

5

properties. (In this and all following tables the survival ratios are those for rats challenged by 2LD₅₀ doses of GB or (VX) and the oxime was employed therapeutically.)

Compounds of Formula III showed reactivation rates very close to those of our preferred group. Thus when X⁻ in Formula III is bromide the reactivation rate constant was 8×10³ as compared to the value for the R=(CH₂)₄ member of our preferred group of 6×10³. For the unsaturated member (Formula III) the survival ratio for rats challenged by GB was only 1/4 as compared to 6/6 for the saturated analogue (Formula I). Both gave complete survival (ratios of 4/4 and 6/6) for animals challenged by VX, however.

Compounds of Formula IVa showed anomalous properties.

They gave reactivation rates which were low, but survival ratios which were high as compared to 2-PAM, as shown by Table 6, X⁻ being bromide.

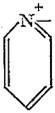
TABLE 6

R	Reactivation rate constant	Survival ratio (GB)
(CH ₂) ₂ -----	3.5×10 ³	4/4
(CH ₂) ₃ -----	4.2×10 ²	3/4

The compounds of group IVb, which are closely related to those of IVa, were somewhat less effective. When X⁻ was bromide the compound had the following properties: Reactivation Rate Constant 2×10², Survival Ratio (GB)—2/4.

The compounds of group V were another group in which the results of therapeutic treatment against GB were better as compared to 2-PAM than the reactivation rate constants would suggest, as shown by the following table, X⁻ being bromide.

TABLE 7

R''≡N ⁺ —	Reactivation rate constant	Survival ratio (GB)
	1.3×10 ³	4/4
(C ₂ H ₅) ₃ N ⁺ -----	1.2×10 ³	4/4

The compounds of Formulas VI, VII and VIII, while being of different structure are alike in exhibiting reactivation rate constants which are very low as compared to 2-PAM but giving high survival ratios as shown by Table 8, X⁻ being bromide in each case.

TABLE 8

Formula No.	Reactivation rate	Survival ratio (GB)
VI-----	69-----	4/4
VII-----	Negligible	4/4
VIII-----	67-----	4/4

Preparation of Compounds

4-pyridinecarboxaldehyde oxime was prepared by warming on a steam bath a neutralized aqueous solution of 4-pyridinecarboxaldehyde and hydroxylamine hydrochloride. The oxime had a melting point of 130–130.5° C. The 2- and 3-oximes were produced by similar methods.

The quaternization to produce dioximes was carried out by reacting the proper oxime with a 1, n dihaloalkane, (CH₂)_n X₂ employing a 3:1 molar ratio of oxime to

6

halide. The unsymmetrical quaternary monoximes were obtained by reacting the pyridine oxime with the appropriate omega-halopropyl quaternary salt in a 1.5:1 molar ratio. Two procedures were utilized.

Procedure A.—A mixture of the pyridine oxime and halide was dissolved in sufficient ethanol and refluxed for the period of time specified in Table 9.

Procedure B.—A mixture of the oxime and halide was dissolved in about 100 ml. of ethanol and heated in a 200 ml. capped pressure bottle (carbonated beverage type) for the length of time specified. The reaction mixtures were cooled to room temperature and the product removed by filtration. In several instances it was necessary to add absolute ether to effect complete precipitation. The products were recrystallized from ether. This procedure was usually employed because of its simplicity.

Table 9 gives the procedure, yields and melting points for representative compounds.

TABLE 9

Formula No.	Substituents			Conditions	Yield per cent	Melting (m) or decomposition (d) point, °C.
	Halide	R	R''			
25						
I-----	Br	(CH ₂) ₂ -----	-----	A, 31 hr..	35.0	>300 m.
I-----	Br	(CH ₂) ₃ -----	-----	B, 48 hr..	88.2	238-241 d.
I-----	Br	(CH ₂) ₄ -----	-----	B, 16 hr..	81.0	239-241 d.
I-----	Br	(CH ₂) ₅ -----	-----	B, 95 hr..	95.0	208-210 d.
I-----	Br	(CH ₂) ₁₀ -----	-----	B, 8 hr..	85.0	219-223 d.
30						
II-----	01-----	-----	-----	B, 68 hr..	70	>300 m.
IVa-----	Br	(CH ₂) ₃ -----	-----	B, 60 hr..	68	208-211 m.
IVa-----	Br	(CH ₂) ₅ -----	-----	B, 60 hr..	80	226-231 m.
IVb-----	Br	-----	-----	B, 20 hr..	83.5	243-251 m.
V-----	Br	(C ₂ H ₅) ₃ -----	-----	B, 69 hr..	43	230-231 d.
V-----	Br	Pyridine ring.	-----	B, 64 hr..	10	223-226 d.
35						
VIII-----	Br	-----	-----	B, 90 hr..	16	201-203 d.

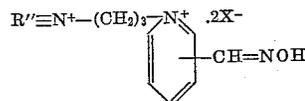
Further details regarding the preparation and properties of certain of our compounds are given in the following publications; by us and our associates.

"Pyridine Aldoximes" by Edward J. Poziomek, Brennie E. Hackley, Jr. and George M. Steinberg, "Journal of Organic Chemistry," vol. 23, pp. 714-717 (May 1958); and "Chemotherapeutic Effectiveness of Trimethylene bis (4-formyl pyridinium bromide) dioxime in Anticholinesterase Poisoning" by Edmund Bay, S. Kropp and L. F. Yates, Proceedings of the Society for Experimental Biology and Medicine, vol. 98, pages 107-109 (May 1958). These articles are to be considered incorporated by reference in this specification.

While we have shown a number of specific examples of compounds and their use, it will be obvious that various changes can be made without departing from our invention, which is defined by the following claims.

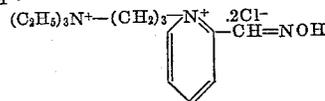
We claim:

1. A compound of the formula



wherein R'' is selected from the group consisting of three lower alkyl groups and the hydrocarbon portion of the pyridine ring, and where X⁻ is selected from the class consisting of chloride, bromide and iodide.

2. A compound of the formula



3. A compound of the formula

