United States Patent Office

3,135,761

Patented June 2, 1964

3,135,761
BIS QUATERNARY OXIMES

Brennie E. Hackley, Jr., and Edward J. Poziomek, Edgewood, and George M. Steinberg, Baltimore, Md., assignors to the United States of America as represented by the Secretary of the Army

No Drawing. Original application Apr. 28, 1959, Ser. No. 809,578, now Patent No. 3,077,476, dated Feb. 12, 1963. Divided and this application Oct. 11, 1961, Ser. No. 151,122

7 Claims. (Cl. 260—296)

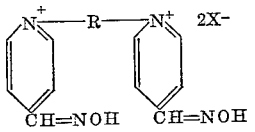
(Granted under Title 35, U.S. Code (1952), sec. 266)

This invention described herein may be manufactured and used by or for the Government of the United States of America for governmental purposes without the payment to us of any royalty thereon.

This is a division of application Serial No. 809,578, filed April 28, 1959, now Patent No. 3,077,476, granted February 12, 1963.

This invention is directed to certain diquaternary pyridinium halide oximes which are useful as chemotherapeutic and prophylactic agents for mammals poisoned by anticholinesterases, particularly the "nerve gas" known as GB or sarin, i.e., isopropyl methylphosphonofluoridate.

The invention relates to 1,1′-polymethylene bis (4-formylpyridinium) halide dioximes wherein the polymethylene group contains from 2 to 6 carbon atoms. These compounds have the structural formula

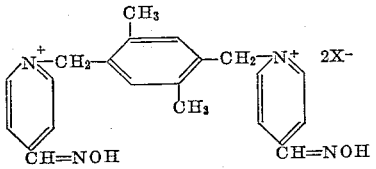


(I)

where R is a polymethylene group having from two to six carbon atoms and X^- is chloride, bromide or iodide.

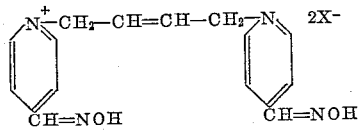
This invention further includes compounds of Formula I, but in which R is a polymethylene group containing from seven to ten carbon atoms.

This invention further includes 1,1′-(2,5-dimethyl-p-phenylenedimethylene) bis (4-formylpyridinium) halide dioximes of the formula



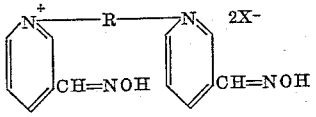
(II)

The invention also relates to 1,1′-(2-butenylene) bis (4-formylpyridinium) halide dioximes of the formula



(III)

The invention further relates to 1,1′-ploymethylene bis (3-formylpyridinium) halide dioximes of the formula

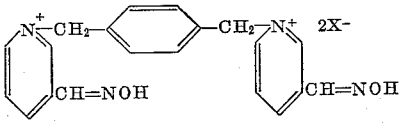


(IVa)

wherein R is a polymethylene group containing from 2 to 6 carbon atoms

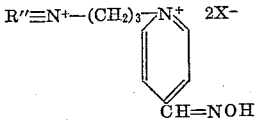
Another class of compounds included are the 1,1′-(p-

phenylenedimethylene) bis (3-formylpyridinium) halide dioximes of the formula



(IVb)

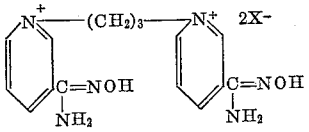
This invention further relates to unsymmetrical bisquaternary 4-formylpyridinium halide monoximes of the formula



(V)

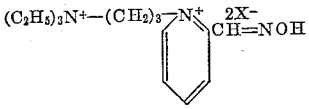
wherein R″ represents either three lower alkyl groups or the hydrocarbon portion of the pyridine ring.

This invention also relates to the 1,1′-trimethylene bis (3-amidooximopyridinium) halides



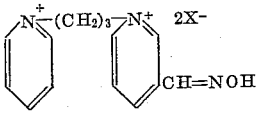
(VI)

This invention also relates to the compounds



(VII)

The invention also relates to the compounds



(VIII)

While all these compounds are useful in varying degree for the purposes set out above, the different groups exhibit quite striking differences in effectiveness. In all the above formulas X^- is chloride, bromide or iodide, which appear to be equivalents as to physiological action, except for their effect on solubility.

Wilson et al., in Patent No. 2,816,113, granted Dec. 10, 1957, disclose a group of compounds which are effective as antidotes for treatment of mammals poisoned by compounds of high anticholinesterase activity, such as the "nerve gases" diisopropylphosphorofluoridate (DFP), isopropyl methylphosphonofluoridate (GB), and O-ethyl, N,N-dimethyl phosphoroamidocyanidate (GA), as well as other related organic phosphorus compounds, including many insecticides. The compound of the Wilson et al. group which has received by far the most attention is 2-formyl-1-methyl pyridinium iodide oxime, commonly known as 2-pyridine aldoxime methiodide or 2-PAM. This compound is outstanding in its ability to reactivate, in vitro, acetyl cholinesterase which has been inhibited by, for example, GB. Thus, even as compared to the very closely related 4-PAM, disclosed in Example II of the Wilson patent, 2-PAM shows much greater activity. With isopropyl methylphosphonylated acetylcholinesterase the rate constant at pH 7.4 and 25° C. in the presence of 10^{-3} M acetylcholine is 2×10^3 per mole per minute for 2-PAM and 1.4×10^2 per mole per minute for 4-PAM. The Wilson patent shows a high rate of survival in mice which had been poisoned with paraoxon and then treated with 2-PAM.

Nerve gas poisoning has been treated symptomatically with drugs which are pharmacologically antagonistic to acetyl choline. Such a compound is atropine and it is at