QUATERNARY PYRIDINEDIALDOXIMES AS A NEW TYPE OF CHOLINESTERASE REACTIVATORS

J. Bielavský and F. Ornst

Purkyně Military Medical Institute for Research and Postgradual Education, 500 00 Hradec Králové

Received March 28th, 1972

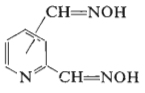
Two monoquaternary and two bisquaternary derivatives of 2,4- and 2,5-pyridinedialdoxime have been prepared as potential reactivators of cholinesterase after inhibition caused by organophosphorus compounds. The ultraviolet spectra, dissociation constants, and solubility of the parent tertiary compounds and of the quaternary salts have been measured.

In spite of the wide knowledge on the chemistry of pyridine, there are only few papers on pyridinedialdoximes and their derivatives. While the quaternary salts of pyridinaldoximes (2-PAM, TMB-4, Toxogonin^R are used in medical praxis as antidotes against poisoning caused by organophosphorus inhibitors of cholinesterase, there are not any reports on a similar activity of quaternary pyridinedialdoxime derivatives. It may be expected that the antidote effect, *i.e.*, the ability to reactivate the phosphorylated cholinesterase could be higher in the case of some isomeric quaternary pyridinedialdoximes (particularly with the 2,4-isomer) than with the corresponding pyridinemonoaldoxime quaternary salts.

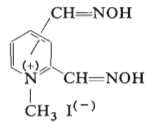
The recent investigations of Queguiner and Pastour[1] in the field of pyridinedialdehydes and related compounds led to a convenient synthesis of pyridinedialdehydes by a partial reduction of the corresponding methyl pyridinedicarboxylates with lithium aluminium hydride or diisobutylaluminium hydride at −70°C. Other procedures are based on the catalytic oxidation of dialkylpyridines with air oxygen in the gas phase[2], oxidation of 2,4- or 2,6-lutidine with iodine and dimethyl sulfoxide[3], and ozonolysis of stilbazoles[4]. All the isomeric pyridinedialdoximes may be quaternised except for the 2,6-isomer (sterical hindrance, *cf.*[5]). 2,4-Pyridinedialdoxime methiodide[3] and its tetraphenylborate salt[6] have been reported in the literature.

In the present paper, we wish to report the synthesis of four quaternary pyridinedialdoximes. The pyridinedialdoximes *I* were prepared by a modification of the method of Queguiner and Pastour[1]. Quaternisation of oximes *I* with methyl iodide afforded the monoquaternary reactivators of the type *II*. The maximum activity was expected with the bisquaternary derivatives *III* obtained (only from the 2,4-isomer) by quaternisation with bis(bromomethyl) ether and 1,4-dibromobutene.

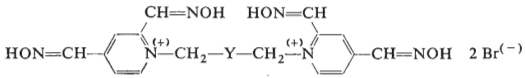
The purification of pyridinedialdoximes may be performed by passage through a column of diethylaminoethyl cellulose in ethanol or acetone as solvent and the subsequent recrystallisation from aqueous ethanol; such a purification, however, is accompanied by a considerable loss of material. For this reason, the quaternisation



Ia, isomer 2,4
Ib, isomer 2,5



IIa, isomer 2,4
IIb, isomer 2,5



IIIa, Y = O
IIIb, Y = CH=CH (*trans*)

TABLE I

Tertiary and Quaternary Pyridinedialdoximes; Ultraviolet Spectra, pK'_a Values and Solubility in Water

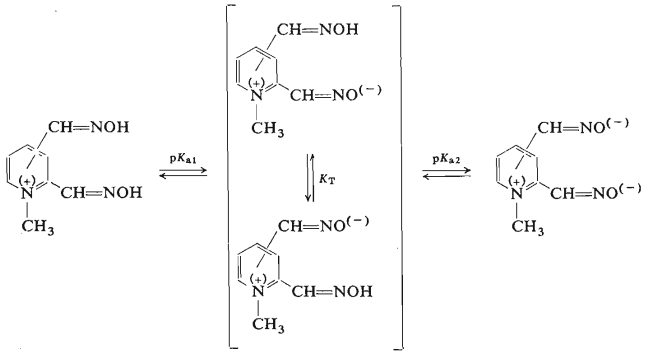
Compound M.p., °C	Calculated/Found % C	% H	% N	% X	λ_{max}	log ε	Medium	pK'_a (solubility[a])
Ia	—	—	—	—	310	4·07[b]	0·5M-HCl	3·04[c,d]
					295	4·74[e]	pH 6	(0·39)
					282	4·42[f]	0·1M-NaOH	
Ib	—	—	—	—	317	4·07[b]	0·5M-HCl	2·47[c,d]
					295	4·03[e]	pH 6	(0·32)
					318	4·17[g]	pH 11	
					327	4·15[f]	0·1M-NaOH	
IIa	31·29	3·28	13·68	41·42	290—310	4·08[b]	0·05M-HCl	7·70[h]
175—178[i,j]	31·62	3·64	13·33	41·19	360	4·31[f]	0·1M-NaOH	8·98[h]
								(168)
IIb	31·29	3·28	13·68	41·42	322	4·24[b]	0·05M-HCl	7·60[d]
205—207[i]	31·56	3·40	13·96	41·08	363	4·37[g]	pH 8·6	9·60[d]
					372	4·38[f]	0·1M-NaOH	(30·8)
IIIa	35·98	3·40	15·73	29·92	305	4·44[b]	0·05M-HCl	—
158—159	36·09	3·55	15·81	29·83	375	4·61[f]	0·05M-NaOH	(46)
IIIb	39·73	3·70	15·44	29·37	300	4·44[b]	0·05M-HCl	—
[k]	40·08	4·15	15·20	29·17	365	4·64[f]	0·05M-NaOH	(7·3)

[a] Measured in water at 20°C, g/l; [b] cation; [c] protonation of the pyridine nitrogen; [d] measured spectrophotometrically; [e] the neutral form; [f] the fully dissociated form; [g] monoanion or betain; [h] calculated according to Speakmann[10] from the potentiometric titration curve; [i] decomposition; [j] 176—178°C (ref.[3]); [k] decomposition above 210°C.

was performed with the use of crude pyridinedialdoximes. The monoquaternary salts were prepared as usual. The preparation of the TMB-4 analogue containing a trimethylene chain by bisquaternisation failed probably because of the unfavourable effect of the aldoxime group at the α-position of the pyridine ring, as observed by Berry and coworkers[7]. Successful bisquaternisations were performed with the use of agents containing an activated halo atom such as bis(bromomethyl) ether or 1,4-dibromobutene. (For the tertiary amines and quaternary salts see Table I).

When compared with those of pyridinemonoaldoximes, the ultraviolet spectra of compounds *I–III* exhibit a bathochromic effect due to the presence of an additional chromogenic group. The difference between the 2,4- and 2,5-substitution is reflected in spectra of the ionised forms. With compounds *Ib* and *IIb*, the shifted absorption maximum length of the dianion in comparison with the monoanion (the extinction coefficient remains unchanged) indicates an interaction of the two aldoxime groups. With compounds *Ia*, *IIa*, and *IIIa,b* the second dissociation leads to an increase of the extinction coefficient. Also the dissociation constants of hydrogens of the oxime groups are influenced by the interaction of aldoxime residues. The difference between pK_{a1} and pK_{a2} is rather low in the case of compound *IIa* since the oxime groups assume an equivalent position in respect to the quaternary nitrogen atom (*cf.* the stabilisation of the betain by mesomerism[8]) and may interact by the inductive effect only. The magnitude of the equilibrium constant K_T may be estimated from the dissociation constant ratio of 2- and 4-pyridinealdoxime which is equal to about 2·4.

The dissociation of the second aldoxime group of compound *IIb* is suppressed



SCHEME 1

by the +M effect of the ionised oxime group; furthermore, in β-position there is no possibility of a stabilisation by mesomerism. It may be therefore assumed that the tautomeric equilibrium (Scheme 1) is strongly shifted in favour of the dissociation of the aldoxime group at position 2 and that the K_T value should be higher than the ratio (13·1) of dissociation constants of 2- and 3-pyridinaldoxime.

The bisquaternary pyridinedialdoximes *IIIa,b* represent a complex system of a four-basic acid. When two equivalents of a base are taken up, a potentiometric jump occurs but the titration is made difficult by precipitation of the sparingly soluble betain with the minimum solubility at the equivalence point (pH 7·8, c $3{\cdot}7 \cdot 10^{-5}$). For the ultraviolet maxima, pK'_a values and solubility in water see Table I.

EXPERIMENTAL

Melting points are uncorrected. Ultraviolet spectra and spectral measurements of pK_a values were performed on VSU-1 (Zeiss, Jena) and UV-127 (Perkin-Elmer) spectrophotometers. Potentiometric measurements were carried our on a E-512 (Metrohm) pH-meter.

2,4-Pyridinedialdoxime (*Ia*)

A suspension of lithium aluminium hydride (2·2 g) in tetrahydrofuran (100 ml) was added dropwise under stirring to a solution of dimethyl 2,4-pyridinedicarboxylate (9·75 g; 0·05 mol) in tetrahydrofuran (200 ml) at the temperature between −60°C and −70°C. The stirring was then continued for one hour at the same temperature. A mixture of tetrahydrofuran (25 ml), water (10 ml), and acetic acid (20 ml) was added and the organic solvent evaporated under diminished pressure. The residue was repeatedly extracted with ether (positive dinitrophenylhydrazine test) and the combined extracts were evaporated. A solution of hydroxylamine hydrochloride (6·0 g) neutralised with sodium hydrogen carbonate was then added to the residue and the mixture kept at room temperature for 8 h to deposit the product which was collected with suction and washed with water and then ether. Yield, 4·5 g (54%) of the dioxime *Ia*, m.p. 221−224°C; reported, m.p.[3] 225−227°C and m.p.[9] 240°C.

2,5-Pyridinedialdoxime (*Ib*)

The preparation was performed analogously to that of compound *Ia* in tetrahydrofuran (400 ml) as solvent; reaction time, 3 h. Yield, 28% of the dioxime *Ib*, m.p. 217−222°C; reported[4], m.p. 233°C.

Quaternary Salts

1-*Methyl*-2,4-*bis*(*hydroxyiminomethyl*)*pyridinium iodide* (IIa). A mixture of the dioxime *Ia* (1·65 g; 0·01 mol), methyl iodide (6·0 g), and methanol (20 ml) was refluxed for 30 h and evaporated under diminished pressure. The residue solidified on standing. The solid was washed with acetone and recrystallised from 1-propanol. Yield, 1·6 g (53%).

1-*Methyl*-2,5-*bis*(*hydroxyiminomethyl*)*pyridinium iodide* (IIb). The preparation was performed analogously to that of compound *IIa* from the dialdoxime *Ib* with the use of acetone (25 ml) and dimethylformamide (4 ml) as solvents; refluxing time, 20 h. The solid was collected with suction, washed with acetone, and recrystallised from ethanol. Yield, 1·0 g (32%).

1,3-*Bis*[2,4-*bis*(*hydroxyiminomethyl*)*pyridinium*]-2-*oxapropane dibromide* (IIIa). The dioxime *Ia* (3·3 g; 0·02 mol) was dissolved in hot acetone (600 ml), the solution cooled down, treated with bis(bromomethyl) ether (2·1 g; 0·01 mol), and the mixture kept at room temperature for 4 days. Yield, 3·5 g (65%) of a yellowish brown substance.

1,4-*Bis*[2,4-*bis*(*hydroxyiminomethyl*)*pyridinium*]-2-*butene dibromide* (*trans*-isomer, *IIIb*). A solution of the dioxime *Ia* (3·3 g; 0·02 mol) and 1,4-dibromo-2-butene (2·15 g; 0·01 mol) in dimethylformamide (20 ml) was kept at room temperature for 14 days to deposit 1·1 g (20%) of a chromatographically homogeneous substance.

REFERENCES

1. Queguiner G., Pastour P.: Bull. Soc. Chim. France *10*, 4117 (1968).
2. Mathes W., Sauermilch W.: Chem. Ber. *88*, 1276 (1955).
3. Markovec A., Stevens C. L., Ash A. B., Hackley B. E.: J. Org. Chem. *35*, 841 (1970).
4. Queguiner G., Pastour P.: Compt. Rend. *262 C*, 1335 (1966).
5. Hackley B. E., Poziomek E. J., Steinberg B. M., Mosher N. M.: J. Org. Chem. *27*, 4220 (1962).
6. Roth H. J., Surborg K. H.: Arch. Pharm. *301*, 686 (1968).
7. Berry W. K., Davies D. R., Green A. L.: Brit. J. Pharmacol. *14*, 186 (1959).
8. Engelhard N., Werth B.: Tetrahedron Letters *1963*, 661.
9. Queguiner G., Pastour P.: Compt. Rend. *258*, 5903 (1964).
10. Speakman D.: J. Chem. Soc. *1940*, 855.

Translated by J. Pliml.