

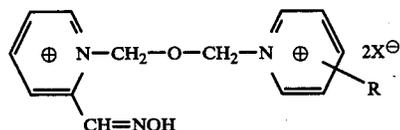
# BIS-QUATERNARY PYRIDINIUM-2-ALDOXIME SALTS AND A PROCESS FOR THEIR PREPARATION

## BACKGROUND OF THE INVENTION

This invention relates to novel antidotes for poisoning by phosphorus-containing cholinesterase inhibitors.

## SUMMARY OF THE INVENTION

In a compositional aspect, this invention relates to a bis-quaternary pyridinium-2-aldoxime salt of Formula I



wherein R is  $-\text{CO}-\text{R}^1$ ,  $-\text{CO}-\text{NR}^2\text{R}^3$  or  $-\text{COOR}^4$ ;  $\text{R}^1$  is alkyl of 1-6 carbon atoms, cyclohexyl, Ar or benzyl;  $\text{R}^2$  is H, alkyl of 1-6 carbon atoms, cyclohexyl, Ar, aralkyl of 7-13 carbon atoms or 2-pyrimidyl;  $\text{R}^3$  is alkyl of 2-6 carbon atoms, cyclohexyl, Ar, aralkyl of 7-13 carbon atoms or 2-pyrimidyl;  $\text{R}^4$  is alkyl of 2-6 carbon atoms, cyclohexyl, Ar or benzyl; Ar is phenyl, naphthyl or phenyl substituted by up to 5 of alkyl of 1-4 carbon atoms, methoxy or Cl; and X is Cl, Br or I.

In another compositional aspect, this invention relates to a pharmaceutical composition, comprising a compound of Formula I, in admixture with a pharmaceutically acceptable carrier.

In a preparative aspect this invention relates to a process for preparing a pyridinium-2-aldoxime salt of Formula I, by reacting a 1-X-methoxymethyl-2-hydroxyiminomethylpyridinium halide wherein X is as above with a pyridine compound of Formula II



wherein R is as above.

In a method-of-use aspect, this invention relates to a prophylactic or therapeutic method of treating a person or animal for intoxication with a phosphorus-containing cholinesterase inhibitor, comprising administering to the person or animal a compound of Formula I in an amount effective as an antidote for the cholinesterase inhibitor and in admixture with a pharmaceutically-acceptable carrier.

## DETAILED DESCRIPTION

In Formula I, R is most preferably in the 3-position, and is secondarily preferred in the 4-position, of the pyridine ring. R can also be in the 2-position.

In  $\text{R}^1$  and Ar, "alkyl" is preferably methyl, ethyl or tert.-butyl, as well as n-propyl, isopropyl, n-butyl, isobutyl or sec.-butyl. In  $\text{R}^3$  and  $\text{R}^4$ , "alkyl" is preferably tert.-butyl or ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.-butyl, 1-, 2-, or 3-pentyl, 2-methyl-1-butyl, isopentyl (3-methyl-1-butyl), tert.-pentyl (2-methyl-2-butyl), 3-methyl-2-butyl, neopentyl (2,2-dimethyl-1-propyl), 1-, 2- or 3-hexyl, 2-methyl-1-, -2-, or -3-pentyl, 3-methyl-1-, -2- or -3-pentyl, 4-methyl-1- or -2-pentyl,

2-ethyl-1-butyl, 2,3-dimethyl-1- or -2-butyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl or pinacolyl (3,3-dimethyl-2-butyl).

Ar is preferably phenyl, 1-naphthyl or 2-naphthyl. If Ar is substituted phenyl, the substitution is preferably monosubstitution or di-substitution. In the case of polysubstituted aryl, the substituents are preferably identical. Accordingly, Ar is preferably o-, m- or p-tolyl; o-, m-, or p-ethylphenyl; o-, m- or p-n-propylphenyl; o-, m- or p-isopropylphenyl; o-, m- or p-n-butylphenyl; o-, m-, or p-isobutylphenyl; o-, m- or p-sec.-butylphenyl; o-, m- or p-tert-butylphenyl; o-, m- or p-methoxyphenyl; o-, m- or p-chlorophenyl; 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethylphenyl or 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dichlorophenyl. Ar can also be phenyl substituted by up to five substituents, for example, dimethoxyphenyl, such as 3,4-dimethoxyphenyl; trimethoxyphenyl, such as 3,4,5-trimethoxyphenyl; pentamethylphenyl; pentachlorophenyl or 2,6-dimethyl-4-tert.-butylphenyl.

Aralkyl is preferably benzyl; o-, m- or p-alkylbenzyl, wherein alkyl is of 1-4 carbon atoms, most preferably, tert.-butyl; 1-phenylethyl or 2-phenylethyl; 1-, 2- or 3-phenylpropyl, 1-, 2-, 3- or 4-phenylbutyl or diphenylmethyl.

Other examples of preferred  $\text{R}^1$  are phenyl or cyclohexyl,  $\text{R}^2$  is preferably H, and  $\text{R}^3$  and  $\text{R}^4$  are preferably alkyl of 2-6 carbon atoms, most preferably tert.-butyl.

Preferred compounds of Formula I are all those in which at least one of the substituents is as indicated above. Some exemplary preferred groups of compounds of Formula I are those wherein:

(Ia) R is in the 3- or 4-position and is  $-\text{CO}-\text{R}^1$ ;

(Ib) R is in the 3- or 4-position and is  $-\text{CO}-\text{NR}^2\text{R}^3$ ;

(Ic) R is in the 3- or 4-position and is  $-\text{COOR}^4$ ;

(Id) R is in the 3- or 4-position and is  $-\text{COR}^1$  and  $\text{R}^1$  is alkyl of 1-4 carbon atoms, cyclohexyl, phenyl, alkylphenyl of 1-4 carbon atoms in the alkyl, methoxyphenyl, dichlorophenyl or benzyl;

(Ie) R is in the 3- or 4-position and is  $-\text{CO}-\text{NR}^2\text{R}^3$  and  $\text{R}^3$  is alkyl of 2-6 carbon atoms, cyclohexyl, phenyl, alkylphenyl of 1-4 carbon atoms in the alkyl, dichlorophenyl, benzyl, alkylbenzyl of 1-4 carbon atoms in the alkyl, or diphenylmethyl;

(If) R is in the 3- or 4-position and is  $-\text{COOR}^4$  and  $\text{R}^4$  is alkyl of 2-6 carbon atoms, cyclohexyl, phenyl, naphthyl or benzyl;

(Ig) R is in the 3-position;

(Ih) R is in the 3-position and is  $-\text{COC}_6\text{H}_5$ ;

(Ii) R is in the 3-position and is  $-\text{CONHR}^3$  and  $\text{R}^3$  is tert.-butyl or phenyl;

(Ij) R is in the 3-position and is  $-\text{COOR}^4$  and  $\text{R}^4$  is alkyl of 2-4 carbon atoms;

(Ik) R is in the 3-position and is  $-\text{CO}-\text{cyclohexyl}$ ;

(Il) R is in the 3-position and is  $-\text{CONH-tert.-butyl}$ ; and

(Im) R is in the 3-position and is  $-\text{COO-tert.-butyl}$ .

Other compounds are those of Formula I wherein:

(In) R is in the 2-position, and is  $-\text{COR}^1$ ;

(Io) R is in the 2-position and is  $-\text{CONR}^2\text{R}^3$ ;

(Ip) R is in the 2-position and is  $-\text{COOR}^4$ ;

(Iq)  $\text{R}^1$  is alkyl of 1-6 carbon atoms, including each of (Ia) and (In);

(Ir)  $\text{R}^1$  is 2-pyrimidyl, including each of (Ia) and (In);

(Is)  $\text{R}^2$  is H, including each of (Ib), (Ie) and (Io);

(It)  $\text{R}^2$  is alkyl of 1-6 carbon atoms including each of (Ib), (Ie) and (Io);