-N-ethyl-α-phenylcinnamamide
30 N-(β-diethylaminoethyl)-α-decyl-p-dimethylaminocinnamamide
β-(phenyl-ethyl-amino)-ethyl α-phenylcinnamate

35 The utilizable quaternizing agents include: dialkyl sulfates (e. g. diethyl sulfate), alkyl halides (e. g. ethyl bromide, methyl iodide), aryl halides (e. g. benzyl chloride, α-naphthyl methyl chloride), esters (e. g. ethyl chloroacetate, methyl p-toluene-sulfonate, ethyl α-bromopropionate, n-octyl iodoacetate), alkyl haloalkyl ethers (e. g. bromomethoxybutane), alkenyl halides (e. g. methallyl chloride), haloalkyl haloalkaryl ethers (e. g. chloromethyl o-cresoxy ethyl chloride). The following examples are illustrative of the
45 invention:

EXAMPLE 1

[β-(α-phenylcinnamido)ethyl]-triethylammonium bromide

50 A solution of 38.8 g. N,N-diethyl-ethylenediamine is added to 75 g. α-phenylcinnamoyl chloride in 200 ml. of benzene. The mixture is refluxed for two hours, cooled, and filtered. The product is recrystallized from 375 ml. isopropanol to give 90 grams of N-(β-diethylaminoethyl)-α-phenylcinnamamide hydrochloride. This material is dissolved in water, alkalized with potassium carbonate and extracted with ether. After the ether extracts have been dried

3

(and the ether removed), the residue is dissolved in 300 ml. benzyl alcohol and 30 grams of ethyl bromide. This solution is then heated at 100° C. for three days; at which time the solution is cooled and diluted with ether. The product is recrystallized from an alcohol-ether solution to give about 80 grams of a white crystalline material, M. P. about 166–168° C.

EXAMPLE 2

[β -(α -phenylcinnamido)ethyl]-trimethylammonium iodide

Using 33.4 g. of N,N-dimethyl-ethylenediamine in place of N,N-diethyl-ethylenediamine, in Example 1, the product N-(β -dimethylaminoethyl)- α -phenylcinnamamide hydrochloride is obtained, M. P. about 140–141° C. This intermediate is similarly treated with alkali and heated with 43 g. of methyl iodide to yield a white crystalline material [β -(α -phenylcinnamido)ethyl]-trimethylammonium iodide, M. P. about 180–181° C.

EXAMPLE 3

[β -(α -phenylcinnamoyloxy)ethyl]diethylmethylammonium bromide

A solution of 30 grams β -(diethylaminoethyl)- α -phenylcinnamate hydrochloride in 200 ml. of water is alkalized with potassium carbonate and extracted with 275 ml. ether and dried. The ether is distilled off and to the residue (19.6 g.) is added a solution of 16 g. of methyl bromide in 40 ml. alcohol. After three days of solution is diluted with 80 ml. ether and filtered. The product is recrystallized from 90 ml. methyl ethyl ketone to give about 14 g. of product melting at about 130–131° C.

EXAMPLE 4

[β -(β -phenylcinnamido)ethyl]-triethylammonium bromide

50 g. methyl β -phenylcinnamate and 70 g. N,N-diethylethylenediamine are refluxed together for twenty-four hours; and the excess amine removed under reduced pressure. The residue is taken up in 400 ml. ether and extracted with 5% hydrochloric acid. The acid extract is then washed with 100 ml. ether, alkalized with potassium carbonate; and the base obtained is extracted with ether, and dried. When the ether is distilled, there is obtained about 34 g. N-(β -diethylaminoethyl)- β -phenylcinnamide. This material is dissolved in 200 ml. benzyl alcohol containing 120 g. ethyl bromide and heated at 60° C. for two days, and the solution is then diluted with 550 ml. ether. The product, filtered and recrystallized from 120 ml. methyl ethyl ketone, is [β -(β -phenylcinnamido)ethyl]triethylammonium bromide.

EXAMPLE 5

Using a molar equivalent of diethyl sulfate in place of ethyl bromide in Example 1, [β -(α -phenylcinnamido)ethyl]triethylammonium ethyl sulfate is obtained.

EXAMPLE 6

Using a molar equivalent of methyl p-toluene-sulfonate in place of ethyl bromide in Example 1, [β -(α -phenylcinnamido)ethyl]-diethylmethylammonium p-toluene-sulfonate is obtained.

4

EXAMPLE 7

Using a molar equivalent of benzyl bromide in place of ethyl bromide in Example 1, [β -(α -phenylcinnamido)ethyl]-benzyltriethylammonium bromide is obtained.

EXAMPLE 8

[β -(α -decylcinnamido)ethyl]triethylammonium bromide

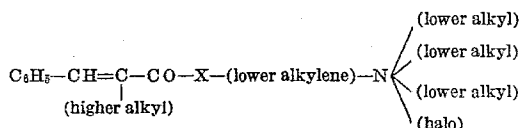
A solution of 27 g. of N-(β -diethylaminoethyl)- α -decylcinnamamide, B. P. 198–200° C./1 mm., 100 ml. benzyl alcohol and 100 ml. ethyl bromide is allowed to stand at room temperature for three days. The benzyl alcohol is then removed under reduced pressure; and 100 ml. dry hexane is added. The hexane is also removed under reduced pressure and the procedure is repeated to yield a viscous residue. Anhydrous ether (200 ml.) is added and the residue crystallizes, yielding about 18 g. of solid product melting at about 99–100° C. After crystallization from hexane the melting point is about 99–100° C.

The following compounds are prepared in an analogous manner: [β -(α -decylcinnamoyloxy)ethyl]-triethylammonium bromide, a viscous liquid with the same solubility as the corresponding amide; [β -(α -hexylcinnamido)ethyl]-triethylammonium bromide, M. P. about 137–139° C.; [β -(α -decylcinnamoyloxy)propyl]-triethylammonium bromide, a viscous syrup; [β -(α -tetradecylcinnamido)ethyl]-triethylammonium bromide, M. P. about 93–94° C.

The invention may be embodied in various other ways within the scope of the appended claims.

I claim:

1. Compounds of the general formula



wherein X is a member of the class consisting of O and NH.

2. Compounds of claim 1, wherein X is O.

3. Compounds of claim 1, wherein X is NH.

4. [β -(α -decylcinnamido)ethyl]-triethylammonium bromide.

5. [β -(α -decylcinnamoyloxy)ethyl]-triethylammonium bromide.

6. [β -(α -hexylcinnamido)ethyl]-triethylammonium bromide.

7. [β -(α -decylcinnamoyloxy)propyl]-triethylammonium bromide.

8. [β -(α -tetradecylcinnamido)ethyl]-triethylammonium bromide.

WILLIAM A. LOTT.

References Cited in the file of this patent

UNITED STATES PATENTS

Number	Name	Date
2,139,687	Lott	Dec. 13, 1938
2,310,973	Lott	Feb. 16, 1943

OTHER REFERENCES

Voigt et al.: Chem. Abstracts, vol. 36, page 6652 (1942).

Jensen et al.: Acta Chemica Scandinavica, 2, 381 (1948).