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* To whom communications regarding this paper should be addressed.

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Structure-Activity Relations in Organophosphorus-Inhibited Acetylcholinesterase Reactivators II: Methiodides of Hydroxyimino Derivatives of 1-Pyridyl-2-phenylethanes

PALMARISA FRANCHETTI*, MARIO GRIFANTINI, and SANTE MARTELLI

Abstract □ A series of methiodides from *syn*-2-hydroxyimino-1-pyridyl-2-phenylethanes, *syn*-1-hydroxyimino-1-pyridyl-2-phenylethan-2-ones, *syn*- and *anti*-2-hydroxyimino-1-pyridyl-2-phenylethan-1-ones, and *syn*-1,2-di(hydroxyimino)-1-pyridyl-2-phenylethanes was prepared. The influence of the structure of these new compounds on the *in vitro* reactivation of acetylcholinesterase inhibited by TEPP or DFP was investigated. The results obtained confirmed that quaternary pyridine derivatives containing a hydroxyimino group in the β position of the side chain generally keep a reactivating ability, in whatever position the connection with the ring may be; in some cases this activity is higher than that of the isomer containing the same group in the α position.

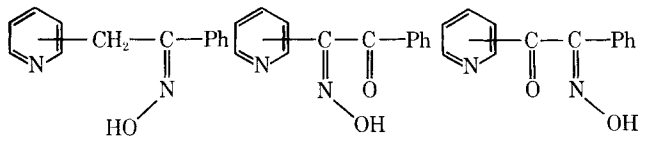
Keyphrases □ Acetylcholinesterase reactivators—structure-activity relationships □ Organophosphorus-inhibited cholinesterase—reactivators □ 1-Pyridyl-2-phenylethanes, hydroxyimino methiodides—synthesis □ UV spectrophotometry—identity, structure

It is well known that some quaternary pyridyloximes are used to reactivate the enzymatic activity of organophosphorus-inhibited acetylcholinesterase (1, 2). The most active are those in which the hydroxyimino group is placed on side chains in the 2 or 4 position of the ring (1, 3). Concerning the structure-activity relations of these drugs, Wilson (4) presented the hypothesis that reactivation principally depends on three factors: (*a*) nucleophilic reactivity; (*b*) stereochemistry; (*c*) complementarity of the molecule of the reactivator to enzymatic active sites. The *anti*-configurations in 2- and 4-formyl-*N*-methylpyridinium oxime iodides (2-PAM, 4-PAM) satisfy the stereochemical requirements so that the displacement of the organophosphorus group takes place. This assumption proved to be partly wrong when Poziomek *et al.* (5) succeeded in synthesizing the second isomer of 4-PAM, and were able to ascribe, unmistakably, the steric structure to the two geometric isomers by comparing their NMR spectra. Reactivation measurements showed the *syn*-isomer to be 2.5 times more effective.

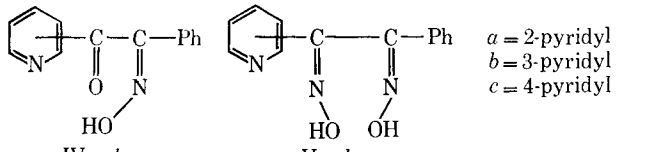
In order to obtain more knowledge of structure-activity relations, the authors have recently undertaken a study on the reactivating properties of quaternary derivatives of pyridine containing either two hydroxyimino groups close to each other in the side chain or of one such group in the β position. In a preceding note (6) the results obtained on a series of methiodides of isomeric mono- and bis-hydroxyimino-β-pyridyl-propioanilides were reported; they pointed out the effectiveness of the hydroxyimino group situated one carbon atom distant from the ring.

In order to confirm these results, a series of methiodides of hydroxyimino derivatives of 1-pyridyl-2-phenylethanes, whose geometric configurations would be identical to those of the products reported previously

(6), but whose conformations, because of the presence of the phenyl group instead of the amide one were probably different, were synthesized and subjected to *in vitro* assay. The products considered belong to the following five types: *syn*[1]-2-hydroxyimino-1-pyridyl-2-phenylethanes (I), *syn*-1-hydroxyimino-1-pyridyl-2-phenylethan-2-ones (II), *anti*- (III), and *syn*-(IV) 2-hydroxyimino-1-pyridyl-2-phenylethan-1-ones, and *syn*-1,2-di(hydroxyimino)-1-pyridyl-2-phenylethanes (V).



Ia, b, c IIa, b, c IIIa, b, c



IVa, b, c Va, b, c

a = 2-pyridyl
b = 3-pyridyl
c = 4-pyridyl

EXPERIMENTAL[2]

Syn-2-Hydroxyimino-1-pyridyl-2-phenylethanes (Ia, b, c)—*Syn*-2-Hydroxyimino-1-(2′-pyridyl)-2-phenylethane (I*a*) and *syn*-2-hydroxyimino-(4′-pyridyl)-2-phenylethane (I*c*) were reported (7, 8); their configurations were ascertained by the Beckmann transposition (8, 9). The nicotinic derivative was synthesized too (10), but its configuration was not investigated; by comparing UV spectral data it was possible to assign the *syn*-configuration also to this isomer. These three substances show an absorption maximum between 249 and 252 mμ ($\epsilon \simeq 1.1 \times 10^4$) assignable to the chromophore —C(=N—OH)—Ph (11).

Syn-1-Hydroxyimino-1-pyridyl-2-phenylethan-2-ones (II a, b, c)—*Syn*-1-Hydroxyimino-1-(2′-pyridyl)-2-phenylethan-2-one (II*a*) was synthesized by Dornow and Bruncken (12) by nitrosation of 2-phenacylpyridine with $NaNO_2$ in HCl 2 *N;* the *anti*-pyridyl configuration was shown by the red-colored complex given with ferrous sulfate (13). In a similar manner the isonicotinic isomer (II*c*) was obtained: 2 g. of 4-phenacylpyridine was dissolved in 40 ml. of ethanol and HCl 2 *N* mixture. A solution of 1.4 g. of $NaNO_2$ in 20 ml. of water was added dropwise with stirring in 10 min. and stirring was continued for 1 hr. During this time a white product precipitated. By adding a dilute solution of $NaHCO_3$ to neutrality a precipitate was formed, which was filtered, washed with water and dried. The crude compound was crystallized from ethanol, m.p. 194–196°.

Anal. ($C_{13}H_{10}N_2O_2$) C, H, N.

Because of the difficulty in obtaining 3-phenacylpyridine (10), the nicotinic isomer was prepared using a different procedure: a mixture of 1.8 g. of 1-(3′-pyridyl)-2-phenyl-1,2-ethandione (14) and 1.3 g. of hydroxylamine hydrochloride in 30 ml. of ethanol was refluxed for 1 hr. Then a dilute solution of $NaHCO_3$ was added up to alkalinity, and the mixture was extracted with ethyl acetate. After evaporation of the solvent, a residue was obtained which was chromatographed on a column of silica gel with a 50:50 ethyl acetate–benzene mixture. From the first two fractions two compounds were isolated, which melted at 168–170° and 195–197°, respectively. The compound melting at 168–170° was identical with the *syn*-2-hydroxyimino-1-(3′-pyridyl)-2-phenylethan-1-one (IV*b*), whose preparation is described below. To the compound melting at 195–197°, whose elemental analysis corresponds to a formula of $C_{13}H_{10}N_2O_2$, was assigned the structure of *syn*-1-hydroxyimino-1-(3′-pyridyl)-2-phenylethan-2-one (II*b*) since it gives no precipitate with nickel salts (15). The three isomers II*a*, *b*, *c* have similar UV spectra with an absorption maximum between 250 and 252 mμ ($\epsilon \simeq 2 \times 10^4$).

Anti-2-Hydroxyimino-1-pyridyl-2-phenylethan-1-Ones (IIIa, b, c)—Kuczyński and Respond (16) have recently described the synthesis of three ring positional isomers of the 2-hydroxyimino-1-pyridyl-2-phenylethan-1-one without investigating the steric structure of the products obtained. By repeating their synthesis it was possible to verify that the products obtained were *anti*-isomers, as they give yellow-green precipitates with nickel salts (15).

Syn-2-Hydroxyimino-1-pyridyl-2-phenylethan-1-Ones (IVa, b, c)—The *syn*-2-hydroxyimino-1-(2′-pyridyl)-2-phenylethan-1-one (IV*a*) was obtained by heating 0.5 g. of *anti*-derivative (III*a*) dissolved in 5 ml. of concentrated HCl for 20 min. The solution was cooled, diluted with water, made basic with Na_2CO_3, and extracted with ethyl acetate. After evaporation of the solvent, a residue was obtained which was chromatographed on a silica gel column with a 50:50 ethyl acetate–benzene mixture. By evaporation of the first eluates a residue was obtained, which was chromatographed again with ethyl acetate–benzene (80:20). From the third fraction a residue was obtained, which was recrystallized from methanol and melted at 110–112°.

Anal. ($C_{13}H_{10}N_2O_2$) C, H, N.

The nicotinic isomer (IV*b*) was prepared in a similar way; from the first eluates of the chromatography (ethyl acetate–benzene 50:50) a residue was obtained which was crystallized from methanol and melted at 168–170°.

Anal. ($C_{13}H_{10}N_2O_2$) C, H, N.

By subjecting the *anti*-2-hydroxyimino-1-(4′-pyridyl)-2-phenylethan-1-one (III*c*) to the same type of isomerization, the *syn*-1-hydroxyimino-1-(4′-pyridyl)-2-phenylethan-2-one (II*c*) was obtained. A hydrolytic reaction occurred, followed by the formation of the most stable hydroxyimino derivative. The desired *syn*-isomer (IV*c*) was obtained by subjecting Compound III*c* to controlled fusion. A melt of 0.4 g. of *anti*-isomer was kept at 175° for 2 min.; after cooling, the solid mass was chromatographed on silica gel with a 50:50 ethyl acetate–benzene mixture. From the first fractions a product was obtained which was crystallized from ethyl acetate–benzene and melted at 169–171°.

Anal. ($C_{13}H_{10}N_2O_2$) C, H, N.

These products gave no precipitate with nickel salts.

Syn-1,2-Di(hydroxyimino)-1-pyridyl-2-phenylethanes (Va,b,c)—The compound V*a* was obtained by refluxing the compound II*a* with two equivalents of hydroxylamine hydrochloride in highly alkaline ethanol, for 5 hr. The acidified solution was concentrated and the precipitate was filtered, dried, and chromatographed on silica gel (50:50 ethyl acetate–benzene). From the second fraction a product was obtained which was crystallized from ethanol and melted at 235–236°.

Anal. ($C_{13}H_{11}N_3O_2$) C, H, N.

The isomer V*c* was prepared from II*c* in the same way: m.p. 195–197°.

Anal. ($C_{13}H_{11}N_3O_2$) C, H, N.

The isomer V*b* was obtained by executing the same reaction on the compound IV*b*. After heating, 50 ml. of water was added to the neutralized solution, which was left to stand for 1 hr. During this period the original product, which had not reacted, precipitated; the filtered solution was extracted with ethyl acetate. By evaporation of the solvent a residue was obtained which was recrystallized from ethyl acetate–benzene and melted at 230–232°.

Anal. ($C_{13}H_{11}N_3O_2$) C, H, N.

These isomers have a *syn*-structure since they gave no precipitate with nickel salts (17); moreover, the isomer V*a* gives a red color with ferrous sulfate, due to the *anti*-pyridyl position of the hydroxyimino group adjacent to the ring. This configuration was confirmed by UV spectra; the three isomers show an absorption maximum at 247–252 mμ ($\epsilon \simeq 1.9 \times 10^4$) (11).

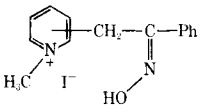
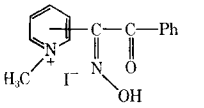
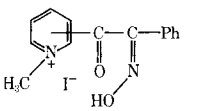
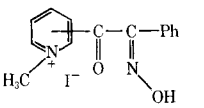
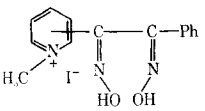
1-Methyl-pyridinium Iodides—The above products, by reaction with methyl iodide in anhydrous ethanol in sealed vessels at 60°

[1] The terms *syn* and *anti* refer to the aliphatic carbon atom.

[2] All melting points are uncorrected. When no unusual spectral features were observed with the compounds described, no absorption peaks are listed. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

[3] Since the same quaternary salt originates from both isomers III*c* and IV*c*, it was not possible to assign either configuration to the product obtained. However, as it gives, like the isomers IX*a* and IX*b*, a yellow color with nickel salts, it is probably an *anti*-configuration.

Table I—Methylpyridinium Iodides

No.	Compd.	Crystn. Solvent	M.p., °C.	Formula	Anal.
VI*a*		MeOH	190–192	$C_{14}H_{15}IN_2O$	C, H, N
VI*b*		H_2O	112–114	$C_{14}H_{15}IN_2O$	C, H, N
VI*c*		Me_2CO	151–152	$C_{14}H_{15}IN_2O$	C, H, N
VII*a*		MeOH	202–204	$C_{14}H_{13}IN_2O_2$	C, H, N
VII*b*		MeOH	214–216	$C_{14}H_{13}IN_2O_2$	C, H, N
VII*c*		Me_2CO	191–193	$C_{14}H_{13}IN_2O_2$	C, H, N
VIII*a*		Me_2CO	183–185	$C_{14}H_{13}IN_2O_2$	C, H, N
VIII*b*		MeOH	154–156	$C_{14}H_{13}IN_2O_2$	C, H, N
IX*a*		MeOH	198–200	$C_{14}H_{13}IN_2O_2$	C, H, N
IX*b*		MeOH	240–242	$C_{14}H_{13}IN_2O_2$	C, H, N
IX*c*		MeOH	208–210	$C_{14}H_{13}IN_2O_2$	C, H, N
X*a*		MeOH	193–195	$C_{14}H_{14}IN_3O_2$	C, H, N
X*b*		MeOH–Et_2O	240–242	$C_{14}H_{14}IN_3O_2$	C, H, N
X*c*		MeOH	224–226	$C_{14}H_{14}IN_3O_2$	C, H, N

for 72 hr., gave the quaternary salts reported in Table I. It was not possible to obtain the quaternary salt corresponding to the product III*c*, as in the reaction an isomerization is produced which leads, to the formation of the quaternary salt of the *anti*-isomer.[3]

All the compounds obtained were subjected to biological assay. The *in vitro* reactivating velocity of acetylcholinesterase inhibited by TEPP or DFP was measured according to the technique described by Ashani *et al.* (18). Table II shows the results obtained.

RESULTS AND DISCUSSION

From hydrolysis velocity measures, the following conclusions can be drawn.

Syn-2-Hydroxyimino-1-pyridyl-2-phenylethane Methiodides (VIa, b,c)—The only active product of this series in relation to the enzyme inhibited both by TEPP and DFP is the derivative with the chain in position 2. This result confirms the reactivating ability of the hydroxyimino group situated one carbon atom distant from the pyridine ring. Reduction of activity in comparison with that of 2-PAM is evident if the enzyme has been inhibited by TEPP. This seems to be due to the low acidity of this hydroxyimino group, more than to lack of structural requirements. The nicotinic and isonicotinic isomers were inactive even though they have a slightly higher dissociation constant; evidently in this case the steric factor becomes more important.

Syn-1-Hydroxyimino-1-pyridyl-2-phenylethan-2-one Methiodides (VIIa,b,c)—Comparison of the activities of the three isomers shows that, in relation to the enzyme inhibited by TEPP, the isomers VII*a* and VII*b* have the same activity. This result is in contrast with the theory of Wilson (4), according to which the nicotinic hydroxyimino derivatives next to the ring do not have suitable structural requirements for reactivation. In the case of DFP inhibition, the nicotinic isomer is the least active.

Syn- and Anti-2-Hydroxyimino-1-pyridyl-2-phenylethan-1-one Methiodides (VIIIa,b; IXa,b,c)—The products of this series keep a certain reactivating ability. The influence of the configuration varies according to the position in which the side chain is attached to the ring. In the case of the picolinic derivative, the isomer with an *anti*-configuration is about ten times more active than the *syn*-isomer in TEPP poisoning, while in DFP poisoning no difference in activity can be noticed. In the nicotinic series no reliable comparison can be made, since the *anti*-derivative has a solubility lower than that of a useful experimental concentration.

Table II—Reactivation of Inhibited Bovine Erythrocytes Acetylcholinesterase by Means of Oximes VI–X (pH 7.4 and 25°C.)[a,b]

Oximes (iodides) ($5 \times 10^{-3}M$)	pKa′	pKa″	Inhibiting Group: Diethyl Phosphoryl $K_{obs.}$	Diethyl Phosphoryl Relative Rate Constant	Diisopropyl Phosphonyl $K_{obs.}$	Diisopropyl Phosphonyl Relative Rate Constant
2-PAM	7.9		9.3×10^{-3}	1	1.8×10^{-3}	1
VI*a*	10.1		1.3×10^{-4}	1.4×10^{-2}	3.3×10^{-4}	1.8×10^{-1}
VI*b*	9.7		None	—	None	—
VI*c*	9.6		None	—	None	—
VII*a*	5.4		3.5×10^{-4}	3.7×10^{-2}	2.4×10^{-4}	2.5×10^{-1}
VII*b*	8.1		3.6×10^{-4}	3.8×10^{-2}	3.4×10^{-5}	3.6×10^{-2}
VII*c*	7.1		1.5×10^{-4}	1.6×10^{-2}	1.6×10^{-4}	8.8×10^{-2}
VIII*a*	5.6		1.4×10^{-4}	1.5×10^{-2}	1.8×10^{-5}	1.0×10^{-2}
VIII*b*	8.75		5.8×10^{-5}	6.2×10^{-3}	1.7×10^{-5}	9.4×10^{-3}
IX*a*	6.1		1.2×10^{-3}	1.3×10^{-1}	1.0×10^{-5}	5.5×10^{-3}
IX*b*[c]	6.0		None	—	None	—
IX*c*	6.9		4.5×10^{-5}	4.8×10^{-3}	5.1×10^{-5}	2.8×10^{-2}
X*a*	7.8	10.0	8.4×10^{-4}	9.0×10^{-2}	1.1×10^{-3}	6.1×10^{-1}
X*b*	7.2	9.8	None	—	6.8×10^{-5}	3.7×10^{-2}
X*c*	7.3	9.9	7.8×10^{-5}	8.4×10^{-3}	1.2×10^{-4}	6.6×10^{-2}

[a] $K_{obs.}$ is in $min.^{-1}$ [b] pKa values were obtained by potentiometric titration and, for overlapping values, by application of the calculation method due to Noyes, as given by Albert and Serjeant (19). [c] This compound, because of its lower solubility, was assayed as a $2.5 \times 10^{-3}M$ solution.

Syn-1,2-Di(hydroxyimino)-1-pyridyl-2-phenylethane Methiodides (Xa,b,c)—In this series the general effectiveness of the various isomers should be pointed out; in the case of DFP inhibition the picolinic and isonicotinic derivatives have an activity comparable with that of 2-PAM and 4-PAM respectively. The activity diminishes in the case of TEPP inhibition; in this case the X*b* isomer is inactive.

In conclusion it is possible to affirm that, as it had already been found in the series reported in the preceding note (6), quaternary pyridine derivatives containing a hydroxyimino group in the β position of the side chain generally retain a reactivating activity, in whatever position the attachment to the ring may be; in some case this activity is higher than that of the isomer containing the same group in the α-position.

Since a phenyl group can shield the hydroxyimino group in relation to the active site of enzyme, a series of β-hydroxyimino derivatives containing hydrogen instead of the phenyl group was synthesized; the activity of these products will be reported in a following note.

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The Synthesis of Pyrrolidine-Substituted Nicotine Analogs

NEAL CASTAGNOLI, Jr., ARMEN P. MELIKIAN, and VITTORIO ROSNATI*

Abstract □ As part of a program to synthesize nicotine homologs and analogs, the potentially versatile condensation of 3-pyridyl lithium with a 1-pyrroline-1-oxide (cyclic nitrone) has been studied. The product, an *N*-hydroxynornicotine derivative, was obtained in moderate yield and could be converted by way of the corresponding myosmine and nornicotine compounds to the desired gem-dimethylnicotine homolog. Spectral characteristics of these and certain side products are reported.

Keyphrases □ Nicotine analog, pyrrolidine substituted—synthesis □ UV spectrophotometry—structure □ IR spectrophotometry—structure □ NMR spectroscopy—structure

Nicotine (I), the principal alkaloid found in most varieties of tobacco, has served as a valuable chemical probe in the investigation of peripheral cholinergic transmission (1). More recently, increasing attention has been directed to nicotine's central activity (2, 3) and has included psychopharmacological studies relating to animal behavior (4, 5). These interests have led to many attempts to define the structural parameters responsible for this compound's cholinomimetic activity (6–8). Studies directly concerned with structural features of nicotine itself suggest that, for nonquaternary compounds capable of exerting effects within the CNS, the 3-pyridylaminomethyl system, II, is essential for high nicotinic activity (9–11). In order to explore the effects on central and peripheral activity of compounds closely related to nicotine, a program has been initiated to synthesize nicotine-like compounds in which the pyrrolidine ring is substituted. In this paper the authors report their studies on the synthesis of the gem-dimethylnicotine homolog, III, by a reaction sequence that should be applicable to a large number of such derivatives. The methylnornicotine, IV, (12) and the carboxynicotine, V (13), both presumably as diastereoisomeric mixtures, were the only such nicotine analogs found in the literature.

THEORETICAL

Nicotine has been prepared by several routes (14, 15); however, on review, none of these appeared to offer the required versatility demanded by the present problem. The fact that 1-pyrroline-1-