United States Patent Office

3,137,702

Patented June 16, 1964

3,137,702
PREPARATION OF BIS-QUATERNARY PYRIDINIUM SALTS

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No Drawing. Filed Aug. 11, 1961, Ser. No. 132,265
Claims priority, application Germany Aug. 13, 1960
4 Claims. (Cl. 260—296)

This invention relates to the preparation of novel pyridinium salts which, in particular, are potent reactivators for inhibited acetylcholinesterase.

It is well known that the so-called military "nerve gases," as well as many of the more prosaic insecticides, are comprised of organophosphorous compounds such as diisopropylphosphofluoridate (DEP), and tetraethylpyrophosphate (TEPP). These compounds are potent toxic agents because of their inhibitory effect on certain fundamental enzymes, particularly acetylcholinesterase which under normal conditions catalyzes the necessary hydrolysis of nervous tissue.

Due not only to the military aspects of these enzyme inhibitors, but due also to the fact that these organophosphorous compounds are being sold in abundant quantities to both the farmer and the home gardener, it is necessary to provide an effective antidote for these inhibitors, as a matter of public health. Whereas certain antidotes have been suggested, such as pyridine-2-aldoxime-methiodide ("PAM"), I. B. Wilson and F. Sondheimer, Archives of Biochemistry and Biophysics, vol. 69, p. 468 (1957), and trimethylene-1-3-bis-(4-formylpyridiniumbromide)-dioxime ("TMB4"), E. J. Poziomek, B. E. Hackley, Jr., and G. M. Steinberg, Journal of Organic Chemistry, vol. 23, p. 714 (1958), nevertheless these compounds have not been accepted as the ultimate antidotes.

The object of this invention, therefore, is to provide novel and highly potent antidotes which can reactivate acetylcholinesterase which has been inhibited by organophosphorous poisons.

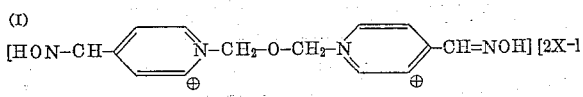
Another object of the invention is to provide novel intermediates which can be utilized to prepare more sophisticated compounds in an attempt to discover even more efficacious reactivators for inhibited acetylcholinesterase.

Still a further object of this invention is to provide a novel process for preparation of the novel compounds herein disclosed.

Upon further study of the specification and appended claims, other objects and advantages of this invention will become apparent.

To attain the objects of this invention, it has been discovered that at least about a 3-fold increase in reactivation power can be obtained by bis-quaternary pyridinium salts of the following formula—

(I)



wherein X is an equivalent of a monovalent or polyvalent anion.

In brief, the novel compounds of this invention are prepared by reacting pyridine-4-aldoxime with a bis-substituted ether of the following formula

(II) $Y—CH_2—O—CH_2—Y$

wherein Y is a halogen atom, preferably a chlorine or bromine atom. The substituent Y of the methylether appears as anion X in the obtained pyridinium salts. Subsequently, the halogen anion X can be exchanged, if desired, for other anions by conventional techniques such as ion exchange or metathesis or reaction with acids or other salts.

The reaction of the ether and the pyridine-4-aldoxime is preferably conducted in a solvent in which both reactants are soluble. Of course innumerable solvents are available for this purpose, and they can be selected from either literature data, or by a simple test. Among the possible solvents, it is preferred to employ aliphatic alcohols having from 1 to 5 carbon atoms, hydrocarbons such as benzene, or hydrocarbon derivatives such as chloroform, dichloromethane, and dimethyl formamide.

Any concentration of the reactants in the chosen solvent can be employed as long as the reactants are, in fact, in solution. Of course, it is desirable, from the standpoint of economics, to employ higher concentration of the reactants rather than lower concentrations.

The ratio of the reactants can also be varied, a stoichiometric ratio being satisfactory.

As a preferred technique for conducting the reaction, it is advantageous to form a first solution of the pyridine-4-aldoxime, and then to pass a second solution of the substituted methyl ether into the first solution. By this technique, the formation of mono-derivatives is avoided, and the pure reaction product is obtained directly in very high yields.

In general, the reaction can be conducted at from 0–120° C., preferably 20–80° C. For the sake of convenience, it is desirable to employ an operating temperature equal to the boiling point of the reaction medium, so that reflux conditions can be observed without the necessity of superatmospheric pressures. However, if it is desired, higher than reflux temperature can be employed by providing pressure vessels and associated equipment.

With respect to the time necessary for the completion of the reaction, it of course is dependent on the nature of the substituted-methyl ether and also on the operating temperature, but in general about 30 minutes are required for the completion of the reaction. After the reaction is completed, it is convenient to continue the agitation of the reaction mixture for about 10 minutes in order to improve the physical properties, such as filterability, of the precipitated product. The precipitate is then filtered and washed with absolute acetone to remove impurities. The mother liquor, if desired, can be reused as a reaction media to additional products.

With respect to the product, Formula I, it is preferred that X is a halide (bromide, fluoride, iodide and chloride), and particularly a chloride ion. Other preferred anions are also anions of relatively strong acids such as for example, the perchlorate anion. In general, however, the anion merely has to meet the requirement of being capable of forming a salt with the quaternary pyridinium base. An example of a multivalent anion is, for example, the succinate anion.

In order to obtain the preferred anions in the products of this invention, there can be employed as the bis-substituted methyl ethers, dihalogendimethyl ethers, such as the α,α'-dichloro- and the α,α'-dibromo-dimethyl ether. In addition, once the product is formed, the halogen anion can be exchanged with other anions by conventional methods. For example, if X is a chloride ion, it can be treated with perchloric acid to form the corresponding bis-perchlorate salt, or it can be treated with the silver salt of succinic acid to obtain the succinate.

The novel pyridinium salts of this invention are crystalline and water-soluble. They are capable of reactivating the enzyme acetylcholinesterase which has been previously inhibited by organophosphorous pesticides or chemical warfare agents. This reactivation effect is considerably