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# Structure-Activity Relationships in Reactivators of Organophosphorus-Inhibited Acetylcholinesterase. 7. 1-Aryl-2-hydroxyiminomethyl-3-methylimidazolium Iodides†,[1]

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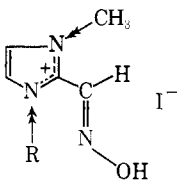
A series of 1-aryl-2-hydroxyiminomethyl-3-methylimidazolium iodides, where the aryl group is either phenyl or substituted phenyl, was prepared and tested for their reactivating potency on phosphorylated acetylcholinesterase (AChE) and for *anti*-AChE activity. The *in vitro* testing revealed that some of the new compounds are good reactivators. Correlations between their structure and biological activities have been attempted.

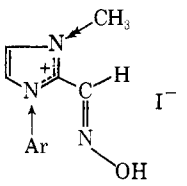
Wilson and coworkers[2] gave some important criteria for reactivation of phosphorylated acetylcholinesterase (AChE) by oximes. The high potency of 2-hydroxyiminomethyl-1-methylpyridinium iodide (2-PAM) was attributed to its capacity for forming a complex with the phosphorylated enzyme in such a way that the nucleophilic oxime group is suitably oriented toward the phosphorus atom.[3,4]

Ashani and Cohen[5] found that at physiological pH, the value of the reactivation rate constant is more a function of the basicity of the reactivator molecule than of its nucleophilic reactivity, reaching an optimum for compounds with $pK_a$ values in the range of 7.6-8.0. Salvador and coworkers[6] supported these observations after studying the activity of some trifluoromethyl ketoximes.

In the course of our research on reactivators of phosphorylated AChE, we found that the methiodides of 1-methyl- and 1-benzyl-2-hydroxyiminomethylimidazole (**1a** and **b**) are only slightly less effective than 2-PAM as reactivators of bovine erythrocyte AChE inhibited by diisopropylphosphorofluoridate (DFP).[7] As these compounds have a $pK_a$ of 8.3, which is thus higher than the optimal values, it was decided to modify the structure of the imidazole oximes by replacing an alkyl group with an aryl group on one of the ring nitrogen atoms. As a consequence of the smaller inductive effect of an aryl group relative to that of an alkyl group, the positive charge delocalized between the nitrogen atoms would be increased and better able to stabilize the oximate anion.




**1a**, R = $CH_3$
**b**, R = $CH_2C_6H_5$




**2**

We thus prepared a series of methiodides of 1-aryl-2-hydroxyiminomethylimidazoles **2** variously substituted in the aromatic ring so as to modulate the acidity of the oxime function by means of inductive effects.

**Chemistry.** 2-Hydroxyiminomethyl-1-phenylimidazole was prepared by treating 1-phenylimidazole-2-aldehyde[8,9] with hydroxylamine hydrochloride. The other oximes listed in Table VI were obtained in the same way. The hitherto unknown imidazole aldehydes were prepared as shown in Scheme I.

Marckwald's classical synthesis[10] comprising the first four steps shown in Scheme I was used for the preparation of the 1-arylimidazoles **7**. By hydroxymethylation with formaldehyde, the arylimidazoles were converted into the alcohols **8**, which were oxidized with $SeO_2$ to give the corresponding aldehydes **9**.

In the reaction between the aldehydes and hydroxyl-

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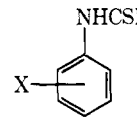
‡This paper is dedicated to Professor Alfred Burger, remembering his kindness and stimulating teaching during a year spent on a fellowship in his laboratory.

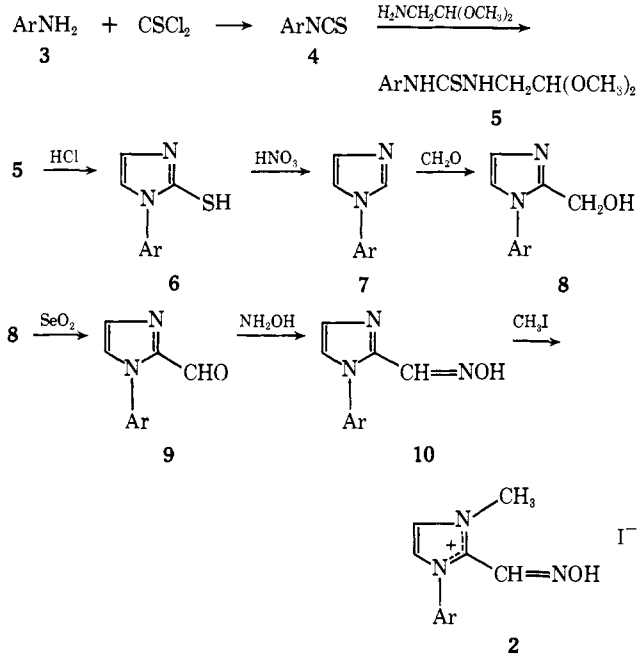
**Table I.** *N*-Aryl-*N'*-dimethoxyethylthioureas



| Compd[a] | X | Yield, % | Mp, °C | Recrystn solvent | Method | Formula[b] |
|---|---|---|---|---|---|---|
| **5b** | *o*-Cl | 38 | 98–99 | EtOH | A | $C_{11}H_{15}ClN_2O_2S$ |
| **5c** | *m*-Cl | 20 | 62–63 | EtOH | B | $C_{11}H_{15}ClN_2O_2S$ |
| **5d** | *p*-Cl | 43 | 121–122 | EtOH | A | $C_{11}H_{15}ClN_2O_2S$ |
| **5e** | *o*-$OCH_3$ | 50 | 88–89 | EtOH | B | $C_{12}H_{18}N_2O_3S$ |
| **5f** | *m*-$OCH_3$ | 30 | 59–60 | EtOH | B | $C_{12}H_{18}N_2O_3S$ |

[a]For compound **5a** (X = H), see ref 10 and A. L. Johnson, J. C. Kauer, D. C. Sharma, and R. I. Dorfman, *J. Med. Chem.*, **12**, 1024 (1969). Compounds **5g** (X = *p*-$OCH_3$) and **5i** (X = *m*-$NO_2$) were not characterized: see Johnson, *et al.* [b]All compounds were analyzed for C, H, N, and S.

**Scheme I**

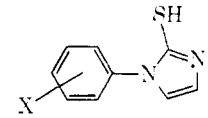


amine hydrochloride a single product **10** was usually isolated. Only in the case of 1-*m*-chloro- and of 1-*m*-methoxyphenylimidazole-2-carboxaldehydes **9c,f** did the oximation reaction give geometrical isomers which were separated by chromatography on silica gel. Comparison of the nmr spectra in dimethyl sulfoxide revealed that in the low-melting isomers **11c,f** the OH proton was considerably deshielded, whereas the proton ($H_b$) linked to the trigonal carbon of the oxime group gave a signal upfield relative to that of the corresponding proton of the high-melting isomers. These chemical shift differences allow the assignment of the anti configuration to the low-melting isomers and the syn configuration to the others.[11] The $H_b$ chemical shift differences reflect the anisotropic effect of the N–O bond in the syn configuration.

The nmr spectra of the oximes obtained from the other aldehydes (Table VI) in each case showed two signals with chemical shifts similar to those of the protons in the oxime group of the syn isomers. Thus, it is reasonable to assign the same configuration to these compounds.

Lastly, the quaternization of oximes having a syn configuration with MeI afforded the methiodides **2a–j**. The absence of conjugation between the heterocyclic system and the aromatic ring in the 1-arylimidazolium salts was suggested by their uv spectra. Indeed, 1-methyl-2-hydroxyiminomethyl-3-methylimidazolium iodide (**1a**) showed an absorption maximum at 273 nm (log $\epsilon$ 3.98), which is

**Table II.** 1-Aryl-2-mercaptoimidazoles



| Compd[a] | X | Yield, % | Mp, °C | Recrystn solvent | Formula[b] |
|---|---|---|---|---|---|
| **6b** | *o*-Cl | 68 | 249–250 | EtOH | $C_9H_7ClN_2S$ |
| **6c** | *m*-Cl | 72 | 159–160 | EtOH | $C_9H_7ClN_2S$ |
| **6d** | *p*-Cl | 61 | 228–229 | EtOH | $C_9H_7ClN_2S$ |
| **6e** | *o*-$OCH_3$ | 50 | 224–226 | EtOH | $C_{10}H_{10}N_2OS$ |
| **6f** | *m*-$OCH_3$ | 65 | 146–148 | EtOH | $C_{10}H_{10}N_2OS$ |

[a]For compounds **6a** (X = H),[10] **6g** (X = *p*-$OCH_3$), and **6i** (X = *m*-$NO_2$), see A. L. Johnson, *et al.*, *J. Med. Chem.*, **12**, 1024 (1969). [b]See footnote *b*, Table I.

similar to that of this new series of compounds (Table VII). As Sitkina and coworkers[9] had already deduced from dipole moment measurements carried out on 1-arylimidazoles, the absence of any bathochromic effect is an indication of the noncoplanarity of the two rings.

## Experimental Section

Melting points were determined by a capillary method in a Büchi apparatus and are uncorrected. The uv spectra were recorded on a Unicam SP-800 spectrophotometer in EtOH solution; the nmr spectra were measured on a Jeol JNH-MH-60 spectrometer using DMSO-$d_6$ as solvent and sodium 3-(trimethylsilyl)propanesulfonate as internal standard. Uv, ir, and nmr spectra were in accord with the proposed structures. Where analyses are indicated only by symbols of the elements, the analytical results obtained for these elements were within 0.4% of the theoretical values.

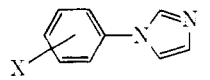
***N*-Aryl-*N'*-dimethoxyethylthioureas (5b–f, Table I). Method A.** To a solution of 0.1 mol of aminoacetaldehyde dimethylacetal in 100 ml of EtOH, 0.1 mol of aryl isothiocyanate was slowly added with stirring. The mixture was refluxed for 2 hr. Upon partial evaporation of the solvent, a dense oil which slowly solidified was obtained. The product was filtered and recrystallized.

**Method B.** This method is similar to method A. In this case, upon evaporation of the solvent a residue was obtained which was chromatographed on a silica gel column with $C_6H_6$–EtOAc (80:20) as eluent. By evaporation of the eluates, after a few secondary products, a solid was obtained which was recrystallized.

**1-Aryl-2-mercaptoimidazoles (6b–f, Table II).** The corresponding dimethoxyethylthiourea (0.1 mol) in 300 ml of 10% HCl was refluxed for 1 hr. The reaction mixture was allowed to cool; the solid obtained was dissolved in dilute aqueous NaOH solution. The mercaptoimidazole was precipitated with dilute aqueous HCl solution and recrystallized.

**1-Arylimidazoles (7b–f, Table III).** A suspension of 0.2 mol of the appropriate 1-aryl-2-mercaptoimidazole in 200 ml of 20% $HNO_3$ was heated gently on a water bath. After the initial rapid evolution of gas, the solution was heated for 10 min at 100° and then cooled. After basification to pH 8 with 4 *N* NaOH, the solution was extracted several times with $CHCl_3$. Evaporation of the

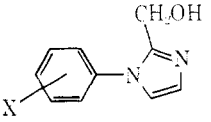
**Table III.** 1-Arylimidazoles



| Compd[a] | X | Yield, % | Mp or bp (mm), °C | Recrystn solvent | Formula[b] |
|---|---|---|---|---|---|
| **7b** | *o*-Cl | 51 | 123–125 (0.4) | | $C_9H_7ClN_2$ |
| | Picrate | | 153–155 | EtOH | $C_{15}H_{10}ClN_5O_7$ |
| **7c** | *m*-Cl | 82 | 122–123 (0.2) | | $C_9H_7ClN_2$ |
| | Picrate | | 158–160 | EtOH | $C_{15}H_{10}ClN_5O_7$ |
| **7d** | *p*-Cl | 74 | 85–87 | *i*-PrOH | $C_9H_7ClN_2$ |
| **7e** | *o*-$OCH_3$ | 66 | 129–130 (0.5) | | |
| | | | 54–56 | $Et_2O$ | $C_{10}H_{10}N_2O$ |
| **7f** | *m*-$OCH_3$ | 73 | 127–129 (1) | | $C_{10}H_{10}N_2O$ |
| | Picrate | | 142–144 | EtOH | $C_{16}H_{13}N_5O_8$ |

[a]For **7a** (X = H),[10] **7g** (X = *p*-$OCH_3$), **7h** (X = *o*-$NO_2$), and **7j** (X = *p*-$NO_2$), see A. L. Johnson, *et al.*, *J. Med. Chem.*, **12,** 1024 (1969). (**7h** and **7j** were obtained by nucleophilic displacement of the nitrophenyl fluorides by imidazole.) [b]All compounds were analyzed for C, H, and N.

**Table IV.** 1-Aryl-2-hydroxymethylimidazoles



| Compd[a] | X | Yield, % | Bp (mm) or mp, °C | Recrystn solvent | Method | Formula[b] |
|---|---|---|---|---|---|---|
| **8b** | *o*-Cl | 60 | 125–127 | $C_6H_6$ | B | $C_{10}H_9ClN_2O$ |
| **8c** | *m*-Cl | 75 | 140–142 | $Me_2CO$ | C | $C_{10}H_9ClN_2O$ |
| **8d** | *p*-Cl | 82 | 145–147 | EtOH | A | $C_{10}H_9ClN_2O$ |
| **8e** | *o*-$OCH_3$ | 30 | 156 (0.3) | | B | $C_{11}H_{12}N_2O_2$ |
| | | | 133–135 | EtOAc | | |
| **8f** | *m*-$OCH_3$ | 43 | 148–150 | $Me_2CO$ | A | $C_{11}H_{12}N_2O_2$ |
| **8h** | *o*-$NO_2$ | 52 | 168–169 | EtOH | A | $C_{10}H_9N_3O_3$ |
| **8j** | *p*-$NO_2$ | 45 | 202–203 | EtOH | A | $C_{10}H_9N_3O_3$ |

[a]For compounds **8a** (X = H), **8g** (X = *p*-$OCH_3$), and **8j** (X = *m*-$NO_2$), see ref 9 where also **8h** should be described, although it is not reported in *Chem. Abstr.*, **70,** 87674g (1969). [b]See footnote *b*, Table III.

extracts afforded a residue which was purified either by distillation or by recrystallization.

**1-Aryl-2-hydroxymethylimidazoles (8b–f,h,j, Table IV).** The arylimidazole (0.1 mol) in 50 ml of 40% aqueous HCHO was heated in a sealed vessel at 140° for 6 hr. The pure compound was isolated using one of the following methods.

**Method A.** Evaporation of the solution under reduced pressure to about half its volume and cooling afforded a solid which was filtered and recrystallized.

**Method B.** The residue obtained by evaporating the solution under reduced pressure was extracted with $CHCl_3$. Evaporation of the $CHCl_3$ gave an oily residue which was distilled *in vacuo*. The oil thus obtained rapidly solidified and was crystallized.

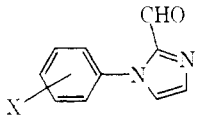
**Method C.** The oily residue from the $CHCl_3$ extracts, on addition of a small amount of $C_6H_6$, gradually solidified; the solid was filtered and recrystallized.

**1-Arylimidazole-2-carboxaldehydes (9b–h,j, Table V).** To 0.05 mol of the alcohol 8, dissolved in a mixture of 150 ml of dioxane and 10 ml of $H_2O$, 0.03 mol of finely powdered $SeO_2$ was added. The reaction mixture was refluxed while being stirred for 6 hr. Se was removed by filtration; evaporation of the filtrate gave a residue which was taken up with $H_2O$ and extracted with EtOAc. Concentration of the organic extract left a residue which was chromatographed on a silica gel column with EtOAc as eluent (in the case of **9c** the eluent was a 50:50 EtOAc–$C_6H_6$ mixture). Evaporation of the first fraction of eluate gave a solid residue which was recrystallized.

**1-Aryl-2-hydroxyiminomethylimidazoles (10a,b,d,e,g–j, Table VI).** A mixture of 0.05 mol of aldehyde and 0.15 mol of $NH_2OH \cdot HCl$ in 100 ml of EtOH was refluxed for 1 hr. Evaporation of the solvent gave a residue which was dissolved in $H_2O$. The solution was made basic with dilute aqueous $Na_2CO_3$ and the resulting precipitate was filtered and recrystallized.

***anti-* and *syn*-1-*m*-Chlorophenyl-2-hydroxyiminomethylimidazoles (11c and 10c, Table VI).** The reaction was carried out in a way similar to the preceding one. After treatment with base, the precipitate was found to consist of a two-component mixture, which was separated by column chromatography with EtOAc–$C_6H_6$ (50:50) as eluent. Evaporation of the first fraction of eluate gave the anti isomer **11c** as a solid (11% yield); after recrystallization from EtOH, it melted at 130–131°. *Anal.* ($C_{10}H_8ClN_3O$) C, H, N. Evaporation of the second fraction of eluate gave a solid (**10c**, 50% yield), which was recrystallized.

**Table V.** 1-Arylimidazole-2-carboxaldehydes



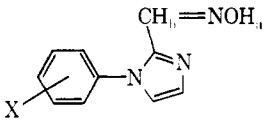
| Compd[a] | X | Yield, % | Mp, °C | Recrystn solvent | Formula[b] |
|---|---|---|---|---|---|
| **9b** | o-Cl | 20 | 87–89 | $C_6H_6$ | $C_{10}H_7ClN_2O$ |
| **9c** | *m*-Cl | 45 | 123–125 | $C_6H_6$ | $C_{10}H_7ClN_2O$ |
| **9d** | *p*-Cl | 25 | 117–119 | $C_6H_6$ | $C_{10}H_7ClN_2O$ |
| **9e** | *o*-$OCH_3$ | 70 | 73–75 | $C_6H_6$ | $C_{11}H_{10}N_2O_2$ |
| **9f** | *m*-$OCH_3$ | 25 | 90–92 | $C_6H_6$ | $C_{11}H_{10}N_2O_2$ |
| **9g** | *p*-$OCH_3$ | 55 | 93–95 | $C_6H_6$ | $C_{11}H_{10}N_2O_2$ |
| **9h** | o-$NO_2$ | 48 | 108–110 | EtOH | $C_{10}H_7N_3O_3$ |
| **9j** | *p*-$NO_2$ | 60 | 168–170 | EtOH | $C_{10}H_7N_3O_3$ |

[a]For compounds **9a** (X = H) and **9i** (X = *m*-$NO_2$), see ref 9. For compound **9h** see A. M. Simonov and I. G. Uryokina, *Khim. Geterotsikl. Soedin.*, 570 (1971); *Chem. Abstr.*, **76,** 25242n (1972). [b]See footnote *b*, Table III.

***anti-* and *syn*-1-*m*-methoxyphenyl-2-hydroxyiminomethylimidazoles (11f and 10f, Table VI)** were prepared in a fashion similar to that described above. Basification of the aqueous solution gave a solid consisting of two products. After being crystallized twice from MeOH, the syn isomer was obtained (**10f**, Table VI) in 55% yield. Evaporation of the mother liquor gave a residue which was chromatographed on silica gel with 50:50 EtOAc–$C_6H_6$ as eluent. From the first fraction of eluate the anti isomer **11f** (10% yield) was obtained which, crystallized from $C_6H_6$, melted at 114–116°. *Anal.* ($C_{11}H_{11}N_3O_2$) C, H, N.

***syn*-1-Aryl-2-hydroxyiminomethyl-3-methylimidazolium Io-**

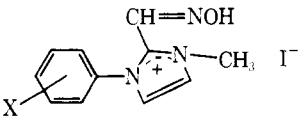
**Table VI.** 1-Aryl-2-hydroxyiminomethylimidazoles



| Compd[a] | X | Configuration | Yield, % | Mp, °C | Recrystn solvent | Nmr (τ) $H_a$ | Nmr (τ) $H_b$ | Formula[b] | Uv (EtOH) $\lambda_{max}$, nm | Uv (EtOH) Log ε |
|---|---|---|---|---|---|---|---|---|---|---|
| **10a** | H | Syn | 82 | 180–182 | EtOH | −1.65 | 1.95 | $C_{10}H_9N_3O$ | 273 | 4.17 |
| **10b** | *o*-Cl | Syn | 75 | 178–180 | EtOH | −1.50 | 2.00 | $C_{10}H_8ClN_3O$ | 273 | 3.99 |
| **10c** | *m*-Cl | Syn | 71 | 147–148 | EtOH | −1.84 | 1.81 | $C_{10}H_8ClN_3O$ | 276 | 3.98 |
| **11c** | *m*-Cl | Anti | 11 | 130–131 | EtOH | −3.66 | 2.33 | $C_{10}H_8ClN_3O$ | 277 | 3.96 |
| **10d** | *p*-Cl | Syn | 85 | 209–211 | EtOH | −1.54 | 1.95 | $C_{10}H_8ClN_3O$ | 273 | 4.01 |
| **10e** | *o*-$OCH_3$ | Syn | 78 | 193–195 | EtOH | −1.62 | 2.03 | $C_{11}H_{11}N_3O_2$ | 274 | 4.15 |
| **10f** | *m*-$OCH_3$ | Syn | 73 | 215–217 | MeOH | −1.86 | 1.80 | $C_{11}H_{11}N_3O_2$ | 277 | 4.13 |
| **11f** | *m*-$OCH_3$ | Anti | 10 | 114–116 | $C_6H_6$ | −3.93 | 2.30 | $C_{11}H_{11}N_3O_2$ | 278 | 4.01 |
| **10g** | *p*-$OCH_3$ | Syn | 84 | 225–227 | EtOH | −1.58 | 1.98 | $C_{11}H_{11}N_3O_2$ | 273 | 4.09 |
| **10h** | *o*-$NO_2$ | Syn | 65 | 224–226 | EtOH | −1.60 | 1.92 | $C_{10}H_8N_4O_3$ | 265 | 4.14 |
| **10i** | *m*-$NO_2$ | Syn | 68 | 206–207 | EtOH | −1.72 | 1.80 | $C_{10}H_8N_4O_3$ | 266 | 4.21 |
| **10j** | *p*-$NO_2$ | Syn | 60 | 218–220 | EtOH | −1.60 | 1.85 | $C_{10}H_8N_4O_3$ | 267 | 4.25 |

[a]For compound **10h**, see I. G. Uryokina, A. M. Simonov, and R. A. Ovchinnikova, *Khim. Geterotsikl. Soedin.*, 1558 (1972); *Chem. Abstr.*, **78**, 58345t (1973). [b]See footnote *b*, Table III.

**Table VII.** *syn*-1-Aryl-2-hydroxyiminomethyl-3-methylimidazolium Iodides



| Compd | X | Yield, % | Mp, °C | Recrystn solvent | Method | Uv (EtOH) $\lambda_{max}$, nm | Uv (EtOH) Log ε | Formula[a] |
|---|---|---|---|---|---|---|---|---|
| **2a** | H | 81 | 224–226 | $Me_2CO$ | A | 273 | 4.08 | $C_{11}H_{12}IN_3O$ |
| **2b** | *o*-Cl | 85 | 200–202 | EtOH | A | 273 | 4.07 | $C_{11}H_{11}ClIN_3O$ |
| **2c** | *m*-Cl | 91 | 205–206 | MeOH | A | 275 | 4.13 | $C_{11}H_{11}ClIN_3O$ |
| **2d** | *p*-Cl | 52 | 194–196 | EtOH | B | 272 | 4.11 | $C_{11}H_{11}ClIN_3O$ |
| **2e** | *o*-$OCH_3$ | 63 | 179–181 | EtOH | A | 274 | 4.18 | $C_{12}H_{14}IN_3O_2$ |
| **2f** | *m*-$OCH_3$ | 61 | 214–216 | MeOH | C | 275 | 4.15 | $C_{12}H_{14}IN_3O_2$ |
| **2g** | *p*-$OCH_3$ | 65 | 184–186 | EtOH | B | 273 | 4.37 | $C_{12}H_{14}IN_3O_2$ |
| **2h** | *o*-$NO_2$ | 38 | 197–199 | EtOH | C | 266 | 4.21 | $C_{11}H_{11}IN_4O_3$ |
| **2i** | *m*-$NO_2$ | 65 | 190–191 | MeOH | A | 262 | 4.22 | $C_{11}H_{11}IN_4O_3$ |
| **2j** | *p*-$NO_2$ | 30 | 225–227 | EtOH | B | 256 | 4.15 | $C_{11}H_{11}IN_4O_3$ |
| | | | | | | 282 sh | 3.90 | |

[a]See footnote *b*, Table III.

**dides (2a–j, Table VII). Method A.** To 0.01 mol of oxime dissolved in 100 ml of $Me_2CO$, 2.5 ml (0.04 mol) of $CH_3I$ was added. The solution was allowed to stand at ambient temperature for 10 days. The quaternary salt, which separated at crystals, was filtered and recrystallized.

**Method B** was similar to method A. In this case, however, evaporation of the solvent gave a residue which was washed with EtOAc and chromatographed on a preparative silica gel plate with EtOAc. The silica gel containing the product with lower $R_f$ was extracted with MeOH. Evaporation of the extract gave a solid which was recrystallized.

**Method C.** To 0.01 mol of oxime dissolved in 100 ml of MeOH, 2.5 ml (0.04 mol) of $CH_3I$ was added. The solution was heated in a sealed vessel for 4 days at 60°. Evaporation of the solvent gave a residue which solidified after being washed with $Me_2CO$. The product was filtered and crystallized.

**Enzymatic Assays.** The *in vitro anti*-AChE activity and the reactivating potency of the products **1a** and **2a–j** were determined on electric eel AChE (Sigma Chemical Co.), using a solution of 100 units of the enzyme in 15 ml of diethyl barbital buffer (0.12 *M*, pH 7.4). The results were compared to the activity of 2-PAM determined in parallel experiments (Table VIII).

**Reactivation of Inhibited AChE.** In order to obtain the inhibited enzyme, the above solution was incubated for 30 min with 5 × $10^{-6}$ *M* DFP; 1 ml of the mixture and 1 ml of 2 × $10^{-3}$ *M* solution in diethyl barbital buffer of the sample to be tested were introduced into the reaction vessel of an automatic titrator (Copenhagen TTT1d radiometer). After adjusting the pH to 7.4, the mixture was incubated under $N_2$ at 25°. At various time intervals, the solution was diluted with buffer (3 ml) and water (4 ml), 1 ml of 0.1 *M* solution of ACh perchlorate was added, and the enzyme activity was determined by pH-stat.

The bimolecular rate constants were calculated from the first-order rate constants and the concentration of the reactivator as described by Barfknecht and coworkers.[12]

**$ID_{50}$ Determination.** The inhibiting activity was determined by the same procedure as in the reactivation test but without DFP. At least four concentrations between 30 and 70% inhibition were used. The $ID_{50}$ values were obtained from plots of per cent inhibition *vs.* log inhibitor concentration.

## Discussion

As can be seen from the results in Table VIII, the introduction of the aryl group shifts the $pK_a$ values of the imidazole oximes methiodides into the range 7.6–8.0, which has been indicated as optimal for AChE-reactivating capacity. The potency of these compounds as reactivators of electric eel AChE inhibited by DFP is generally high. If the reactivation data are corrected for *anti*-AChE activity, for some of the new products the reactivating potency results are slightly higher than that of 2-PAM.

In contrast with the oxime derived from *N*-*n*-alkylimidazolium salts,[1] the reactivating capacity in the oximes containing a substituted aryl group (**2b–j**) is related to inhibiting activity in that the compounds which are more active as inhibitors are *generally* better reactivators. This result is easily rationalized. Apparently the stronger the

**Table VIII.** Activities of 1-Aryl-2-hydroxyiminomethyl-3-methylimidazolium Iodides on AChE and on DFP-Inhibited AChE

| Compd | $pK_a$[a] | $K_2$, l./mol/min[b] | Rel potency as reactivator of oxime, $1 \times 10^{-3}$ M | | Rel reactivation by oximate ion[c] | % inhibition by oxime, $1 \times 10^{-3}$ M | $ID_{50}$, M |
|---|---|---|---|---|---|---|---|
| | | | A[b] | B[c] | | | |
| 2-PAM | 7.82 | $2.10 \times 10^4$ | 1 | 1 | 1 | 12.5 ± 0.9[d] | $4.8 \times 10^{-3}$ |
| **1** | 8.30 | $1.11 \times 10^4$ | 0.53 ± 0.08[d] | 0.67 | 1.65 | 39.5 ± 0.7 | $2.2 \times 10^{-3}$ |
| **2a** | 7.82 | $1.57 \times 10^4$ | 0.75 ± 0.06 | 0.80 | 0.80 | 19.1 ± 0.5 | $4.2 \times 10^{-2}$ |
| **2b** | 7.77 | $1.68 \times 10^4$ | 0.80 ± 0.05 | 1.29 | 1.19 | 73.0 ± 0.8 | $7.7 \times 10^{-4}$ |
| **2c** | 7.96 | $1.49 \times 10^4$ | 0.71 ± 0.02 | 1.10 | 1.40 | 67.2 ± 0.6 | $8.4 \times 10^{-4}$ |
| **2d** | 7.94 | $1.03 \times 10^4$ | 0.49 ± 0.04 | 0.47 | 0.58 | 8.5 ± 0.4 | $9.5 \times 10^{-3}$ |
| **2e** | 7.96 | $1.62 \times 10^4$ | 0.77 ± 0.03 | 0.82 | 1.04 | 19.4 ± 0.7 | $6.0 \times 10^{-3}$ |
| **2f** | 8.00 | $2.36 \times 10^4$ | 0.65 ± 0.05 | 0.80 | 1.10 | 35.1 ± 0.6 | $2.3 \times 10^{-3}$ |
| **2g** | 8.02 | $0.98 \times 10^4$ | 0.47 ± 0.05 | 0.52 | 0.73 | 22.2 ± 0.4 | $4.7 \times 10^{-3}$ |
| **2h** | 7.67 | $0.90 \times 10^4$ | 0.43 ± 0.03 | 0.44 | 0.35 | 14.6 ± 0.5 | $2.3 \times 10^{-2}$ |
| **2i** | 7.76 | $0.98 \times 10^4$ | 0.47 ± 0.04 | 0.68 | 0.61 | 57.0 ± 0.8 | $6.7 \times 10^{-4}$ |
| **2j** | 7.66 | $0.52 \times 10^4$ | 0.25 ± 0.03 | 0.31 | 0.24 | 37.5 ± 0.6 | $2.9 \times 10^{-3}$ |

[a] $pK_a$ values were obtained by potentiometric titration. [b] The A values are the mean of four experiments. [c] Corrected for anticholinesterase activity of the oximes. The correction was made by taking into account the per cent inhibition due to the reactivator at $1 \times 10^{-3}$ M. [d] S.D.

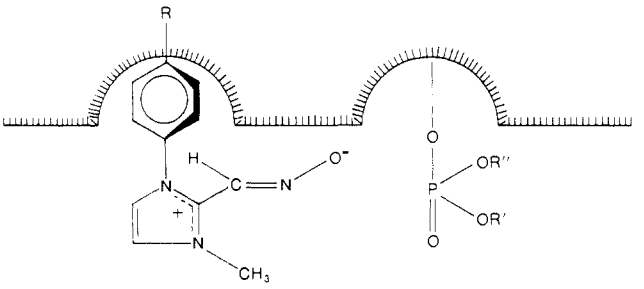



**Figure 1.** Possible mode of interaction of 1-aryl-2-hydroxyiminomethylimidazolium iodides with phosphorylated AChE enzyme.

binding to the active site of the enzyme, the more potent is the molecule as both reactivator and inhibitor. Where a flexible alkyl long chain is present (as in compounds of ref 1), the interactions perhaps occur also with other regions of the enzyme not directly concerned with catalytic activity.

Relative to the substituent effect, in the case of ortho and meta isomers activity decreases in the order Cl > $OCH_3 \simeq H > NO_2$. In similar series the para isomer is always less potent. A hypothesis that might rationalize the lower activity of para-substituted 1-arylimidazoles is that, for that molar fraction which forms a bond with the anionic site through the phenyl-substituted nitrogen, para substitution interferes with interaction of the aryl group with the enzyme surface, as shown in the Figure 1, or interferes with accessory receptor areas.

The lower activity of the derivatives **2h–j** may be explained in terms of steric factors which, owing to the bulky nitro group, prevent the molecule from easily interacting with the receptor site.

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