was recrystallized from ethanol–ethyl acetate to give compound **5x** (79%) as colorless crystals: see Table I; ^{1}H NMR (DMSO-d_6) δ 13.41 (s, 1 H, NOH), 8.70 (s, 1 H, C*H*=NOH), 8.00 (s, 2 H, aryl), 4.65 (t, 2 H, J = 5 Hz, NCH_2), 4.00 (s, 3 H, NCH_3), 3.48 (t, 2 H, J = 5 Hz, NCH_2), 2.90 (s, 6 H, 2 CH_3).

Acknowledgment. This investigation was supported by the U.S. Army Medical Research and Development Command, Department of the Army, under contract DAMD17-85-C-5154; this paper has been designated as Contribution No. 1873 to the U.S. Army Drug Development Program. We thank Dr. Robert R. Engle of the Walter Reed Army Institute of Research for encouragement and enlightening discussions and thank Dr. Barrett P. Eynon of SRI International for providing the statistical limits for all kinetic data. All in vivo biological test results were obtained at Battelle under the auspices of the Drug Assessment Division, U.S. Army Medical Research Institute of Chemical Defense.

Registry No. **2**, 616-47-7; **3**, 13750-81-7; **5a**, 132540-00-2; **5b**, 132540-01-3; **5c**, 132540-02-4; **5d**, 132540-03-5; **5e**, 132540-04-6; **5f**, 132540-05-7; **5g**, 132540-06-8; **5h**, 132540-07-9; **5i**, 132540-08-0; **5j**, 132540-09-1; **5k**, 132540-10-4; **5l**, 132540-11-5; **5m**, 132540-12-6; **5n**, 132540-13-7; **5o**, 132540-14-8; **5p**, 132540-15-9; **5q**, 132540-16-0; **5r**, 132540-17-1; **5s**, 132540-18-2; **5t**, 132540-19-3; **5u**, 132540-20-6; **5v**, 132540-21-7; **5w**, 132540-22-8; **5x**, 132540-23-9; **5y**, 132540-24-0; **5z**, 132540-25-1; soman, 96-64-0; tabun, 77-81-6; $HO(CH_2)_4OC(O)$Ph-2'-OH, 13461-42-2; $HO(CH_2)_4OH$, 110-63-4; $HO(CH_2)_2NHCH_3$, 109-83-1; $HO(CH_2)_2N(CH_3)SO_2CH_3$, 87113-83-5; $HO(CH_2)_2N(CH_3)SO_2$Ph, 59724-60-6; $ClCH_2O(CH_2)_2OCH_3$, 3970-21-6; $ClCH_2O(CH_2)_2CH(OCH_3)CH_3$, 132539-87-8; $ClCH_2O(CH_2)_2Si(CH_3)_3$, 76513-69-4; $ClCH_2O(CH_2)_3Si(CH_3)_3$, 122100-58-7; $ClCH_2O(CH_2)_4Cl$, 3970-17-0; $ClCH_2O(CH_2)_3Br$, 54314-83-9; $ClCH_2OCH_2C(CH_3)_2CH_2Br$, 132564-31-9; $ClCH_2O(CH_2)_2NO_2$, 54266-58-9; $ClCH_2OCH_2C(CH_3)_2NO_2$, 57039-05-1; $ClCH_2O(CH_2)_2SO_2CH_3$, 129499-56-5; $F_3CSO_2O(CH_2)_2CN$, 132539-88-9; $F_3CSO_2O(CH_2)_3CN$, 132539-89-0; $F_3CSO_2O(CH_2)_4CN$, 87019-99-6; $F_3CSO_2O(CH_2)_5CO_2CH_3$, 132539-90-3; $F_3CSO_2O(CH_2)_4OC(O)$Ph-2'-OH, 132539-91-4; $F_3CSO_2O(CH_2)_2F$, 95353-04-1; $F_3CSO_2O(CH_2)_2O(CH_2)_2F$, 132539-92-5; $F_3CSO_2O(CH_2)_2O(CH_2)_2Cl$, 132539-93-6; $F_3CSO_2O(CH_2)_2Br$, 103935-47-3; $F_3CSO_2O(CH_2)_2NO_2$, 132539-94-7; $F_3CSO_2O(CH_2)_2SO_2CH_3$, 126748-92-3; $F_3CSO_2O(CH_2)_2N(CH_3)_2$·HCl, 132539-95-8; $F_3CSO_2O(CH_2)_2N(CH_3)SO_2CH_3$, 132539-97-0; $F_3CSO_2O(CH_2)_2N(CH_3)SO_2CF_3$, 132539-98-1; $F_3CSO_2O(CH_2)_2N(CH_3)SO_2$Ph, 132539-99-2; $HO(CH_2)_2CN$, 109-78-4; $HO(CH_2)_3CN$, 628-22-8; $HO(CH_2)_4CN$, 2427-16-9; $HO(CH_2)_5C(O)OCH_3$, 4547-43-7; $HO(CH_2)_2F$, 371-62-0; $HO(CH_2)_2O(CH_2)_2F$, 373-22-8; $HO(CH_2)_2O(CH_2)_2Cl$, 628-89-7; $HO(CH_2)_2Br$, 540-51-2; $HO(CH_2)_2NO_2$, 625-48-9; $HO(CH_2)_2SO_2CH_3$, 15205-66-0; $HO(CH_2)_2N(CH_3)_2$·HCl, 2498-25-1; $HO(CH_2)_2N(CH_3)SO_2CF_3$, 40657-06-5; $HO(CH_2)_2OCH_3$, 109-86-4; $HO(CH_2)_2CH(CH_3)OCH_3$, 2517-43-3; $HO(CH_2)_2Si(CH_3)_3$, 2916-68-9; $HO(CH_2)_3Si(CH_3)_3$, 2917-47-7; $HO(CH_2)_4Cl$, 928-51-8; $HO(CH_2)_3Br$, 627-18-9; $HOCH_2C(CH_3)_2CH_2Br$, 40894-00-6; $HO(CH_2)_2NO_2$, 625-48-9; $HOCH_2C(CH_3)_2NO_2$, 76-39-1; $HO(CH_2)_2SO_2CH_3$, 15205-66-0; methyl salicylate, 119-36-8; 1-pyrrolidineethanol (triflate ester)hydrochloric acid, 132539-96-9; 1-pyrrolidineethanol hydrochloric acid, 30727-31-2.

Quaternary Salts of 2-[(Hydroxyimino)methyl]imidazole. 5.[1] Structure–Activity Relationships for Side-Chain Nitro-, Sulfone-, Amino-, and Aminosulfonyl-Substituted Analogues for Therapy against Anticholinesterase Intoxication

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Several quaternary imidazolium oxime derivatives incorporating side chains bearing nitro, sulfone, amino, and aminosulfonyl substituents were prepared and evaluated as treatment therapeutics for anti-AChE intoxication. In vivo test results in the mouse revealed that many of these compounds are highly effective in providing life-saving protection against the extremely toxic cholinesterase inhibitors soman and tabun. Several structure–activity relationships were noted that were characteristic of the side-chain substituent. In vivo test results for additional selected derivatives of some of the more therapeutically active compounds indicated that the quaternary heteroaryl nucleus is essential for activity whereas a nucleophilic moiety (i.e., oxime) is not. In support of previous suspicions, these results afforded additional evidence suggesting that reactivation is not the main mode of antidotal action by the imidazolium oximes. An alternative antidotal mechanism is postulated that is consistent with all data and that involves enzyme protection by the compounds.

There is presently a need in medical defense for effective, stable antidotal drugs that can be stored and used for emergency treatment of poisoning by chemical warfare nerve agents such as 3,3-dimethyl-2-butyl methylphosphonofluoridate (soman), a compound that systemically acts to phosphorylate and thereby irreversibly inhibit the esteratic site of acetylcholinesterase (AChE). Current therapeutics for organophosphorus (OP) inhibited AChE intoxication (e.g., 2-[(hydroxyimino)methyl]-1-methylpyridinium chloride, 2-PAM), which function as reactivators by bimolecularly displacing AChE from OP moieties, are ineffective against soman. This inadequacy presumably arises because of the tendency of the AChE-bound soman residue to rapidly undergo a unimolecular deal-

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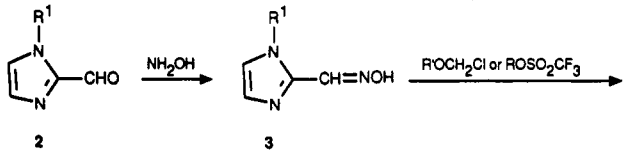
(1) Preceding papers: (a) Bedford, C. D.; Harris, R. N., III; Howd, R. A.; Miller, A.; Nolen, H. W., III; Kenley, R. A. *J. Med. Chem.* **1984**, *27*, 1431. (b) Bedford, C. D.; Harris, R. N., III; Howd, R. A.; Goff, D. A.; Koolpe, G. A.; Petesch, M.; Miller, A.; Nolen, H. W., III; Musallam, H. A.; Pick, R. O.; Jones, D. E.; Koplovitz, I.; Sultan, W. E. *J. Med. Chem.* **1989**, *32*, 493. (c) Bedford, C. D.; Harris, R. N., III; Howd, R. A.; Goff, D. A.; Koolpe, G. A.; Petesch, M.; Koplovitz, I.; Sultan, W. E.; Musallam, H. A. *J. Med. Chem.* **1989**, *32*, 504. (d) Goff, D. A.; Koolpe, G. A.; Kelson, A. B.; Vu, H. M.; Taylor, D. L.; Bedford, C. D.; Musallam, H. A.; Koplovitz, I.; Harris, R. N., III *J. Med. Chem.*, preceding article in this issue.

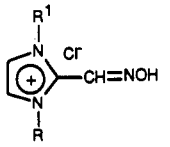
0022-2623/91/1834-1368$02.50/0

Scheme I



2 3

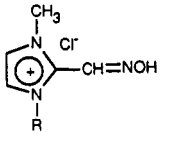
a $R^1 = CH_3$
b $R^1 = CH_2CH_3$
c $R^1 = CH_2CH_2CH_3$



4

kylation which leaves the inhibited esteratic site in an ionized form that is refractory to nucleophilic attack.[2] Indeed, in vivo reactivation of soman-inhibited AChE is yet to be conclusively demonstrated.[3]

In our preceding article,[1d] we reported the preparation and antidotal test results for a series of structurally related quaternary salt derivatives of 2-[(hydroxyimino)-methyl]-1-methylimidazole that were designed to be AChE reactivators and that had side chains bearing various substituents. The type and position of the side-chain substituent greatly influenced the antidotal effectiveness of these compounds against soman and tabun and certain members of the series, compounds 1, were noted as being

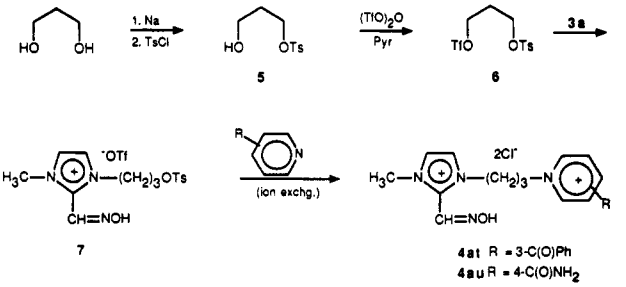


1

a $R = CH_2OCH_2C(CH_3)_2NO_2$
b $R = CH_2OCH_2CH_2SO_2CH_3$
c $R = CH_2CH_2N(CH_3)_2$
d $R = CH_2CH_2N(CH_3)SO_2CH_3$
e $R = CH_2CH_2N(CH_3)SO_2CF_3$
f $R = CH_2CH_2N(CH_3)SO_2Ph$

some of the most potent in vivo treatment agents known for anti-AChE intoxication. However, in vitro test results for compounds 1 against EPMP[1d] [ethyl (4-nitrophenyl)-methylphosphonate] along with earlier in vitro test results for related compounds against soman[1a-c] suggested that the antidotal efficacy of the quaternary imidazolium oximes is not due to enzyme reactivation. Furthermore,

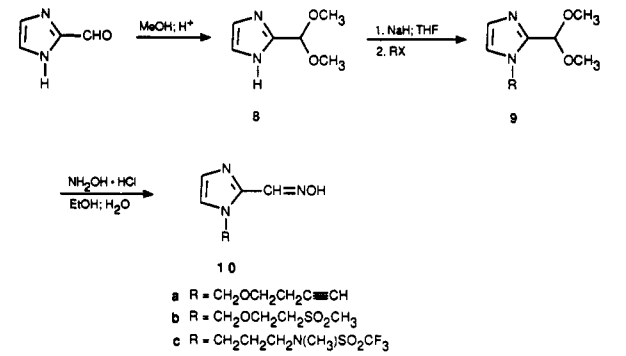
Scheme II



5 6 7

4at R = 3-C(O)Ph
4au R = 4-C(O)NH_2

Scheme III



8 9 10

a $R = CH_2OCH_2CH_2C{\equiv}CH$
b $R = CH_2OCH_2CH_2SO_2CH_3$
c $R = CH_2CH_2CH_2N(CH_3)SO_2CF_3$

results from muscarinic and nicotinic receptor-binding assays for compounds related to 1 indicated that the observed antidotal efficacy is not likely due to neuromuscular or ganglionic blocking of cholinergic receptors.[1b] To further determine the structural parameters that enhance the antidotal activity of 1 and hopefully gain some insight into the protective mechanism(s) provided by these compounds, we elected to prepare and test additional derivatives that incorporated the above (compounds 1) side-chain substituents. We now report the biological test results for these compounds and offer additional evidence suggesting that the antidotal protection provided by type 1 compounds is not due to enzyme reactivation but is most likely due to enzyme protection.

Chemistry

Most of the test compounds 4 (Scheme I) were prepared by the previously described procedures[1d] of reacting the appropriate oxime with the appropriate chloromethyl ether derivative (procedure A) or with the appropriate triflate ester (procedure B). Oximes 3 were prepared from the corresponding aldehydes 2 which in turn were prepared by the previously described[1d] procedure of reacting the appropriate 1-alkyl-2-lithioimidazole with *N,N*-dimethylformamide (DMF) followed by acid hydrolysis. Chloromethyl ethers and triflate esters were all prepared from the corresponding alcohol by using previously described procedures.[1,6]

The bisquaternary salts **4au** and **4av** (Scheme II) were prepared by reacting the bifunctional electrophile **6** with oxime **3a** followed by reaction of the resulting intermediate **7** with the appropriate pyridine derivative. Compound **6** proved to be especially useful as a differentially activated, bifunctional alkylating agent and served to virtually eliminate the formation of undesirable, symmetrically alkylated products. Structures and selected physical data for all type 4 oximes are listed in Table I.

In addition to quaternary oximes 4, nonquaternary oximes 10 (Scheme III) were prepared by alkylating the anion

(2) Karczmar, A. G.; Usdin, E.; Wills, J. H. *International Encyclopedia of Pharmacological Therapy*, 2nd ed.; Karczmar, A. G., Ed.; Pergamon Press: New York, 1970; Section 13, Vol. I.

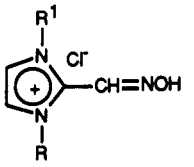
(3) We wish to qualify our statement by pointing out that in vitro reactivation of soman-inhibited AChE has been convincingly demonstrated.[4] However, although there are several known bispyridinium oximes (e.g., HI-6, HGG-12, and others)[5] that are effective antidotes against soman in animal models, to our knowledge, no one to date has unequivocally demonstrated that the observed in vivo efficacy by these oximes is due to enzyme reactivation.[5d]

(4) Schoene, K. *Biochem. Pharm.* **1973**, *22*, 2997. De Jong, L. P. A.; Wolring, G. Z. *Biochem. Pharm.* **1980**, *29*, 2379.

(5) (a) Oldiges, H.; Schoene, K. *Arch. Toxicol.* **1970**, *26*, 293. (b) Boskovic, M.; Stern, P. *Arch. Toxicol.* **1970**, *26*, 306. (c) Schoene, K. *Monogr. Neural Sci.* **1980**, *7*, 85. (d) Hamilton, M. G.; Lundy, P. M. *Arch. Toxicol.* **1989**, *63*, 144.

(6) Goff, D. A.; Harris, R. N., III; Bottaro, J. C.; Bedford, C. D. *J. Org. Chem.* **1986**, *51*, 4711.

Table I. Physical Data for Quaternary Imidazolium Oximes 4



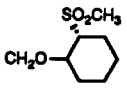
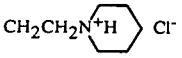
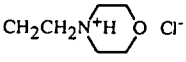
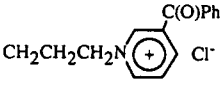
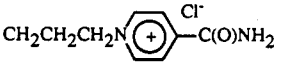
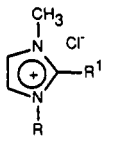
compd	R	R^1	procedure[a]	% yield[b]	mp, °C	log P[c]	formula	anal.[d]
				Nitro				
4a	$CH_2CH(CH_3)NO_2$	CH_3	B	20	171–172 dec	*e*	$C_8H_{13}N_4O_3Cl$	C, H, N, Cl
4b	$CH_2CH_2CH_2C(CH_3)_2NO_2$	CH_3	B	67	173–174 dec	−2.18	$C_{11}H_{19}N_4O_3Cl$	C, H, N, Cl
4c	$CH_2CH_2CH_2C(CH_3)_2NO_2$	CH_2CH_3	B	43	147–148	−1.80	$C_{12}H_{21}N_4O_3Cl$	C, H, N, Cl
4d	$CH_2CH_2CH(CH_3)C(CH_3)_2NO_2$	CH_3	B	50	188–190 dec	−1.61	$C_{12}H_{21}N_4O_3Cl$	C, H, N, Cl
4e	$CH_2OCH(CH_3)CH_2NO_2$	CH_3	A	84	139–140 dec	*e*	$C_9H_{15}N_4O_4Cl$	C, H, N, Cl
4f	$CH_2OCH_2CH(CH_3)NO_2$	CH_3	A	66	132–133	*e*	$C_9H_{15}N_4O_4Cl$	C, H, N
4g	$CH_2OCH(CH_3)CH(CH_3)NO_2$	CH_3	A	79	157–158 dec	*e*	$C_{10}H_{17}N_4O_4Cl$	C, H, N, Cl
4h	$CH_2OCH(CH_3)CH(CH_3)NO_2$	CH_2CH_3	A	53	142–145 dec	*e*	$C_{11}H_{19}N_4O_4Cl$	C, H, N
4i	$CH_2OC(CH_3)_2CH_2NO_2$	CH_3	A	84	149–150 dec	*e*	$C_{10}H_{17}N_4O_4Cl$	C, H, N, Cl
4j	$CH_2OC(CH_3)_2CH_2NO_2$	CH_2CH_3	A	73	124–127 dec	*e*	$C_{11}H_{19}N_4O_4Cl$	C, H, N, Cl
4k	$CH_2OCH_2C(CH_3)_2NO_2$	CH_2CH_3	A	70	128–129 dec	−1.77	$C_{11}H_{19}N_4O_4Cl$	C, H, N, Cl
4l	$CH_2OC(CH_3)_2CH(CH_3)NO_2$	CH_3	A	84	145–146 dec	*e*	$C_{11}H_{19}N_4O_4Cl$	C, H, N, Cl
4m	$CH_2OC(CH_3)_2CH(CH_3)NO_2$	CH_2CH_3	A	72	130–131 dec	*e*	$C_{12}H_{21}N_4O_4Cl$	C, H, N, Cl
4n	$CH_2OCH(CH_3)C(CH_3)_2NO_2$	CH_3	A	51	178–179 dec	−1.75	$C_{11}H_{19}N_4O_4Cl$	C, H, N, Cl
4o	$CH_2OCH_2CH_2CH_2NO_2$	CH_3	A	89	117–119 dec	−2.65	$C_9H_{15}N_4O_4Cl$	C, H, N
4p	$CH_2OCH(CH_3)CH_2CH_2CH_2NO_2$	CH_3	A	71	105–106	−2.11	$C_{11}H_{19}N_4O_4Cl$	C, H, N
				Sulfone				
4q	$CH_2CH_2SO_2CH_2CH_3$	CH_3	B	50	165–166	−2.96	$C_9H_{16}N_3O_3SCl$	C, H, N, Cl
4r	$CH_2CH_2CH_2SO_2CH_3$	CH_3	B	54	162–163 dec	−2.70	$C_9H_{16}N_3O_3SCl$	C, H, N, S
4s	$CH_2CH_2CH_2SO_2CH_3$	CH_2CH_3	B	66	164–166 dec	−2.60	$C_{10}H_{18}N_3O_3SCl$	C, H, N, S, Cl
4t	$CH_2CH_2CH_2CH_2SO_2CH_3$	CH_3	B	76	175–176 dec	−3.40	$C_{10}H_{18}N_3O_3SCl$	C, H, N, S
4u	$CH_2OCH_2CH_2SO_2CH_3$	CH_2CH_3	A	68	143–144 dec	<−3.00	$C_{10}H_{18}N_3O_4SCl$	C, H, N, S, Cl
4v	$CH_2OCH_2CH_2SO_2CH_3$	$(CH_2)_2CH_3$	A	72	149–150 dec	<−3.00	$C_{11}H_{20}N_3O_4SCl$	C, H, N, S, Cl
4w	$CH_2OCH_2CH_2SO_2CH_2CH_3$	CH_3	A	80	119–121 dec	<−2.70	$C_{10}H_{18}N_3O_4SCl$	C, H, N, S, Cl
4x	$CH_2OCH_2CH_2SO_2CH_2CH_3$	CH_2CH_3	A	68	111–114 dec	−2.67	$C_{11}H_{20}N_3O_4SCl$	C, H, N, S, Cl
4y	$CH_2OCH(CH_3)CH_2SO_2CH_3$	CH_3	A	31	152–154 dec	−2.66	$C_{10}H_{18}N_3O_4SCl$	C, H, N, S, Cl
4z	$CH_2OCH(CH_3)CH_2SO_2CH_2CH_3$	CH_3	A	37	141–143 dec	−2.70	$C_{11}H_{20}N_3O_4SCl$	C, H, N, S, Cl
4aa	$CH_2OCH(CH_3)CH(CH_3)SO_2CH_3$ (threo)	CH_3	A	55	148–150 dec	−2.79	$C_{11}H_{20}N_3O_4SCl$	C, H, N, S, Cl
4ab	$CH_2OCH(CH_3)CH(CH_3)SO_2CH_3$ (threo)	CH_2CH_3	A	47	141–142 dec	−2.68	$C_{12}H_{22}N_3O_4SCl$	C, H, N, S, Cl
4ac	$CH_2OCH(CH_3)CH(CH_3)SO_2CH_3$ (erythro)	CH_3	A	54	150–151 dec	−2.09	$C_{11}H_{20}N_3O_4SCl$	C, H, N, S, Cl
4ad	$CH_2OCH_2CH_2CH_2SO_2CH_3$	CH_3	A	84	143–144 dec	−2.50	$C_{10}H_{18}N_3O_4SCl$	C, H, N, S
4ae	$CH_2OCH_2CH_2CH_2CH_2SO_2CH_3$	CH_3	A	58	143–144 dec	−3.11	$C_{11}H_{20}N_3O_4SCl$	C, H, N, S
4af	$CH_2CH_2OCH_2CH_2SO_2CH_3$	CH_3	B	82	147–148	<−3.00	$C_{10}H_{18}N_3O_4SCl$	C, H, N, Cl
4ag	$CH_2OCH_2CH_2SO_2Ph$	CH_3	A	75	138–139 dec	−2.39	$C_{14}H_{18}N_3O_4SCl$	C, H, N, S
4ah		CH_3	A	64	153–155 dec	−2.59	$C_{13}H_{22}N_3O_4SCl$	C, H, N, S, Cl
				Amine				
4ai	$CH_2CH_2N^+H(CH_3)_2\ Cl^-$	CH_2CH_3	B	35	210–211 dec	−2.71	$C_{10}H_{20}N_4OCl_2 \cdot {}^1/_2H_2O$	C, H, N
4aj	$CH_2CH_2N^+H(CH_3)_2\ Cl^-$	$(CH_2)_2CH_3$	B	35	217–218 dec	−2.73	$C_{11}H_{22}N_4OCl_2 \cdot {}^1/_4H_2O$	C, H, N
4ak	$CH_2CH_2N^+H(i\text{-}Pr)_2\ Cl^-$	CH_3	B	70	234–235 dec	−1.79	$C_{13}H_{26}N_4OCl_2 \cdot H_2O$	C, H, N, Cl
4al	$CH_2CH(CH_3)N^+H(CH_3)_2\ Cl^-$	CH_3	B	34	214–215 dec	−2.81	$C_{10}H_{20}N_4OCl_2$	C, H, N
4am	$CH_2CH(CH_2CH_3)N^+H(CH_3)_2\ Cl^-$	CH_3	B	43	233–234 dec	−2.57	$C_{11}H_{22}N_4OCl_2$	C, H, N
4an	$CH_2CH_2CH_2N^+H(CH_3)_2\ Cl^-$	CH_3	B	32	229–230	<−3.00	$C_{10}H_{20}N_4OCl_2 \cdot {}^1/_4H_2O$	C, H, N, Cl
4ao	$CH_2CH_2CH_2N^+H(CH_2CH_3)_2\ Cl^-$	CH_3	B	45	236–238	−2.78	$C_{12}H_{24}N_4OCl_2$	C, H, N, Cl
4ap	$CH_2CH_2N^+(CH_3)_3\ Cl^-$	CH_3	B	67	227–228 dec	−2.61	$C_{10}H_{20}N_4OCl_2 \cdot H_2O$	C, H, N
4aq	$CH_2CH_2N^+CH_3(CH_2CH_3)_2\ Cl^-$	CH_3	B	64	188–189 dec	<−3.00	$C_{12}H_{24}N_4OCl_2 \cdot H_2O$	C, H, N, Cl
4ar		CH_3	B	51	268–269 dec	−2.32	$C_{12}H_{22}N_4OCl_2$	C, H, N, Cl
4as		CH_3	B	49	259–260 dec	−2.91	$C_{11}H_{20}N_4O_2Cl_2$	C, H, N, Cl
4at		CH_3	B	26	194–195 dec	−2.62	$C_{20}H_{22}N_4O_2Cl_2 \cdot 1{}^1/_4H_2O$	C, H, N
4au		CH_3	B	50	220–221 dec	<−3.00	$C_{14}H_{19}N_5O_2Cl_2 \cdot H_2O$	C, H, N, Cl
				Aminosulfonyl				
4av	$CH_2CH_2N(CH_2CH_3)SO_2CH_3$	CH_3	B	78	129–130	−2.72	$C_{10}H_{19}N_4O_3SCl \cdot H_2O$	C, H, N, S
4aw	$CH_2CH_2CH_2N(CH_3)SO_2CH_3$	CH_3	B	93	179–180	−2.63	$C_{10}H_{19}N_4O_3SCl$	C, H, N, S

Table I (Continued)

compd	R	R^1	procedure[a]	% yield[b]	mp, °C	log P[c]	formula	anal.[d]
4ax	$CH_2CH_2CH_2N(CH_2CH_3)SO_2CH_3$	CH_3	B	89	184–185	−2.69	$C_{11}H_{21}N_4O_3SCl \cdot {}^1/_2EtOH$	C, H, N, S
4ay	$CH_2CH_2N(H)SO_2CF_3$	CH_3	B	69	202–203	−1.20	$C_8H_{12}F_3N_4O_3SCl$	C, H, N, S
4az	$CH_2CH_2N(CH_3)SO_2CF_3$	CH_2CH_3	B	55	158–159	−1.19	$C_{10}H_{16}F_3N_4O_3SCl$	C, H, N, S
4ba	$CH_2CH_2N(CH_2CH_3)SO_2CF_3$	CH_3	B	83	205–206	−1.03	$C_{10}H_{16}F_3N_4O_3SCl$	C, H, N, S
4bb	$CH_2CH_2N(CH_2CH_2CH_3)SO_2CF_3$	CH_3	B	58	177–178 dec	−0.69	$C_{11}H_{18}F_3N_4O_3SCl$	C, H, N, S
4bc	$CH_2CH_2N(CH_2Ph)SO_2CF_3$	CH_3	B	51	174–175	−0.01	$C_{15}H_{18}F_3N_4O_3SCl$	C, H, N
4bd	$CH_2CH_2CH_2N(H)SO_2CF_3$	CH_3	B	78	142–143	−1.26	$C_9H_{14}F_3N_4O_3SCl$	C, H, N, S
4be	$CH_2CH_2CH_2N(CH_3)SO_2CF_3$	CH_3	B	76	192–193	−1.37	$C_{10}H_{16}F_3N_4O_3SCl$	C, H, N, S
4bf	$CH_2CH_2CH_2N(CH_2CH_3)SO_2CF_3$	CH_3	B	79	185–186	−1.02	$C_{11}H_{18}F_3N_4O_3SCl$	C, H, N, S
4bg	$CH_2CH_2CH_2N(CH_2Ph)SO_2CF_3$	CH_3	B	60	164–165	+0.06	$C_{16}H_{20}F_3N_4O_3SCl$	C, H, N, S
4bh	$CH_2OCH_2CH_2N(CH_3)SO_2CF_3$	CH_3	B	90	167–168 dec	−1.47	$C_{10}H_{16}F_3N_4O_4SCl$	C, H, N, S
4bi	$CH_2CH_2CH_2CH_2CH_2N(H)SO_2CF_3$	CH_3	B	76	144–145	−1.13	$C_{11}H_{18}F_3N_4O_3SCl$	C, H, N, S
4bj	$CH_2CH_2OCH_2CH_2N(CH_3)SO_2CF_3$	CH_3	B	71	130–131	−1.63	$C_{11}H_{18}F_3N_4O_4SCl$	C, H, N, S
4bk	$CH_2CH(CH_3)N(H)SO_2CF_3$	CH_3	B	46	203–204	−0.82	$C_9H_{14}F_3N_4O_3SCl$	C, H, N, S
4bl	$CH_2CH(CH_2CH_3)N(H)SO_2CF_3$	CH_3	B	61	206–207	−0.42	$C_{10}H_{16}F_3N_4O_3SCl$	C, H, N, S
4bm	$CH_2CH_2N(H)SO_2Ph$	CH_3	B	70	201–202	−1.92	$C_{13}H_{17}N_4O_3SCl$	C, H, N, S
4bn	$CH_2CH_2N(CH_2CH_3)SO_2Ph$	CH_3	B	79	161–162	−1.39	$C_{15}H_{21}N_4O_3SCl$	C, H, N, S
4bo	$CH_2CH_2N(CH_2CH_2CH_3)SO_2Ph$	CH_3	B	76	160–161	−0.94	$C_{16}H_{23}N_4O_3SCl$	C, H, N, S
4bp	$CH_2CH_2N(CH_2Ph)SO_2Ph$	CH_3	B	50	87–88	−0.49	$C_{20}H_{23}N_4O_3SCl \cdot {}^1/_2H_2O$	C, H, N, S
4bq	$CH_2CH_2CH_2N(H)SO_2Ph$	CH_3	B	79	152–153	−1.89	$C_{14}H_{19}N_4O_3SCl$	C, H, N, S
4br	$CH_2CH_2CH_2N(CH_3)SO_2Ph$	CH_3	B	83	196–197 dec	−1.59	$C_{15}H_{21}N_4O_3SCl$	C, H, N, S
4bs	$CH_2CH_2CH_2N(CH_2CH_3)SO_2Ph$	CH_3	B	73	189–190 dec	−1.27	$C_{16}H_{23}N_4O_3SCl$	C, H, N, S

[a] See reference 1d for description of procedures. [b] Yield from immediate precursor. [c] Octanol–buffer (pH 7.4) partition coefficient. Determined spectrophotometrically. [d] Analysis agrees within ±0.4% of the theoretical values. [e] Not determined.

of acetal 8 with the appropriate electrophile followed by hydrolyzing the resulting product in the presence of hydroxylamine. Finally, quaternary nonoxime salts 11 were



11

a R = $CH_2OCH(CH_3)C(CH_3)_2NO_2$; R^1 = $C(O)NH_2$
b R = $CH_2OCH_2CH_2SO_2CH_3$; R^1 = $C(O)NH_2$
c R = $CH_2OCH(CH_3)C(CH_3)_2NO_2$; R^1 = CH_3
d R = $CH_2CH_2CH_2N(CH_3)SO_2CF_3$; R^1 = CH_3

prepared by reacting 1-methyl-2-imidazolecarboxamide or 1,2-dimethylimidazole with the appropriate chloromethyl ether. All oximes were obtained configurationally pure as the *E* isomer as evidenced by ^1H NMR shift values.

Results

Table II lists the antidotal test results in the mouse against soman and occasionally against tabun (ethyl *N,N*-dimethylphosphoramidocyanidate) for all type **4**, **10**, and **11** compounds. These data were obtained by using methods that were described in detail in our preceding article.[1d] For the purpose of discussion, compounds **4** are divided into subgroups that are defined according to the type of side-chain substituent.

It is evident from the consistently high antidotal efficacy exhibited by the nitro and sulfone side-chain substituted analogues that slight to moderate side-chain modifications in these subgroups are readily tolerated. The more drastic change of partially restricting the side-chain substituent conformationally (compound **4ah**) essentially abolished therapeutic activity. This suggests that the side-chain orientation is important for activity and that further optimization of therapeutic efficacy may be possible through other conformationally constrained analogues. It is noteworthy that the toxicities of the sulfone analogues average about $^1/_4$–$^1/_6$ those of the nitro analogues and even though the test doses of the sulfones are accordingly greater, the therapeutic efficacy of these two subgroups are approximately the same. Because the methylsulfonyl substituent is known to provide good binding to AChE,[7] this result is not likely due to differences in binding affinity imparted by the methylsulfonyl and the nitro substituent. However, it could be a result of differences in how these two subgroups distribute systemically.

Although most structural alterations of the amine-substituted derivative **1c** proved to be unrewarding with respect to antidotal activity, a few generalizations regarding structure–activity relationships (SAR) for the amine series (compounds **4ai–au**) were noted. Step-wise homologation of the imidazole N3 alkyl substituent from methyl to *n*-propyl (**4ai**, **4aj**) essentially abolished antidotal activity as did steric bulk at the side-chain amine nitrogen (**4ak**). Although quaternization of the side-chain tertiary amine yielded inactive compounds (**4ap**, **4aq**), the presence of a substituted quaternary pyridinium ring in place of the tertiary amine (**4at**, **4au**) led to a slight enhancement in therapeutic activity relative to that of **1c**. This suggests that the therapeutic enhancement in compounds **4at** and **4au** is more likely a function of the steric characteristics of the pyridinium ring or the substituent in the pyridinium ring, and not the additional quaternary center.

Similar to previous results,[1d] the aminosulfonyl-substituted compounds (**4av–bs**) yielded the most active analogues. Thus, methanesulfonamides (mesylamides), trifluoromethanesulfonamides (triflamides), and benzenesulfonamides all exhibited high activity in certain cases, indicating that flexibility is allowed in the sulfonyl portion of the sulfonamide linkage. This result is especially interesting considering the fairly wide range of partition coefficients (log *P*, Table I) exhibited by this subgroup. Based on these preliminary results, it does not appear that log *P* would be a very sensitive parameter for correlating activity in this series. However, this is yet to be unequivocally determined. Closer examination of the aminosulfonyl subgroup reveals that the mesylamide and triflamide analogues, which should be fairly isosteric with

(7) Cohen, S. G.; Chisti, S. B.; Elkind, J. L.; Reese, H.; Cohen, J. B. *J. Med. Chem.* **1985**, *28*, 1309. Cohen, S. G.; Elkind, J. L.; Chisti, S. B.; Giner, J-L. P.; Reese, H.; Cohen, J. B. *J. Med. Chem.* **1984**, *27*, 1643.

Table II. Antidotal Activity of Imidazolium Compounds against Soman and Tabun in the Mouse

compd[b]	LD_{50},[c] mmol/kg	survival[a] soman 1/64	soman 1/16	soman 1/4	tabun 1/64	tabun 1/16	tabun 1/4
			Nitro				
1a	0.31		8	6		3	6
4a	0.60		0	4			
4b	0.27	0	1	9			
4c	0.61	0	7	6			
4d	0.35	3	3	8			
4e	0.28	0	2	9			
4f	0.22		0	6			
4g	0.25	3	9	9			
4h	0.32	1	1	8			
4i	0.44	0	5	8	0	0	4
4j	0.34	0	0	4			
4k	0.17	5	6	8			
4l	0.29	4	10	9			
4m	0.50	0	8	10			
4n	0.25		5	8		7	6
4o	0.53	2	7	10			
4p	0.33	0	0	0	0	0	3
			Sulfone				
1b	2.70		9	6		1	5
4q	>1.42	0	6	5	0	1	6
4r	>1.48	0	2	6	0	1	9
4s	1.35	0	4	10			
4t	>1.35	0	1	8	2	5	7
4u	>1.28		2	9			
4v	0.39	0	0	9			
4w	1.80	0	4	8	0	3	9
4x	1.23	0	4	9			
4y	>1.28	3	8	5	0	8	6
4z	>1.23	0	3	8	0	1	8
4aa	1.13	3	9	6	0	9	9
4ab	0.68	1	2	10	1	0	5
4ac	0.59	6	7	7	1	10	9
4ad	>1.28	1	9	10	2	5	8
4ae	0.33	0	2	6	0	0	4
4af	0.92		0	6			
4ag	0.65	0	4	8	0	0	7
4ah	0.54	0	0	1	0	0	5
			Amine				
1c	>1.48		0	10			
4ai	1.17	0	0	1			
4aj	0.34	0	0	0			
4ak	0.13	0	0	1	1	0	2
4al	1.41	1	0	8	0	0	5
4am	0.31	1	0	0	0	0	2
4an	1.47		0	8			
4ao	1.67	0	0				
4ap	>1.33	0	0	2			
4aq	>1.21		0	0			
4ar	0.58	0	1	7	0	0	1
4as	>1.29	0	0	3			
4at	0.25	0	3	9	3	7	9
4au	1.10	0	7	10			
			Aminosulfonyl				
1d	0.22	6	10	8	0	7	7
4av	0.71	5	9	7			
4aw	0.66	0	9	8			
4ax	0.69	2	1	5			
4ay	0.28	1	3	7	1	0	8
1e	0.21	3	8	6			
4az	0.66	0	5	7	1	2	7
4ba	0.28	9	10	5	1	8	7
4bb	0.23	0	5	6	0	8	10
4bc	0.06	0	3	4	0	0	5
4bd	0.29	0	0	0	0	0	0
4be	>1.10	0	10	8	1	3	9
4bf	>0.37	0	4	7	2	2	10
4bg	>0.91	2	4	5	0	0	2
4bh	1.01	4	6	5			
4bi	0.95	0	0	0	1	1	1
4bj	>1.01	1	0	1	0	0	2
4bk	1.12	1	5	5			

Table II (Continued)

compd[b]	LD_{50},[c] mmol/kg	survival[a] soman $^1/_{64}$	soman $^1/_{16}$	soman $^1/_4$	tabun $^1/_{64}$	tabun $^1/_{16}$	tabun $^1/_4$
4bl	>0.16	0	0	5			
4bm	0.36	6	10	7	1	10	9
1f	0.03	2	10	8	0	3	10
4bn	0.60	9	7	1			
4bo	0.20	2	9	2	0	8	9
4bp	0.43	0	5	1	0	0	4
4bq	1.11	0	0	4			
4br	>0.17	0	0	2			
4bs	1.03	0	0	1	0	6	2
10a	>1.74		0	1			
10b	>1.41	0	0	0			
10c	0.58	0	0	1	1	1	2
11a	>1.30	0	4	9			
11b	>1.34	1	1	7	0	2	3
11c	0.75	9	8	6	7	8	8
11d	>1.19	0	4	5	2	0	7
2-PAM	0.85	0	0	0	0	0	0
HI-6[d]	1.67	8				0	2

[a] Refers to the number of survivors noted at 24 h out of a population of 10 mice each exposed im to 2 × LD_{50} of the OP agent. Test compound administered im in doses of $^1/_{64}$-, $^1/_{16}$-, and $^1/_4LD_{50}$ concurrently with atropine sulfate (11.2 mg/kg) 10 s after nerve agent challenge. LD_{50} of soman (plus 11.2 mg/kg atropine sulfate) ≃0.13 mg/kg in a 20–30 g mouse; without atropine, LD_{50} soman ≃0.10 mg/kg. [b] See Table I for structures. [c] Determined im in the mouse as previously described.[1b,c] [d] 1-[[(4-Carbamoylpyridinio)methoxy]methyl]-2-[(hydroxyimino)methyl]pyridinium dichloride.

respect to substituent size, exhibit very similar SAR trends. The optimum side-chain separation between imidazolium ring and substituent occurs at two to three methylene units (**4av**, **4aw**, **4ba**, **4be**). In contrast, activity in the benzenesulfonamide series is essentially lost when this spacer is extended beyond two methylene units (compounds **4bq–bs**), suggesting that some limit for side-chain substituent size and placement has been exceeded. The effect of varying the *N*-alkyl substituent of the sulfonamide moiety gave variable results depending on the type of sulfonamide and the length of the side chain. However, in cases where direct comparison of this parameter was made, methyl or ethyl proved to be optimum and about equal whereas hydrogen in place of an alkyl group was effective only in the benzenesulfonamide series. Groups larger than ethyl noticeably decreased activity.

The antidotal test results for nonquaternary compounds **10** reveal that the quaternary cationic imidazolium nucleus is essential for antidotal activity. In terms of reactivation, the requirement of a cationic center in the reactivator serves a 2-fold purpose. The first is to provide coulombic attraction for the anionic subsite of AChE in order that the reactivator may arrive and properly orient for nucleophilic attack on the covalently bound inhibiting residue.[2] The second purpose of the cationic center is to lower the pK_a of the oxime moiety into the optimum range of 7.0–8.0 by serving mesomerically as an "electron sink" for the anionic oximate. Hence, the lack of antidotal activity in nonquaternary compounds **10** could be construed as evidence for the reactivation mechanism by the quaternary derivatives. However, the test results for compounds **11** rebuke this possibility. *Compounds 11, which have no reasonable means of functioning as nucleophilic reactivators, are as effective therapeutically as their oxime counterparts.* Although very informative, this result is not surprising and constitutes further evidence against reactivation being the major mode of antidotal protection by type **4** compounds.

With respect to general SAR trends in Table II, homologation of the imidazolium N3 alkyl substituent from methyl to ethyl to *n*-propyl typically served to progressively attenuate antidotal activity and, in most cases, increase toxicity. More significant, direct comparison of selected examples reveals no obvious therapeutic advantage of the analogues bearing the side-chain β-oxygen atom over the corresponding β-methylene analogues. Therefore, the *O,N*-acetal side-chain linkage that was an original structural feature of this series,[1a] but which imparts a certain degree of hydrolytic lability to the system, can fortunately be replaced with a much more stable linkage without significant decrement to therapeutic activity.

Discussion

The original intention for investigating quaternary derivatives of the 2-[(hydroxyimino)methyl]imidazole system was to search for new, more effective reactivators for soman-inhibited AChE. Indeed, several derivatives of this series have shown high efficacy for the treatment of anti-AChE intoxication under conditions where current drugs are ineffective. However, despite being designed as AChE reactivators, several observations cast considerable doubt on reactivation being the true mode of therapeutic action by these compounds. These observations include the following: (1) no correlation is observed between in vitro reactivation by the compounds and in vivo survival in the mouse;[1] (2) contrary to previous reactivators, the imidazolium oximes exhibit antidotal activity that is independent of the inhibiting agent or, more explicitly, the nature of the inhibited enzyme; and, most significant, (3) some of the most effective examples, in which the oxime has been replaced with a nonnucleophilic moiety, retain in vivo protective ability even though they have no means of functioning as a reactivator. Therefore, alternative protective mechanisms for these compounds must be considered.

The first possibility considered was neuromuscular and ganglionic blockade of peripheral cholinergic sites which would serve in a therapeutic capacity to counteract the build-up of lethal concentrations of acetylcholine. As mentioned introductorily, this possibility is highly unlikely on the basis that measured muscarinic and nicotinic binding potencies of some of the earlier, active analogues were not very significant nor was there noticeable correlation of these potencies with in vivo survival.[1b] The

Table III. Pretreatment Efficacy of Selected Imidazolium Compounds against Soman in the Mouse

	survival[a]					
	15 min			60 min		
compd	$^1/_{64}$	$^1/_{16}$	$^1/_4$	$^1/_{64}$	$^1/_{16}$	$^1/_4$
4ac	3	6	8	3	1	5
4at	2	8	7	0	0	9
4bm	0	3	8	0	2	5
11c	7	8	6	0	5	7

[a] Refers to the number of survivors noted at 24 h out of a population of 10 mice each exposed im to $2LD_{50}$ of soman. Test drug administered im at $^1/_{64}$-, $^1/_{16}$-, or $^1/_4LD_{50}$ and at 15 or 60 min prior to the soman challenge. Atropine sulfate (11.2 mg/kg) and 2-PAM (25 mg/kg) administered im 10 s after soman challenge.

second possibility we consider is direct reaction of the drug with the inhibiting agent to give nontoxic degradation products. More specifically, the drug could be lingering near the enzyme esteratic region and acting as a scavenger for the approaching OP agent, thereby protecting the enzyme from phosphorylation. Although this possibility could be contributing in a minor capacity to the observed activity, it is unlikely to be the major protective mechanism because it would require that the protecting agent incorporate a nucleophilic moiety, a feature which apparently is not necessary for activity as evidenced by the antidotal test results for compounds 11. The third possibility, which we contend is most likely, involves a noncovalent interaction of the drug with the enzyme that reversibly inhibits esteratic activity. This interaction prevents phosphorylation of the esteratic site by physically blocking access of the inhibiting agent and thus allows the inhibiting agent to harmlessly hydrolyze to innocuous degradation products. In addition to being consistent with the above-listed observations, this mechanism is further supported by previous findings that the quaternary imidazolium compounds generally tend to be potent reversible inhibitors of free AChE in vitro.[1] Reversible AChE inhibition by the imidazolium compounds in vivo would lead to increased acetylcholine levels, hence the need for atropine as cotherapy. This proposed prophylactic mechanism finds precedents in the carbamate drugs physostigmine and pyridostigmine which protect AChE by forming a spontaneously hydrolyzable, covalent bond to the esteratic site.[8] However, unlike the carbamate drugs, we speculate that the imidazolium compounds interact with the enzyme in a noncovalent manner.

In a treatment mode of administration, the above-postulated mechanism would require that the drug systemically disperse and arrive at the esteratic site much faster than the inhibiting agent. This could be possible considering that an inhibiting agent like soman, which is very lipophilic, would tend to partition away from areas of the periphery containing the highest amounts of AChE (i.e., the serum) and into hydrophobic regions (i.e., fat tissue), whereas the highly water-soluble quaternary imidazolium salts would be expected to distribute much more rapidly by concentrating in the serum. Furthermore, if a prophylactic mechanism is responsible for the observed antidotal activity, then one would expect these compounds to be at least as effective, if not more so, when administered prior to the inhibiting agent, i.e., as pretreatment drugs. Table III shows the pretreatment test results in the mouse for selected examples. These data reveal that the selected compounds are generally more effective as pretreatments when administered 15 min before the soman challenge than 60 min before, indicating a rapid onset of protection followed by rapid clearing of the drug.

Conclusions

In order to determine the structural and electronic parameters that most influence the observed antidotal activity by the quaternary 2-[(hydroxyimino)methyl]-imidazole system, several derivatives with appropriately substituted side chains were prepared and tested. Based on antidotal test results in the mouse and previous in vitro test results,[1] we draw the following conclusions. Nitro, sulfone, amino, and aminosulfonyl side-chain substituents all impart high antidotal activity, and in most cases the activity seems to be insensitive to minor or moderate side-chain structural modifications, i.e., side-chain alkyl substitution or branching. A cationic quaternary heteroaryl nucleus is essential for activity; the presence of an oxime or other nucleophilic moiety is not. There is a definite optimum range, with respect to therapeutic efficacy, for side-chain separation of the imidazolium nucleus and the side-chain substituent. The exact optimum range depends on the type of side-chain substituent, but generally lies between two and four atoms. This distance corresponds closely to the distance separating the two points of enzyme–substrate interaction in the AChE substrate, acetylcholine. Previous in vitro test results[1] indicate that the imidazolium compounds are not particularly effective as AChE reactivators, but that they are fairly potent reversible, competitive inhibitors of free AChE. On the basis of all of these observations, we conclude that the major mode of antidotal action by the quaternary imidazolium compounds is not enzyme reactivation but is most likely enzyme protection. We speculate that the protective mechanism involves a reversible, noncovalent interaction of the drug with the catalytic region of AChE that serves to protect the esteratic site from phosphorylation by physically blocking access of the inhibiting agent.

Future studies of these compounds will be directed at improving therapeutic activity by incorporating additional side-chain substituents into selected examples, by enhancing drug–enzyme interactions through the use of side-chain conformationally constrained analogues, and by the use of computer-assisted modeling and QSAR. Also, additional supporting evidence for the proposed antidotal mechanism will be sought through in vitro studies to determine the ability of the imidazolium compounds to inhibit AChE phosphorylation and by determining certain relevant pharmacokinetic properties of the imidazolium compounds such as rates of systemic distribution and clearing.

Experimental Section

Melting points were determined in capillary tubes on a Mel-Temp block or Thomas-Hoover Unimelt apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian Associates EM-360 or JEOL FX90 spectrometer and are reported in δ units relative to tetramethylsilane as internal reference. Microanalyses were performed by Desert Analytics, Tucson, AZ. Octanol–pH 7.4 phosphate buffer partition coefficients were determined spectrophotometrically by using the method of Hansch.[9] In vivo antidotal test results were obtained by using methods described in detail in our preceding article.[1d]

Tetrahydrofuran (THF) was distilled from benzophenone ketyl and used immediately. All other solvents were reagent grade.

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Oxime **3a**, chloromethyl ethers, and triflate esters were all prepared by using procedures previously described.[1,6] Quaternary imidazolium oximes **4** were all prepared by reacting the appropriate oxime **3** with the appropriate chloromethyl ether (procedure A) or with the appropriate triflate ester (procedure B), both procedures having been described in detail in our preceding article.[1d] Many of the alcohols required for chloromethyl ethers and triflate esters were commercially unavailable and were obtained by synthesis. The alcohols required for compounds **4b** and **4d** were prepared by Michael reaction of 2-nitropropane with acrolein and crotonaldehyde, respectively,[10] followed by reduction of the resulting nitro aldehydes with sodium borohydride. The alcohol required for compound **4e** was prepared by the Henry reaction[11] of acetaldehyde with nitromethane. The alcohols required for compounds **4i** and **4m** were prepared by the method of Astle and Abbot.[12] The alcohol 3-nitro-1-propanol required for compound **4o** was prepared by reacting 3-bromo-1-propanol with silver nitrite in diethyl ether for 8 days. The alcohol for compound **4p** was prepared by the method of Asaoka et al.[13] The sulfonyl alcohols required for compounds **4s** and **4t** were prepared by tungstic acid catalyzed[14] oxidation of the corresponding thiomethyl alcohols which were prepared by the method of Kirner.[15] The alcohols 1-(methylsulfonyl)-2-propanol and 1-(ethylsulfonyl)-2-propanol required for compounds **4y** and **4z** were prepared by alkylating the sodium thiolate of 1-mercapto-2-propanol with iodomethane or bromoethane followed by oxidation of the resulting thioalkyl alcohols to the corresponding sulfones. The alcohols required for compounds **4aa** and **4ac** were prepared by epoxide ring opening of *cis*- and *trans*-2,3-epoxybutane, respectively, with sodium methylthiolate followed by oxidation to the sulfone. The alcohol required for compound **4ah** was prepared by oxidation of *trans*-2-(methylthio)cyclohexanol which was prepared by the method of Trost et al.[16] The alcohols required for the aminosulfonyl-substituted compounds **4av–bs** were prepared by using procedures described in our preceding article.[1d] All other starting alcohols were commercial materials.

1-Ethyl-2-[(hydroxyimino)methyl]imidazole (3b) and 2-[(Hydroxyimino)methyl]-1-(1′-propyl)imidazole (3c). Oximes **3b** and **3c** were prepared in 48% and 53% overall yields from 1-ethylimidazole and 1-(1′-propyl)imidazole, respectively, using the procedure previously described[1d] for the preparation of oxime **3a**. Compounds **3b** and **3c** exhibited the following properties.

Compound **3b**: mp 165–166 °C; ^{1}H NMR (DMSO-d_6) δ 11.43 (s, 1 H, NOH), 8.10 (s, 1 H, C*H*=NOH), 7.33 and 7.03 (2 s, 1 H each, aryl), 4.30 (q, 2 H, J = 7 Hz, CH_2), 1.28 (t, 3 H, J = 7 Hz, CH_3).

Compound **3c**: mp 105–106 °C; ^{1}H NMR ($CDCl_3$) δ 10.92 (s, 1 H, NOH), 8.37 (s, 1 H, C*H*=NOH), 7.11 and 6.97 (2 s, 1 H each, aryl), 3.89 (t, 2 H, J = 7 Hz, CH_2), 1.82 (m, 2 H, CH_2), 0.87 (t, 3 H, J = 7 Hz, CH_3).

Preparation of 3-[(Tolylsulfonyl)oxy]-1-[[(trifluoromethyl)sulfonyl]oxy]propane (6). A mixture of 1,3-propanediol (22.83 g, 0.30 mol) and sodium (2.41 g, 0.105 mol) was stirred at 80 °C until the sodium had dissolved. The mixture was then cooled in ice and a solution of *p*-toluenesulfonyl chloride (19.07 g, 0.10 mol) in THF (100 mL) was added. After being stirred at 45 °C for 30 min, the mixture was cooled and concentrated to give an oily residue. The residue was taken up in dichloromethane (DCM, 250 mL), washed with water (2 × 120 mL), dried over $MgSO_4$, filtered, and evaporated to give 22.93 g of oil that was flash chromatographed through silica gel and eluted with DCM–ethyl acetate (3:1). There was obtained 13.63 g (59%) of pure tosylate **5** as a colorless oil. Compound **5** (13.41 g) was dissolved in DCM (50 mL) and cooled at 0–5 °C, and pyridine (4.72 mL) was added. The resulting ice-cooled mixture was added via cannula over 45 min to another ice-cooled mixture of triflic anhydride (9.93 mL) in DCM (120 mL) with continuous stirring. After 30 min, the mixture was washed with cold water (2 × 75 mL), dried over $MgSO_4$, and evaporated to give a brown oil. The oil was flash chromatographed through silica gel and eluted with DCM to give 18.55 g (88%) of pure **6** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.80 and 7.37 (2 d, 2 H each, J = 8 Hz, aryl), 4.63 (t, 2 H, J = 6 Hz, CH_2), 4.19 (t, 2 H, J = 6 Hz, CH_2), 2.48 (s, 3 H, CH_3), 2.20 (m, 2 H, CH_2).

Preparation of 1-[2′-[(Hydroxyimino)methyl]-3′-methyl-1′-imidazolyl]-3-(3″-benzoyl-1″-pyridinyl)propane Dichloride (4at) and 1-[2′-[(Hydroxyimino)methyl]-3′-methyl-1′-imidazolyl]-3-(4″-carbamoyl-1″-pyridinyl)propane Dichloride (4au). A solution of compound **6** (24.8 mmol) in nitromethane (10 mL) was added to an ice-cooled, stirred suspension of oxime **3a** (24.8 mmol) in nitromethane (120 mL). The mixture was stirred at room temperature for 2 h and 3-benzoylpyridine (24.8 mmol) was added. After being stirred at 80 °C for 8 days, the solvent was evaporated, and the residue was treated with an aqueous suspension of Amberlite IRA-400 anion exchange (Cl form) resin (100 mL) and stirred for 30 min. The mixture was passed through a column of fresh anion-exchange resin and the eluant was evaporated to dryness to give a tan solid that was recrystallized from 95% ethanol–ethyl acetate to give pure **4at** (26%) as a colorless, crystalline solid (see Table I): ^{1}H NMR (DMSO-d_6) δ 13.27 (s, 1 H, NOH), 9.59–8.81 (m, 4 H, aryl), 8.59 (s, 1 H, C*H*=NOH), 7.53–8.42 (m, 7 H, aryl), 4.89 (t, 2 H, J = 7 Hz, NCH_2), 4.58 (t, 2 H, J = 6 Hz, NCH_2), 3.95 (s, 3 H, CH_3), 2.89 (m, 2 H, CH_2).

With a similar procedure, compound **4au** was prepared in 50% yield from **3a**, **6**, and isonicotinamide: ^{1}H NMR (D_2O) δ 8.57 (s, 1 H, C*H*=NOH), 8.50 and 9.19 (2 d, 2 H each, J = 7 Hz, aryl), 7.65 and 7.73 (2 d, 1 H each, J = 2 Hz, aryl), 4.45–5.10 (m, 4 H, 2 NCH_2), 3.98 (s, 3 H, NCH_3), 2.70 (m, 2 H, CH_2).

Preparation of 2-(Dimethoxymethyl)imidazole (8). A mixture of imidazole-2-carboxaldehyde[17] (73 g, 0.76 mol), absolute methanol (1 L), and sulfuric acid (46.5 mL) was heated at reflux for 24 h. After being cooled, the mixture was neutralized with solid sodium bicarbonate (153 g) and filtered, and the filtrate concentrated to dryness. The tan solid residue was flash-chromatographed through silica gel and eluted with DCM–ethyl acetate (1:1) to give a white solid. Recrystallization from toluene gave pure **8** (80%) as colorless needles: mp 120–121 °C; ^{1}H NMR ($CDCl_3$) δ 8.99 (br s, 1 H, NH), 6.98 (s, 2 H, aryl), 5.43 (s, 1 H, CH), 3.30 (s, 6 H, 2 CH_3).

General Procedure for the Preparation of Compounds 10. Compounds **10** were prepared by the following general procedure.

A mixture of acetal **8** (0.112 mol) and sodium hydride (0.112 mol) in THF (600 mL) was stirred at room temperature for 2 h. The mixture was cooled in ice and then treated dropwise with a solution of the appropriate electrophile (0.112 mol) in DCM (300 mL). After being warmed to room temperature and being stirred for 2 h, the mixture was concentrated, taken up in DCM (300 mL), washed with water, dried, and reconcentrated to give crude acetal **9**. Compound **9** was treated with 800 mL of ethanol–water (3:1) and hydroxylamine hydrochloride (0.113 mol) and refluxed for 4 h. The mixture was then cooled and neutralized with a concentrated aqueous solution of Na_2HPO_4 (0.115 mol). The solid that separated was filtered and recrystallized from methanol to give pure oximes **10** having the following properties.

1-[(3′-Butynyl-1′-oxy)methyl]-2-[(hydroxyimino)methyl]imidazole (10a) was prepared in 66% yield from **8** and 1-(chloromethoxy)-3-butyne: mp 98–99 °C (HCl salt mp 101–102 °C); ^{1}H NMR ($CDCl_3$) δ 10.00 (br s, 1 H, NOH), 8.34 (s, 1 H, C*H*=NOH), 7.20 (s, 2 H, aryl), 5.77 (s, 2 H, OCH_2N), 3.63 (t, 2 H, J = 7 Hz, OCH_2), 2.43 (dt, 2 H, J = 2, 7 Hz, CH_2), 1.97 (t, 1 H, J = 2 Hz, alkynyl). Anal. ($C_9H_{11}N_3O_2$·HCl) C, H, N.

2-[(Hydroxyimino)methyl]-1-[[[2′-(methylsulfonyl)ethyl-1′]oxy]methyl]imidazole (10b) was prepared in 47% yield from **8** and 1-(chloromethoxy)-2-(methylsulfonyl)ethane: mp 143–144 °C (HCl salt mp 144–147 °C dec); ^{1}H NMR ($CDCl_3$) δ 11.55 (br s, 1 H, NOH), 8.10 (s, 1 H, C*H*=NOH), 7.50 and 7.08

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(2 d, 1 H each, J = 2 Hz, aryl), 5.67 (s, 2 H, NCH_2O), 3.84 (t, 2 H, J = 6 Hz, OCH_2), 3.38 (t, 2 H, J = 6 Hz, CH_2SO_2), 2.95 (s, 3 H, SO_2CH_3). Anal. ($C_8H_{13}N_3O_4S$·HCl) C, H, N, S.

2-[(Hydroxyimino)methyl]-1-[3′-[*N*-methyl-*N*-[(trifluoromethyl)sulfonyl]amino]-1′-propyl]imidazole (10c) was prepared in 51% yield from 8 and 3-[*N*-methyl-*N*-[(trifluoromethyl)sulfonyl]amino]-1-propyl triflate: mp 118–119 °C (HCl salt mp 145–146 °C); ^{1}H NMR ($CDCl_3$) δ 11.33 (s, 1 H, NOH), 8.03 (s, 1 H, C*H*=NOH), 7.00 and 7.30 (2 s, 1 H each, aryl), 4.30 (t, 2 H, J = 7 Hz, NCH_2), 3.70–2.90 (m, 5 H, NCH_2, NCH_3), 2.40–1.80 (m, 2 H, CH_2). Anal. ($C_9H_{13}N_4O_3S$·HCl·$^1/_2H_2O$) C, H, N, S.

General Procedure for the Preparation of Compounds 11a–d. Compounds **11a–d** were prepared by adding the appropriate electrophile (1.05 equiv) dropwise to a mixture of 1-methyl-2-imidazolecarboxamide[18] (for compounds **11a**, **11b**) in THF–DMF (5:1) at room temperature or to an ice-cooled mixture of 1,2-dimethylimidazole (for compounds **11c**, **11d**) in THF. After being stirred overnight, the resulting solids were collected by filtration and recrystallized from ethanol–ethyl acetate. Compounds **11a–d** exhibited the following properties.

2-Carbamoyl-3-methyl-1-[[(3′-methyl-3′-nitrobutyl-2′)oxy]methyl]imidazolium chloride (11a) was prepared in 36% yield from 1-methyl-2-imidazolecarboxamide and 2-(chloromethoxy)-3-methyl-3-nitrobutane: mp 140–143 °C; ^{1}H NMR (DMSO-d_6) δ 9.77 and 9.07 (2 br s, 1 H each, NH_2), 8.10 and 8.03 (2 d, 1 H each, J = 2 Hz, aryl), 5.75 (s, 2 H, NCH_2O), 4.33 (q, 1 H, J = 6 Hz, OCH), 4.01 (s, 3 H, NCH_3), 1.43 (s, 6 H, 2 CH_3), 1.10 (d, 3 H, J = 6 Hz, CH_3). Anal. ($C_{11}H_{19}N_4O_4Cl$) C, H, N.

2-Carbamoyl-3-methyl-1-[[[2′-(methylsulfonyl)ethyl-1′-]oxy]methyl]imidazolium chloride (11b) was prepared in 61% yield from 1-methyl-2-imidazolecarboxamide and 1-(chloromethoxy)-2-(methylsulfonyl)ethane: mp 144–145 °C dec; ^{1}H NMR (DMSO-d_6) δ 9.56 and 9.13 (2 br s, 1 H each, NH_2), 8.17 and 8.04 (2 d, 1 H each, J = 2 Hz, aryl), 5.83 (s, 2 H, NCH_2O), 4.04 (s, 3 H, CH_3), 4.00 and 3.50 (2 t, 2 H each, J = 6 Hz, $OCH_2CH_2SO_2$), 3.05 (s, 3 H, CH_3). Anal. ($C_9H_{16}N_3O_4SCl$) C, H, N, S, Cl.

2,3-Dimethyl-1-[[(3′-methyl-3′-nitrobutyl-2′)oxy]methyl]imidazolium chloride (11c) was prepared in 59% yield from 1,2-dimethylimidazole and 2-(chloromethoxy)-3-methyl-3-nitrobutane: mp 175–177 °C dec; ^{1}H NMR (DMSO-d_6) δ 8.08 and 7.83 (2 d, 1 H each, J = 2 Hz, aryl), 5.74 (s, 2 H, NCH_2O), 4.18 (q, 1 H, J = 6 Hz, OCH), 3.85 (s, 3 H, NCH_3), 2.57 (s, 3 H, CH_3), 1.43 and 1.47 (2 s, 3 H each, $C(CH_3)_2NO_2$), 1.23 (d, 3 H, J = 6 Hz, CH_3). Anal. ($C_{11}H_{20}N_3O_3Cl$) C, H, N, Cl.

2,3-Dimethyl-1-[3′-[*N*-methyl-*N*-[(trifluoromethyl)sulfonyl]amino]-1′-propyl]imidazolium chloride (11d) was prepared in 62% yield from 1,2-dimethylimidazole and 3-[*N*-methyl-*N*-[(trifluoromethyl)sulfonyl]amino]-1-propyl triflate. After Cl anion exchange and recrystallization: mp 164–165 °C; ^{1}H NMR (DMSO-d_6) δ 7.77 and 7.68 (2 d, 1 H each, J = 2 Hz, aryl), 4.27 (t, 2 H, J = 7 Hz, NCH_2), 3.77 (s, 3 H, NCH_3), 3.43 (t, 2 H, J = 7 Hz, CH_2N), 3.05 (br s, 3 H, SO_2NCH_3), 2.60 (s, 3 H, CH_3), 2.05 (m, 2 H, CH_2). Anal. ($C_{10}H_{17}F_3N_3O_2SCl$) C, H, N, S.

In Vivo Pretreatment Evaluation of Compounds against Soman. In vivo pretreatment evaluation of selected compounds was determined in male ICR Swiss mice. A group of 10 mice were each injected im in the right hindlimb with $^1/_{64}$, $^1/_{16}$, or $^1/_4LD_{50}$ of the test drug in aqueous solution. As a base reference, a second group of animals were each given only saline. As a positive control, a third group of animals were each given pyrodistigmine bromide (0.1 mg/kg) in place of the test drug. At 15 or 60 min later, each animal was injected im in the left hindlimb with $2LD_{50}$ of soman. All groups received atropine sulfate (11.2 mg/kg) and 2-PAM chloride (25 mg/kg) in the right hindlimb 10 s after the soman challenge. The animals were then all allocated to pretreatment cells in a randomized block design. At 24 h after the soman challenge, the number of survivors in the test-drug group was compared to that in the base-reference group by using Fisher's exact test ($p < 0.05$, n = 10). With this test, a survival difference of at least four is required to identify improved efficacy. Generally, all animals in the base-reference group expired whereas the positive-control group exhibited six to eight survivors. On occasion, as many as two survivors were noted in the base-reference group and accordingly, these were subtracted from the test-drug groups for which the base reference applied.

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Registry No. **1a**, 129251-10-1; **1b**, 129499-50-9; **1c**, 132567-05-6; **1d**, 132567-06-7; **1e**, 132567-11-4; **1f**, 132567-07-8; **2** (R^1 = H), 10111-08-7; **3a**, 20062-62-8; **3b**, 132567-16-9; **3c**, 132567-17-0; **4a**, 132566-38-2; **4b**, 132566-39-3; **4c**, 132566-40-6; **4d**, 132566-41-7; **4e**, 132566-42-8; **4f**, 132566-43-9; **4g**, 132566-44-0; **4h**, 132566-45-1; **4i**, 132566-46-2; **4j**, 132566-47-3; **4k**, 132566-48-4; **4l**, 132566-49-5; **4m**, 132566-50-8; **4n**, 128605-98-1; **4o**, 132566-51-9; **4p**, 132566-52-0; **4q**, 132566-53-1; **4r**, 132566-54-2; **4s**, 132566-55-3; **4t**, 132566-56-4; **4u**, 132566-57-5; **4v**, 132566-58-6; **4w**, 132566-59-7; **4x**, 132566-60-0; **4y**, 132566-61-1; **4z**, 132566-62-2; **4aa**, 132566-63-3; **4ab**, 132566-64-4; **4ac**, 132566-65-5; **4ad**, 132566-66-6; **4ae**, 132566-67-7; **4af**, 132566-68-8; **4ag**, 132566-69-9; **4ah**, 132566-70-2; **4ai**, 132566-71-3; **4aj**, 132566-72-4; **4ak**, 132566-73-5; **4al**, 132566-74-6; **4am**, 132566-75-7; **4an**, 131206-89-8; **4ao**, 132566-76-8; **4ap**, 132566-77-9; **4aq**, 132566-78-0; **4ar**, 132566-79-1; **4as**, 132566-80-4; **4at**, 132566-81-5; **4au**, 129129-64-2; **4av**, 132566-82-6; **4aw**, 132566-83-7; **4ax**, 132566-84-8; **4ay**, 132566-85-9; **4az**, 132566-86-0; **4ba**, 129499-55-4; **4bb**, 132566-87-1; **4bc**, 132566-88-2; **4bd**, 132566-89-3; **4be**, 132566-90-6; **4bf**, 132566-91-7; **4bg**, 132566-92-8; **4bh**, 132566-93-9; **4bi**, 132566-94-0; **4bj**, 132566-95-1; **4bk**, 132566-96-2; **4bl**, 132566-97-3; **4bm**, 132566-98-4; **4bn**, 132566-99-5; **4bo**, 132567-00-1; **4bp**, 132567-01-2; **4bq**, 132567-02-3; **4br**, 132567-03-4; **4bs**, 132567-04-5; **5**, 81842-71-9; **6**, 132566-37-1; **8**, 112655-19-3; **10a**, 132567-08-9; **10b**, 132567-09-0; **10c**, 132567-10-3; **11a**, 132567-12-5; **11b**, 132567-13-6; **11c**, 132567-14-7; **11d**, 132567-15-8; $HO(CH_2)_3OH$, 504-63-2; 1-ethylimidazole, 7098-07-9; 1-propylimidazole, 35203-44-2; 1-methyl-2-imidazolecarboxamide, 20062-51-5; 1,2-dimethylimidazole, 1739-84-0.

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