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OXIMES OF αω-DIQUATERNARY ALKANE SALTS AS ANTIDOTES TO ORGANOPHOSPHATE ANTICHOLINESTERASES

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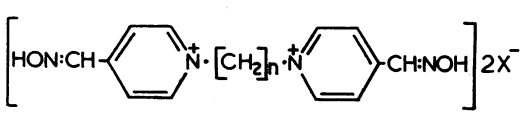
Sixteen compounds of the general structure $\{HON:CH.C_5H_4N^+.[CH_2]_n.R^+\}2Br^-$ have been synthesized in which the position of the oxime group in the pyridine ring, the second charged group R^+ and the number of methylene groups between the charged atoms have been varied. The rate at which these compounds reactivate cholinesterase inhibited by ethyl pyrophosphate has been studied and a number have been found which are more active than 2-hydroxyiminomethyl-*N*-methylpyridinium methanesulphonate. Since considerable variation in structure was found among those compounds which are better reactivators than the latter, the concept that 2-hydroxyiminomethyl-*N*-methylpyridinium salts are unique in their ability to fit the surface of the inhibited enzyme is no longer tenable. The reactivating power of these oximes correlated well with their ability, when given in conjunction with atropine, to save the lives of mice poisoned by ethyl pyrophosphate. The most effective compounds, *NN'*-trimethylenebis-(4-hydroxyiminomethylpyridinium bromide) and *NN'*-hexamethylenebis(2-hydroxyiminomethylpyridinium bromide), contained a further oxime group in R^+, but the second oxime group was not essential for high activity. These new oximes were also superior in saving the lives of mice poisoned with sarin (isopropyl methylphosphonofluoridate), but the improvement was not as dramatic as when the mice were poisoned with ethyl pyrophosphate. The toxicity of the compounds varied with both *n* and R^+ and was unrelated to the therapeutic potency.

Oximes derived from pyridinium aldehydes have been shown to be potent reactivating agents for cholinesterase inhibited by organophosphates and of considerable value in treating organophosphate-poisoned animals, especially when given in conjunction with atropine. Until recently, the most effective compound in both these respects was 2-hydroxyiminomethyl-*N*-methylpyridinium iodide (pyridine-2-aldoxime methiodide; P2AM) or the methanesulphonate (P2S) (for review see Davies and Green, 1959). Poziomek, Hackley and Steinberg (1958) and, independently, Hobbiger, O'Sullivan and Sadler (1958) have described a new group of oximes, *NN'* - polymethylenebis(4 - hydroxyiminomethyl - pyridinium) compounds, with general structure (I) which were reported to be at least as effective,



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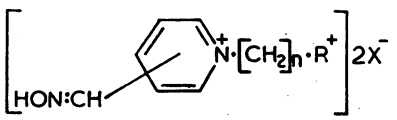

II

or even better, both as reactivators and as antidotes to organophosphates. We have examined sixteen compounds with the more general structure (II), in which we have varied the number of hydroxyiminomethyl groups and their positions in the pyridine ring or rings, the number of carbon atoms between the two charged atoms, and the nature of the second charged group R^+. These compounds have been tested for their ability to inhibit cholinesterase and to reactivate cholinesterase inhibited with organophosphate, for their ability to save the lives of poisoned mice, and for their intrinsic toxicity. A moderately good relationship has been shown between life-saving properties and ability to reactivate, whereas none can be seen between either of these properties and intrinsic toxicity.

METHODS

Preparation of Oximes. — 2-Hydroxyiminomethyl-*N*-methylpyridinium methanesulphonate was prepared as described by Davies, Green, and Willey (1959). Symmetrical compounds of the formula (I), but in which the position of the hydroxyiminomethyl groups in the rings was varied, were obtained by the method of Poziomek *et al.* (1958) from the appropriate pyridine aldoxime. For compounds with the hydroxyiminomethyl group in the 2-position in the pyridine ring, acetone was preferred as a solvent to ethanol, but even so yields were only about 1 to 2%. Unsymmetrical compounds (II) in which R^+ was a charged group such as pyridinium, isoquinolinium, or triethylammonium, were prepared by either of two routes. Yields by both methods were generally satisfactory.

(i) The tertiary nitrogen compound was boiled under reflux with 4 mol. equivalents of the polymethylene dibromide in anhydrous benzene. The *N*-ω-bromoalkyl compound crystallized out on cooling. This compound (in some cases after recrystallization from ethanol) was dissolved in anhydrous ethanol and was boiled under reflux for 16 hr. with 1 mol. equivalent of 4-hydroxyiminomethylpyridine. Sometimes the diquaternary oxime crystallized out on cooling, but in some cases, especially when the second base was aliphatic, the product was obtained on evaporation of the solvent as a deliquescent gum which solidified only after prolonged drying over P_2O_5.

(ii) During the preparation of the symmetrical dioximes, some *N*-(ω-haloalkyl)-hydroxyiminomethylpyridinium halide was often obtained as a by-product. These compounds, when boiled in ethanol with an unsaturated heterocyclic base, gave the desired unsymmetrical diquaternary oximes.

Table I shows the compounds prepared, and their elemental analyses and melting points. For ease of reference the structures have been indicated by the following code: The position of the hydroxyiminomethyl group in the pyridine ring is indicated by the first figure and, in the case of dioximes, also by the third figure. The number of methylene groups between the quaternary atoms is indicated by the second figure. In unsymmetrical compounds the nature of the group R^+ (formula II) is indicated by a terminal letter or letters. For example, *NN'*-hexamethylenebis(4 - hydroxyiminomethylpyridinium bromide) is designated C4.6.4, and trimethylene-1-(3-hydroxyiminomethylpyridinium) - 3 - isoquinolinium dibromide is designated C3.3.IQ. The initial letter C denotes this particular series of synthetic compounds.

Inhibition of Cholinesterase by the Oximes.— Washed human erythrocytes suspended in an equal volume of 0.9% NaCl were used as the source of true cholinesterase. Activity of cholinesterase in the presence of most of the compounds was determined by continuous titration at *p*H 7.4 and 25°. The acid produced when 0.5 ml. of the enzyme preparation was added to a stirred mixture of 4.4 ml. of 0.3M-KCl, 0.5 ml. of 0.1M-acetylcholine iodide, and 0.6 ml. of oxime dissolved in 0.1M-KCl was titrated with 0.1N-NaOH.

Reactivation of Cholinesterase.—Washed human erythrocytes were shaken gently for 30 min. at 25° with an equal volume of 0.9% NaCl containing 10^{-6}M ethyl pyrophosphate. The cells were washed with ice-cold saline to remove excess ethyl pyrophosphate and were then suspended in an equal volume of saline and stored in a refrigerator until used. 10 ml. of the cell suspension was mixed with 10 ml. of a solution of reactivator in barbitone buffer *p*H 7.4 (0.01M barbitone sodium, 0.002M-KH_2PO_4 and 0.3M-KCl) kept at 25°. At suitable times, 1 ml. samples were withdrawn and their cholinesterase activity determined by the electrometric method

TABLE I

COMPOUNDS PREPARED

Code numbers, empirical formulae, analyses, and melting points of the oximes tested. Del. = deliquescent; ST, *S*-thiouronium; P, pyridinium; MP, 4-methylpyridinium; NEt_3, triethylammonium; IQ, isoquinolinium. For explanation of code see text.

Code No.	Empirical Formula	Analysis						M.P. °C.
		C		H		N		
		Calc.	Found	Calc.	Found	Calc.	Found	
C4.3.ST	$C_{10}H_{16}ON_4SBr_2$	30·1	30·1	3·8	4·3			205–6
C4.2.4	$C_{14}H_{16}O_2N_4Br_2$					13·0	12·8	285
C4.3.P	$C_{14}H_{17}ON_3Br_2$					10·4	10·3	212
C2.3.2	$C_{15}H_{18}O_2N_4Br_2$	40·4	40·0	4·1	4·4			226–8
C3.3.3	$C_{15}H_{18}O_2N_4Br_2$	40·4	39·9	4·1	4·4			203
C4.3.4	$C_{15}H_{18}O_2N_4Br_2$	40·4	40·3	4·1	4·3	12·6	12·1	222
C4.3.MP	$C_{15}H_{19}ON_3Br_2$					10·1	9·8	205–6
C4.3.NEt_3	$C_{15}H_{27}ON_3Br_2$	42·4	42·1	6·4	7·0			Del.
C4.4.4	$C_{16}H_{20}O_2N_4Br_2$	41·7	41·1	4·4	4·9			245–6
C3.3.IQ	$C_{18}H_{19}ON_3Br_2$	47·7	47·5	4·2	4·7	9·3	8·7	Del.
C4.3.IQ	$C_{18}H_{19}ON_3Br_2$					9·3	9·1	215–6
C2.3.IQ	$C_{18}H_{19}ON_3I_2$					7·7	7·4	219
C2.6.2	$C_{18}H_{24}O_2N_4Br_2$	44·3	43·5	5·0	5·3	11·5	11·0	205–7
C3.6.3	$C_{18}H_{24}O_2N_4Br_2$	44·3	44·3	5·0	5·3			240
C4.6.4	$C_{18}H_{24}O_2N_4Br_2$	44·3	44·0	5·0	5·6			212–4
C4.10.4	$C_{22}H_{32}O_2N_4Br_2$					10·3	9·6	210–2

(Michel, 1949). In order to measure the total possible extent of reactivation 2 ml. of inhibited enzyme suspension was incubated with 2 ml. 0.02M hydroxyiminoacetone in barbitone buffer for 6 hr. at 25°, when reactivation was effectively complete (Davies and Green, 1956).

Animal Experiments.—All the experiments were carried out on female mice weighing 15 to 25 g. Saline solutions of ethyl pyrophosphate or sarin (isopropyl methylphosphonofluoridate) were injected in a volume of 10 ml./kg. subcutaneously into the loose skin at the back of the neck. The oxime (for doses see tables) and atropine sulphate, 17.4 mg./kg., were given intramuscularly in a volume of 3 ml./kg. into the outer aspect of the hind leg, either 10 min. before or 1 min. after injection of the organophosphate.

RESULTS

Inhibition and Reactivation of Cholinesterase

Table II shows the inhibitory effect of diquaternary oximes on erythrocyte cholinesterase. At 2×10^{-5}M only those compounds in which the two quaternary nitrogen atoms are separated by six or more carbon atoms show any significant inhibition. This increase of inhibitory power with increase in chain length is similar to that found with other diquaternary alkanes (Paton and Zaimis, 1949). Reactivation was carried out with an oxime concentration of 2×10^{-5}M. For assay, the solution was diluted tenfold, thereby reducing the oxime concentration to 2×10^{-6}M. At this concentration, only C4.10.4 gave any measurable inhibition and that only 40%, so any apparent failure to reactivate could not have been due to inhibition by the oxime during assay.

Interpretation of the reactivation experiments is made difficult by the apparent complexity of the kinetics (Fig. 1). Many of the compounds caused fairly rapid reactivation during the first few minutes of contact with the inhibited enzyme, but then reactivation apparently ceased or continued only very slowly (Curve **B**). The level of this apparent plateau in the rate curve for reactivation varied with the concentration of the oxime. Even with those compounds which gave complete reactivation and showed pseudo-unimolecular kinetics (Curve **A**) the apparent second-order rate constant varied with concentration as was found earlier with 2-hydroxyiminomethyl-*N*-methylpyridinium iodide (Green and Smith, 1958). It was thus not possible to use normal kinetic constants as a measure of comparative reactivating power. It was necessary instead to choose some arbitrary parameter to give some indication of the actual relative reactivating potencies. A fixed

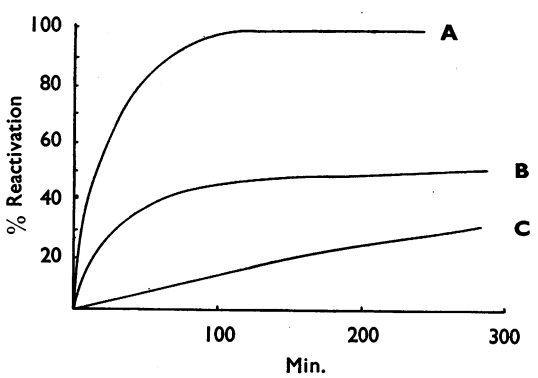

FIG. 1.—Reactivation of cholinesterase inhibited with ethyl pyrophosphate by oximes in concentrations of 2×10^{-5} M, *p*H 7.4 and 25°. A: C2.6.2. B: C4.3.IQ. C: C3.6.3.

TABLE II

INHIBITION OF CHOLINESTERASE, AND REACTIVATION OF DIETHYLPHOSPHORYL-CHOLINESTERASE, BY DIQUATERNARY OXIMES

The concentration used 2×10^{-5} M, *p*H 7·4 and 25°. Compounds marked n.t., not tested.

Compound		Aldoxime Positions or End Group	Chain Length	% Inhibition	Time Required for 25% Reactivation (min.)
2-Hydroxyiminomethyl-*N*-methylpyridinium methanesulphonate				0	60
4-Hydroxyiminomethyl-*N*-methylpyridinium methanesulphonate				0	>300
Group 1 Polymethylene 4,4′-dialdoximes	C4.2.4	4,4′	2	0	5
	C4.3.4	4,4′	3	0	5
	C4.4.4	4,4′	4	0	7
	C4.6.4	4,4′	6	32	25
	C4.10.4	4,4′	10	88	>300
Group 2 Trimethylene dialdoximes	C2.3.2	2,2′	3	0	120
	C3.3.3	3,3′	3	n.t.	220
	C4.3.4	4,4′	3	0	5
Group 3 Hexamethylene dialdoximes	C2.6.2	2,2′	6	32	4
	C3.6.3	3,3′	6	48	180
	C4.6.4	4,4′	6	32	25
Group 4 Monoaldoximes with *iso*-quinolyl-propyl chain	C2.3.IQ	2	3	n.t.	30
	C3.3.IQ	3	3	,,	>300
	C4.3.IQ	4	3	0	15
Group 5 Trimethylene 4-aldoximes with different end groups	C4.3.4	Pyridinium-4-aldoxime (4,4′)	3	0	5
	C4.3.P	Pyridinium	3	n.t.	13
	C4.3.IQ	Isoquinolinium	3	0	15
	C4.3.NEt$_3$	Triethylammonium	3	0	130
	C4.3.ST	Thiouronium	3	0	>300

reactivator concentration of 2×10^{-5}M has been used, and the parameter selected was the time required for 25% of the total inhibited enzyme to be reactivated. With all the compounds that gave a plateau effect, as in Curve **B**, the level of the plateau at this concentration was above 25%, and no reactivators which give only an initially rapid reactivation have been excluded by choosing this parameter. It is probable that 25% recovery of the cholinesterase activity *in vivo* would be more than sufficient to maintain life (Kewitz and Nachmansohn, 1957; Rutland, 1958). The times taken for 25% reactivation are given in Table II.

The effect of the methylene chain length upon reactivating power varied with the position of the hydroxyiminomethyl group in the pyridine ring. In the 4,4′-dioxime series (C4.*n*.4) reactivating power fell as the chain length increased; in the 3,3′-dioxime series (C3.*n*.3) changing the chain length from 3 to 6 carbon atoms had no significant effect, whereas in the 2,2′-dioxime series (C2.*n*.2) increasing the chain length to the same extent very greatly increased the reactivating power. The compounds with the hydroxyiminomethyl group in the 3-position in the pyridine ring were in general very much inferior to those with the hydroxyiminomethyl group in the 2- or 4-position. This might be expected from earlier work with the simple hydroxyiminomethyl-*N*-methylpyridinium iodides (Green and Smith, 1958).

The Toxicity of Diquaternary Oximes.—Table III shows the approximate maximum non-lethal dose of most of the oximes given subcutaneously. The toxicity generally increased with increasing methylene chain length, although even with a fixed chain length there was some variation which depended on the nature of R+. No obvious signs of poisoning were noticed at 5 mg./kg. with any of these compounds, while some of the more promising compounds were not toxic at 50 mg./kg. As with 2-hydroxyiminomethyl-*N*-methylpyridinium methanesulphonate (Davies and Willey, 1958), lethal doses caused muscular tremors, convulsions, cyanosis and death within 15 to 30 min.

TABLE III

TOXICITY TO MICE OF SOME DIQUATERNARY OXIMES

The dose recorded is the maximum at which no deaths occurred. The oximes were given subcutaneously to groups of 5 mice.

Dose (mg./kg.)			
5	10	20	50
C4.10.4	C4.6.4		C4.2.4
			C4.3.4
C2.6.2			C2.3.2
	C3.6.3		C3.3.3
		C4.3.IQ	C3.3.IQ
		$C4.3.NEt_3$	C4.3.P
			C4.3.MP
			C4.3.ST

TABLE IV

EFFECT OF OXIMES ON THE TOXICITY OF ETHYL PYROPHOSPHATE TO MICE

5 mg./kg. of the oxime plus 17·4 mg./kg. atropine sulphate were given intramuscularly 10 min. before subcutaneous ethyl pyrophosphate. Number of deaths/group of 6 mice is recorded. Ethyl pyrophosphate alone caused no deaths at 0·25 mg./kg. and 6 deaths at 0·5 mg./kg.

		Dose of Ethyl Pyrophosphate (mg./kg.)						
		1	2	4	8	16	32	64
Oxime								
2-Hydroxyiminomethyl-*N*-methylpyridinium methanesulphonate		0	2	5				
4-Hydroxyiminomethyl-*N*-methylpyridinium methanesulphonate		5	6					
Group 1	C4.2.4				0	3	6	
	C4.3.4					1	1	4
	C4.4.4				1	4	5	
	C4.6.4		0	3	6	5	5	6
	C4.10.4	2	4	5	6			
,, 2	C2.3.2		3	5	6	6		
	C3.3.3	1	3	5	4	6		
	C4.3.4					1	1	4
,, 3	C2.6.2				0	0	2	2
	C3.6.3			1	2	6		
	C4.6.4		0	3	6	5	5	6
,, 4	C2.3.IQ		1	5	4	6		
	C3.3.IQ		5	6	5	6	6	
	C4.3.IQ				1	3	4	4
,, 5	C4.3.4					1	1	4
	C4.3.P				1	3	4	6
	C4.3.MP				0	2	4	6
	C4.3.IQ				1	3	4	4
	$C4.3.NEt_3$		1	5	6	6		
	C4.3.ST		6	6				

Effect of the Oximes upon the Toxicity of Ethyl Pyrophosphate to Mice.—Table IV shows the effect of 5 mg./kg. of the oximes, given with 17.4 mg./kg. of atropine sulphate 10 min. before various doses of ethyl pyrophosphate. With few exceptions the compounds were at least as effective as 2 - hydroxyiminomethyl-*N*-methylpyridinium methanesulphonate and C4.3.4 and C2.6.2 were outstandingly good. The effect of increasing the methylene chain length varied with the position of the hydroxyiminomethyl group. In the series C4.*n*.4 (Group 1) the best had a 3-carbon chain, whereas with both series C2.*n*.2 and C3.*n*.3 (Groups 2 and 3) six methylene groups were better than three. Of the unsymmetrical oximes (Group 5) those in which the second charged group R+ is a quaternary nitrogen heterocyclic group were much better than those in which it is a thiouronium or triethylammonium group.

TABLE V

EFFECT OF OXIMES ON TOXICITY OF ETHYL PYROPHOSPHATE TO MICE

10 mg./kg. of the oxime plus 17·4 mg./kg. of atropine sulphate were given intramuscularly 1 min. after ethyl pyrophosphate, subcutaneously. Number of deaths in groups of 10 animals is recorded. Ethyl pyrophosphate alone caused no deaths at 0·32 mg./kg., 10 deaths at 0·50 mg./kg. At 10 mg./kg. the animals collapsed before oxime and atropine could be given.

Oxime	Dose of Ethyl Pyrophosphate (mg./kg.)				
	0·8	1·6	3·2	6·3	8·0
2-Hydroxyiminomethyl-*N*-methylpyridinium methanesulphonate	0	7	10		
C4.3.4		0		3	4
C4.3.P			3	3	7

The oximes have been given 1 min. after ethyl pyrophosphate in only a few experiments (Table V). Very good results were again obtained, particularly with C4.3.4. With large doses of ethyl pyrophosphate in excess of twenty times the LD50, the animals collapsed or died before the oxime could be administered. Of those animals which had not collapsed within the first minute, a considerable proportion recovered after treatment.

Effect of Oximes on the Toxicity of Sarin to Mice.—A few of the more promising compounds in the treatment of ethyl pyrophosphate poisoning were also given to mice 10 min. before sarin. Although they were better than 2-hydroxyiminomethyl-*N*-methylpyridinium methanesulphonate (Table VI) the improvement was not as marked as after ethyl pyrophosphate.

A more extended series of tests was carried out giving the oximes one minute after poisoning by sarin (Table VII). Most of them were slightly better than 2-hydroxyiminomethyl-*N*-methylpyridinium methanesulphonate, but none was outstandingly superior.

TABLE VI

EFFECT OF OXIMES ON THE TOXICITY OF SARIN TO MICE

10 mg./kg. of oxime plus 17·4 mg./kg. atropine sulphate were given intramuscularly 10 min. before sarin, subcutaneously. The number of deaths in groups of 6 mice is recorded. Sarin alone caused 1 death at 0·2 mg./kg. and 6 deaths at 0·4 mg./kg. C2.6.2 was tested at 5 mg./kg., since 10 mg./kg. killed all mice in 10 to 12 min.

Oxime	Dose of Sarin (mg./kg.)				
	0·2	0·4	0·8	1·6	3·2
2-Hydroxyiminomethyl-*N*-methylpyridinium methanesulphonate	0	2	5		
C4.3.4		1	3	5	5
C4.3.P		0	5	5	6
C4.3.NEt$_3$	0	1	5	6	
C2.6.2	1	3	2	3	

TABLE VII

EFFECT OF OXIMES ON TOXICITY OF SARIN TO MICE

10 mg./kg. of oxime plus 17·4 mg./kg. of atropine sulphate were given intramuscularly 1 min. after sarin, subcutaneously. The number of deaths in groups of 10 mice is recorded. Sarin alone caused 1 death at 0·16 mg./kg. and 10 deaths at 0·32 mg./kg.

Oxime		Dose of Sarin (mg./kg.)			
		0·32	0·40	0·50	0·63
2-Hydroxyiminomethyl-*N*-methylpyridinium methanesulphonate		4	8	9	
Group 1	C4.2.4	2	5	7	5
	C4.3.4	0	2	4	8
	C4.6.4	1	1	1	7
	C4.10.4	4	7	9	7
,, 2	C2.3.2	0	4	7	9
	C3.3.3	0	2	4	8
	C4.3.4	0	2	4	8
,, 3	C2.6.2	4	7	9	7
	C3.6.3	2	2	7	7
	C4.6.4	1	1	1	7
,, 5	C4.3.4	0	2	4	8
	C4.3.P	0	3	5	8
	C4.3.MP	3	3	6	8
	C4.3.IQ	1	1	6	8
	C4.3.NEt$_3$	2	5	6	9
	C4.3.ST	8	10		

DISCUSSION

Many oximes derived from $\alpha\omega$-diquaternary alkanes have been shown to be better than 2 - hydroxyiminomethyl - *N* - methylpyridinium methanesulphonate, when given at the same dose and with atropine, in saving the lives of mice poisoned with ethyl pyrophosphate. The best of these, C4.3.4 {*NN'* - trimethylenebis(4 - hydroxyiminomethylpyridinium bromide)}, at only 5 mg./kg. raised the LD50 of ethyl pyrophosphate about one hundred fold, whereas the former substance at this dose raised the LD50 only fivefold. In mice, these new oximes are much less effective against sarin poisoning than against ethyl pyrophosphate poisoning, but by analogy with 2-hydroxyiminomethyl-*N*-methylpyridinium methanesulphonate this may not be the case in other species: the latter is far more effective against sarin in rabbits and guinea-pigs than it is in mice (Davies *et al.*, 1959).

Using the time required for recovery of 25% of the enzyme activity (t_{25}) as a basis of comparison many of these newer oximes are better reactivators than 2-hydroxyiminomethyl-*N*-methylpyridinium methanesulphonate. Among the best are the trimethylene 4,4'-dioxime (C4.3.4) and the hexamethylene 2,2'-dioxime (C2.6.2), which are also the most effective in treatment. This relationship between life-saving and reactivating properties is fairly general to all the compounds investigated. Fig. 2 shows the relationship

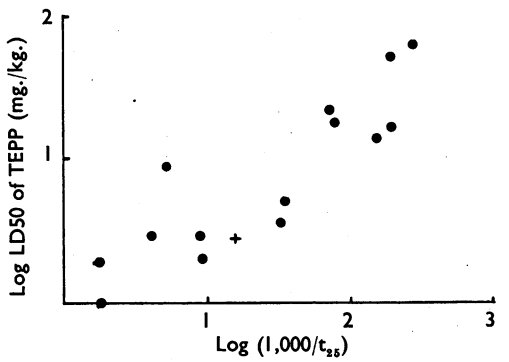

FIG. 2.—Relationship between life-saving and reactivating powers of diquaternary oximes. LD50 of ethyl pyrophosphate (TEPP) calculated from Table IV; t_{25} taken from Table II. + Indicates results for 2-hydroxyiminomethyl-*N*-methylpyridinium methanesulphonate.

between log (LD50) of ethyl pyrophosphate when given 10 min. after the oxime and atropine, and log (1,000/t_{25}).

There appears to be no simple relationship between these biological properties and chemical structure. It is clear, however, that the belief that the 2 - hydroxyiminomethyl-*N*-methylpyridinium salts are unique, owing their high reactivating power to their ability to fit precisely on to the surface of inhibited cholinesterase (Nachmansohn, 1958) is no longer tenable, since in the series examined here considerable variation in structure may be made without affecting their superiority as reactivators.

The good relationship between the therapeutic activity of these oximes and their reactivating powers strongly suggests that the reactivation of inhibited cholinesterase is the primary therapeutic action of these compounds. There are, however, two other properties which could contribute to this therapeutic action. Firstly, these compounds are inhibitors of cholinesterase, and if this inhibition is reversible, as would be expected from their structure (Austin and Berry, 1953), they may have a protective action against irreversible inhibitors similar to that displayed by eserine (Koelle, 1946). However, the lack of any correlation between anticholinesterase and therapeutic action in the present series (see Tables II and IV) makes this unlikely. Secondly, because these oximes have a diquaternary structure, they may block acetylcholine as does hexamethonium, which has been used successfully as an adjuvant to atropine (Parkes and Sacra, 1954). The present compounds have not yet been tested for such actions, but, as the therapeutic activity and reactivating power have been shown to be closely related, it is unlikely that such actions would be of more than secondary importance in this group of compounds as a whole.

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