

higher (almost 3-fold) than prior art substances having reactivation capabilities. For example, the following table compares the effectiveness (antidote effect) of PAM (pyridine-2-aldoxime-methiodide) and TMB4 [trimethylene-1,3-bis-(4-formylpyridiniumbromide)-dioxime] versus Formula I wherein X represents a chloride ion [bis-(4-hydroxy-iminomethylpyridinium-(1)-methyl)-ether dichloride].

TABLE 1

Compound	Michaelis-Menten constants
PAM -----	1.1 · 10 ⁻⁵
TMB4 -----	1 · 10 ⁻⁶
Formula I (chloride) -----	3.1 · 10 ⁻⁷

The "Michaelis-Menten" constants represent the equilibrium in the system enzyme:substrate. The lower the value of the constants, the greater is the reactivation of the enzyme by the reactivator.

The pharmacological investigations were conducted according to the methods described by Hobbiger in Brit. J. Pharmacol., vol. 12, p. 438 (1957), by Büllbring in Brit. J. Pharmacol., vol. 1, p. 38 (1946), and by Bethe et al. in Arch. Exper. Path. Pharmacol., vol. 231, p. 3 (1957). The duration of the activity of the new compounds was tested according to the method described by Kewitz et al. in Arch. Biochem., vol. 64, p. 456 (1957).

Furthermore, the new compound bis-[4-hydroxy-iminomethyl-pyridinium-(1)-methyl]-ether dichloride was found to be very effective as an antidote in O,O-diethyl-O-para-nitrophenyl-thiophosphate intoxication. The therapeutic dose administered twice intravenously in a poisoned subject was 250 mg. The injection instantaneously restored normal blood esterase activity. No side effects were noted.

The new compounds of this invention can be processed into all the conventional forms of pharmaceutical preparations. It is possible, for example, to incorporate the compounds into pills, tablets (sugar coated and otherwise), solutions, emulsions, syrups and solutions for intravenous injections.

To illustrate the invention in even greater detail, the following preferred specific embodiments of the process of this invention are submitted. It is to be understood, however, that the examples are not to be construed as limitative of the specification or appended claims in any way whatsoever.

Example 1

BIS-[4-HYDROXYIMINO-METHYL-PYRIDINIUM-(1)-METHYL]-ETHER-DICHLORIDE

Into a boiling agitated solution of 2.44 g. pyridine-4-aldoxime in 10 cc. absolute ethanol is added dropwise during the course of 25 minutes a solution of 1.14 g. bis-chloromethyl ether in 5 cc. absolute ethanol. The reaction mixture is then refluxed for 35 minutes, and then agitated for 5 hours at room temperature. The precipitate of bis-[4-hydroxyimino-methyl-pyridinium-(1)-methyl]-ether-dichloride is thoroughly washed with absolute acetone. The yield is 3.5 g. which is 98% of the theoretical, and the melting point is 229° C. If convenient, the mother liquor can be reused to make additional product.

Example 2

BIS-[4-HYDROXYIMINO-METHYL-PYRIDINIUM-(1)-METHYL]-ETHER-DICHLORIDE

12.2 g. (0.1 mole) pyridine-4-aldoxime are dissolved with heating in 125 cc. chloroform. Within 25 minutes, 8.5 g. (0.075 mole) α,α' -dichloro-dimethyl-ether in 20 cc. chloroform are added while stirring into the boiling solution. The reaction mixture is heated for another 35 minutes. After standing for several hours, the precipitate is filtered off, washed with absolute ethanol, acetone and ether and dried at 80°. Yield: 17 g.=95% of the theoretical, and the melting point is 225° (with decomposition).

Example 3

BIS-[4-HYDROXYIMINO-METHYL-PYRIDINIUM-(1)-METHYL]-ETHER-DIBROMIDE

12.2 g. (0.1 mole) pyridine-4-aldoxime are dissolved in 200 cc. boiling methylene chloride. To the cooled solution there are added dropwise with stirring 15 g. (0.075 mole) α,α' -dibromo-methyl-ether in 20 cc. methylene chloride. The precipitate is filtered off, washed thoroughly with ethanol, acetone or ether, and dried. Yield: 20.2 g.=90% of the theoretical and the melting point is 202° (with decomposition).

Example 4

BIS-[4-HYDROXYIMINO-METHYL-PYRIDINIUM-(1)-METHYL]-ETHER-SUCCINATE

3.59 g. (0.01 mole) of the bis-[4-hydroxyimino-methyl-pyridinium-(1)-methyl]-ether-dichloride obtained according to Example 2 are dissolved in 70 cc. hot methanol (90%). With stirring, 3.30 g. (0.01 mole) silver succinate are added. The reaction mixture is heated for 5 minutes, then the precipitate is filtered off. Upon addition of ether the succinate crystallizes with 5 moles of water. Yield: 3.16 g.=64% of the theoretical. Melting point 167° (with decomposition). Upon drying in vacuo a yellow mono-hydrate is obtained which regenerates the colorless pentahydrate when stored at the air.

Example 5

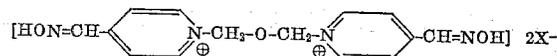
BIS-[4-HYDROXYIMINO-METHYL-PYRIDINIUM-(1)-METHYL]-ETHER-DIPERCHLORATE

2.8 cc. perchloric acid (70%) are added with cooling to a solution of 3.6 g. of the dichloride obtained according to Example 2 in 110 cc. ethanol (75%). After standing for 3 hours, 3.8 g. (=78% of the theoretical) of the diperchlorate are crystallized. Melting point 205° (with decomposition).

From the foregoing description, one skilled in the art can readily appreciate the essential characteristics of this invention, and without departing from the spirit and scope of essential characteristics, one can modify and adapt this invention to various usages and conditions. Such modifications and adaptations of this invention should, and are intended to be within the full range of equivalence of the following claims.

What is claimed is:

1. Pharmaceutically acceptable, non-toxic, crystalline, water-soluble bis-quaternary pyridinium salts conforming to the following structural formula—



wherein X represents one equivalent of an anion.

2. The salts of claim 1 wherein X is selected from the group of anions consisting of halide, perchlorate, and succinate.

3. The salts of claim 1 wherein X is a chloride anion.

4. The salts of claim 1 wherein X is a bromide anion.

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