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United States Patent [19][11] **Patent Number:** **5,223,614**

Schromm et al.

[45] **Date of Patent:** **Jun. 29, 1993**[54] **NEW QUATERNARY AMMONIUM COMPOUNDS, THEIR PREPARATION AND USE**[58] **Field of Search** 564/283, 281, 282, 291; 544/105; 546/184, 221; 548/215, 221; 574/230.5, 299, 330, 375; 568/705[75] **Inventors:** Kurt Schromm, Ingleheim am Rhein; Anton Mentrup, Wiesbaden; Ernst-Otto Renth; Gojko Mualcevic, both of Ingleheim am Rhein; Werner Traunecker, Munster-Sarmsheim, all of Fed. Rep. of Germany[56] **References Cited****U.S. PATENT DOCUMENTS**

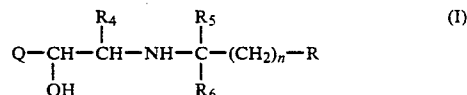
4,599,335 7/1986 Rentzea et al. 564/282

OTHER PUBLICATIONSChemical Abstracts, vol. 101, p. 772, 191939z, 1984.
Chemical Abstracts, vol. 80, p. 274, No. 7, 36875e, 1974.*Primary Examiner*—José G. Dees
Assistant Examiner—Deborah D. Carr
Attorney, Agent, or Firm—D. E. Frankhouser; A. R. Stempel; M-E. M. Timbers[73] **Assignee:** Boehringer Ingelheim GmbH, Ingleheim am Rhein, Fed. Rep. of Germany[21] **Appl. No.:** 603,585[57] **ABSTRACT**[22] **Filed:** Oct. 25, 1990

Compounds of formula

Related U.S. Application Data

[63] Continuation of Ser. No. 286,442, Dec. 19, 1988, abandoned.

**Foreign Application Priority Data**

Dec. 19, 1987 [DE] Fed. Rep. of Germany 3743265

wherein the substituents are defined hereinbelow, useful in the treatment of bronchospasm are described.

[51] **Int. Cl.⁵** C07D 265/36[52] **U.S. Cl.** 544/105; 546/184; 546/221; 548/215; 548/221; 564/281; 564/282; 564/291; 568/705**5 Claims, No Drawings**

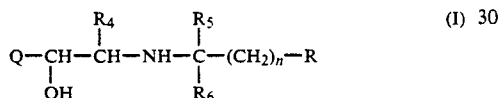
NEW QUATERNARY AMMONIUM COMPOUNDS, THEIR PREPARATION AND USE

This is a continuation, of application Ser. No. 286,442, filed Dec. 19, 1988, now abandoned.

The invention relates to quaternary ammonium compounds, and the preparation and use thereof. The compounds of the invention may be prepared by methods known per se and used as pharmaceuticals, particularly for inhalation.

We have found that the introduction of a quaternary ammonium group at a suitable point in the molecules of known broncholytically active compounds which are effective when inhaled makes it possible to eliminate unwanted systemic side effects to a great extent whilst substantially retaining the broncholytic (topical) effect. We have found that the nature of the quaternary ammonium grouping may be selected from a wide range of variations without crucially affecting the differentiation between desirable and undesirable effects according to the invention.

According to the invention, we provide compounds of formula I



wherein

Q represents a substituted phenyl group;

R represents a group, such as an alkoxy, arylalkoxy, aryloxyalkoxy, aryl, aryloxy arylcarbonamido group, a heterocyclic group or a heterocyclically substituted carbonamido group, which includes also a quaternary ammonium grouping;

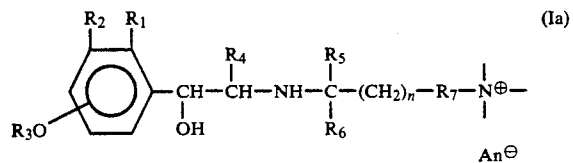
R₄ represents H, CH₃ or C₂H₅;

R₅ represents H or CH₃;

R₆ represents H or CH₃;

n represents an integer selected from 1, 2, 3, 4 and 5.

The compounds of the invention may in one preferred embodiment be represented essentially by the formula Ia



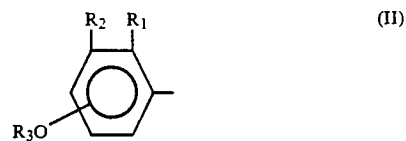
in which, unless otherwise stated,

n represents an integer selected from 1, 2, 3, 4 and 5;

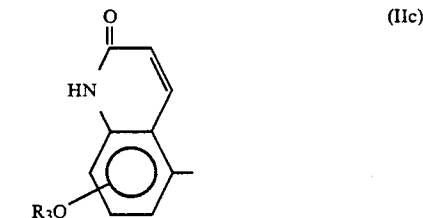
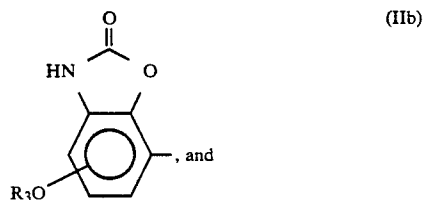
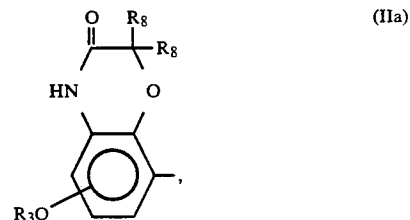
R₁ represents H, CH₃, OCH₃, Cl, or F;

R₂ represents H, R₃O—, —CH₂OH, —NHCHO, —NHCOCH₃, —NHSO₂CH₃, or —NHCONH₂;

R₃ represents H, acyl, or N,N-dialkylcarbamoyl, the groups R₃O being in the 4- or 5- positions; the group II



may also represent one of the groups



wherein R₃ is as hereinbefore defined and

R₈ represents H or CH₃;

R₄ represents H, CH₃, or C₂H₅;

R₅ represents H or CH₃;

R₆ represents H or CH₃;

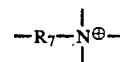
R₇ represents a single bond or a divalent bridging member which may also be bound to the ammonium nitrogen via ring atoms of a heterocyclic group;



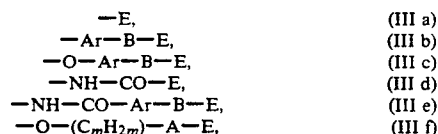
represents a quaternary ammonium group;

An[⊖] represents an anion.

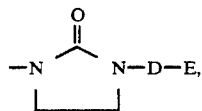
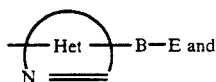
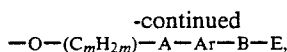
In a further preferred embodiment, the grouping



primarily represents one of the groups



3



n and R₁ to R₆ being as defined hereinbefore.

In the above definitions of (IIIa) to (IIIi), m represents an integer selected from 2, 3, 4, 5 and 6;



represents a nitrogen heterocycle which may be condensed with a benzene ring and which may be substituted or unsubstituted and may optionally contain one or more additional heteroatoms in the ring;

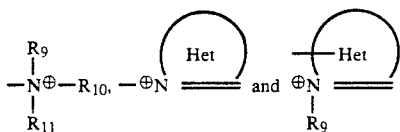
Ar represents arylene, preferably unsubstituted or substituted phenylene or naphthylene;

A represents a single bond or a NH-CO-(C₁₋₄)-alkylene group;

B represents a single bond or an -O-(C₁₋₄)-alkylene, -NH-CO-(C₁₋₄)-alkylene, or -(C₁₋₄)-alkylene group;

D represents a -(C₁₋₄)-alkylene group; and

E represents one of the groups



(in which

R₉ represents a (C₁₋₄)-alkyl group;

R₁₀ represents a (C₁₋₄)-alkyl group; or

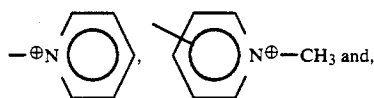
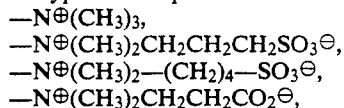
R₉ and R₁₀ together represent a (C₄₋₆)-alkylene group; and

R₁₁ represents a (C₁₋₄)-alkyl, (C₁₋₄)-alkylene-COO[⊖], (C₁₋₄)-alkylene-SO₃[⊖], (C₁₋₄)-alkylene-OH, or (C₃₋₆)-cycloalkyl group; and the group



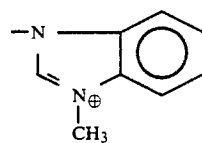
is as defined above).

Typical examples of E include



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-continued



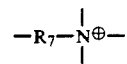
(III g)

(III h)

5

(III i)

Particular mention should be made of the following preferred definitions for the grouping



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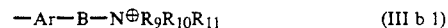
in which the groupings and groups are as defined above:



(III a 2)



(III a 3)



(III b 1)



(III b 2)



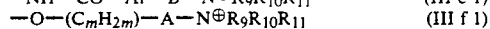
(III c 1)



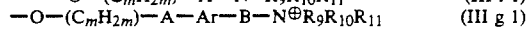
(III d 1)



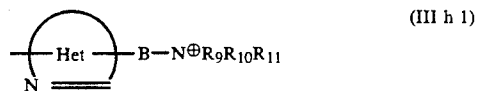
(III e 1)



(III f 1)



(III g 1)

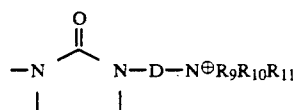


(III h 1)

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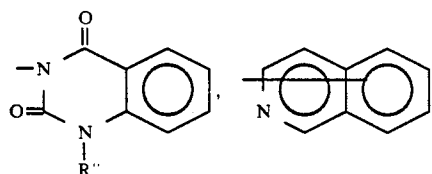
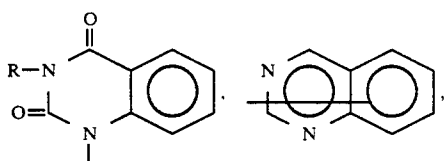
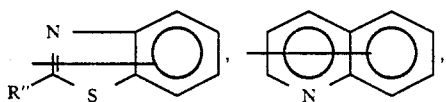
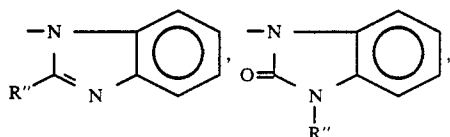
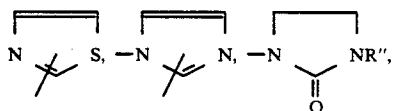
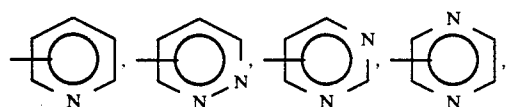
(III i)

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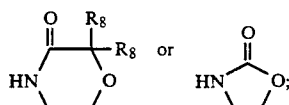
The alkyl and alkylene groups in the above definitions may be straight-chained or branched. Unless otherwise stated, they contain 1 to 6, preferably 1 to 4, and most particularly 1 or 2 carbon atoms. This also applies to the carbon chains which are components of other groups. Examples of substituents in aryl(ene) include, in particular, F, Cl, CH₃ and CH₃O groups. The terms "aryl" and "arylene" refer to the appropriate groups derived from benzene or naphthalene. "Acyl groups" in this case denote carboxylic acid groups with up to 7 carbon atoms, particularly acetyl. The bridge R₇ may be

linked to the nitrogen atom of the quaternary ammonium group. Alternatively, if the quaternary ammonium group is part of a heterocyclic group, the bridge may be connected to another ring atom of the heterocyclic group. Groups falling into this latter category include in particular



(in which R^{11} represents H or C_{1-4} -alkyl), and triazines.

In a further preferred embodiment of the invention R_1 represents H, CH_3 , OCH_3 , Cl or F; R_2 represents OH or, when R_1 equals Cl or F, R_2 may also represent H; or R_1 and R_2 together may also represent



(in which R_8 is as hereinbefore defined)

R_3 represents a hydrogen atom;

R_4 represents H or C_2H_5 ;

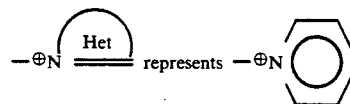
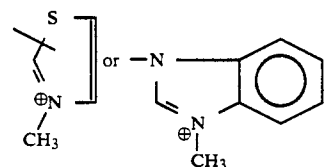
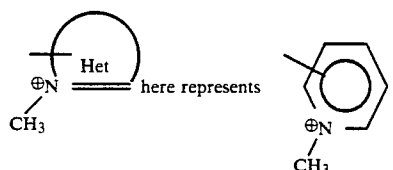
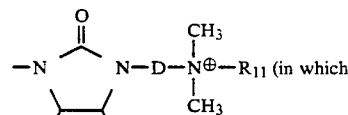
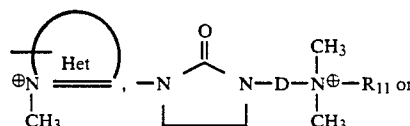
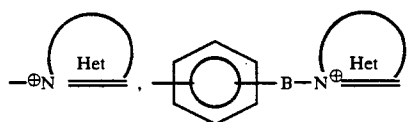
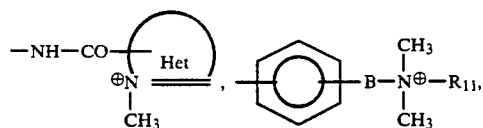
R_5 and R_6 both represent H or both represent CH_3 ;

n represents an integer selected from 1, 2 and 3;

R_7



represents a group



whilst B, D and R_{11} are as hereinbefore defined).

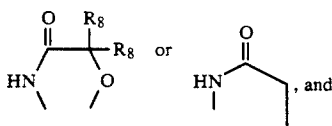
Particular mention should be made of the compounds in which the following combinations of substituents occur:

(a) R_1 represents a methyl or methoxy group, R_2 represents a hydroxyl group, and R_3 represents a 4-hydroxyl group;

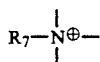
(b) R_1 represents a hydrogen atom, R_2 represents a hydroxyl group, and R_3 represents a 4- or 5-hydroxyl group;

(c) R_1 and R_2 together represent

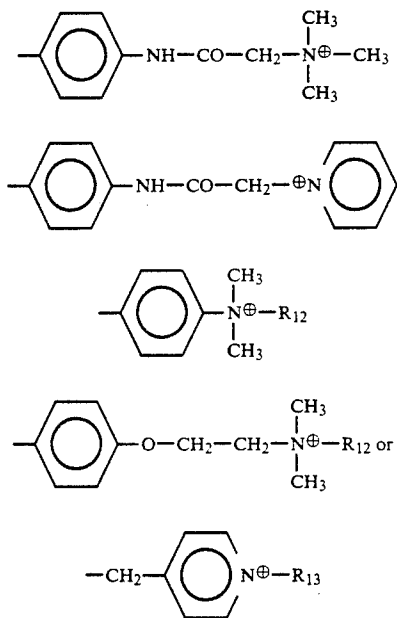
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R_3 represents a 4- or 5-hydroxyl group;
 R_4 represents a hydrogen atom, if R_5 and R_6 represent methyl groups, but C_2H_5 , if R_5 and R_6 represent H;



represents



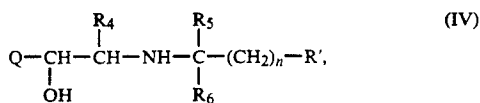
(in which R_{12} and R_{13} represent CH_3 , CH_2-COO^- , $CH_2-CH_2-COO^-$ or $CH_2-CH_2-CH_2-SO_3^-$).

The compounds according to the invention may occur as mixtures of enantiomers, particularly as racemates, and optionally either as pairs of diastereoisomers or as pure enantiomers, and as salts with (preferably physiologically acceptable) acids, and the invention extends to all such forms of the compounds of formula I.

The compounds of the invention may be prepared by a variety of methods.

Accordingly, in a further aspect of the invention, we provide a process for preparing compounds of formula I as described above, wherein

a) a compound of formula IV



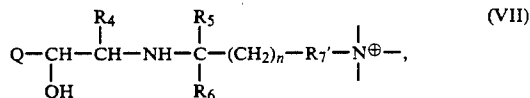
wherein n , Q , R_4 , R_5 and R_6 are as defined above, R' is a tertiary amino group which corresponds at least in part to the quaternary ammonium group-containing

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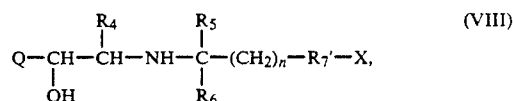
group R , or a protected form thereof in which any hydroxyl group or amino group it is desired to protect is protected by hydrogenolytically-removable protecting groups, is reacted with an alkylating agent, and any protecting groups present are removed by hydrogenolysis;

or

b) if it is desired to prepare a compound of formula VII



wherein n , R_4 , R_5 , R_6 and Q are as defined above and R' represents a group R_7 which is bound to the quaternary ammonium nitrogen via an aliphatic carbon atom, a compound of formula VIII

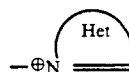


(wherein the symbols are all defined as above and X represents a leaving group is reacted with a tertiary amine



to provide the desired quaternary ammonium compound, followed, if desired, by separation of any mixture of enantiomers into pure enantiomeric forms or other enantiomeric mixtures, and formation of any desired acid addition salts.

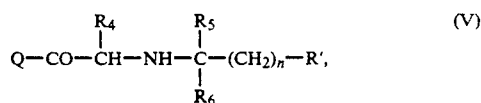
Process (a) above is suitable for preparing compounds of formula I in which the quaternary ammonium group is not in the form



Compounds selected from $Cl-(C_{1-4})\text{-alkylene-SO}_3Na$ and $HO-(C_{1-4})\text{-alkylene-SO}_2-O-(C_{1-4})\text{-alkylene-SO}_3Na$ are particularly suitable for the introduction of a $(C_{1-4})\text{-alkylene-SO}_3^-$ group.

The reaction is expediently carried out in an inert polar solvent at ambient temperature or at an elevated temperature up to about 100°C .

The starting materials of formula IV may be obtained by methods known per se. Thus, aminoketones of formula V



wherein Q , R^4 , R^5 , R^6 , R^1 and n are as defined above, or Schiff base of the formula VI

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