increase might correspond to the situation in which the introduction of the substituent allows it to interact maximally with the most suitable group in the receptor without disturbing the binding of the rest of the molecule.

The maximum effects on affinity of changes in the composition of the onium group are shown in Table III, which includes results obtained in earlier work.[1] Although these may be underestimates because only a limited number of compounds have been examined, they are not much bigger, and in some instances apparently smaller, than the variations observed in the values of log SSI (0.9 log units). It seems unlikely, then, that the variation in stereospecificity arises simply because the positive contribution to binding is bigger in one enantiomer than another. It appears likely that the change in composition affects the stereospecificity because it disturbs the binding more in one enantiomer than the other, though there may be differences in the positive contribution as well.

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Linear Free Energy Relationships in the Hydrolysis of Some Inhibitors of Acetylcholinesterase†

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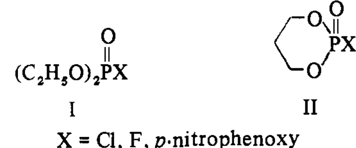
The spontaneous hydrolysis of a series of diethyl phosphates I and 1,3,2-dioxaphosphorinane 2-oxides II has been studied in a number of buffers. The present study shows that the hydroxide ion catalysis of both series I and II obeys a linear Brönsted relationship over a pK_a range extending from $pK_a = 10$ to -7. On the other hand, the data for the water reactions were less conclusive. The possibility that the chloro derivatives hydrolyze *via* an SN1 (phosphorylium ion) mechanism has been excluded. The sharp break in the Brönsted plots for the second-order rate constants in the reactions of series I with eel cholinesterase which was previously reported by us is, therefore, believed to result from a special property of the enzyme reaction. We have rationalized the enzyme reaction in terms of a mechanism involving the formation of two reversible intermediates along the reaction coordinate.

The inhibition of cholinesterase by organophosphates is a nucleophilic substitution reaction in which the enzyme serves as a nucleophile. Recently, we have shown that a plot of the logarithm of the bimolecular rate constant for the inhibition of eel ChE by diethyl phosphates I *vs.* the pK_a of the leaving group has a sharp break in the Brönsted plot.[1] Very limited data for 1,3,2-dioxaphosphorinane 2-oxides II are consistent with a break in the curve which is much less sharp.[2] The observed nonlinearity suggests a change in the rate-determining step of a multistep reaction. However, in



X = Cl, F, *p*-nitrophenoxy

order to determine whether this phenomenon that we observed in the enzymatic reaction with I and II is specific to the enzyme, a kinetic study of the hydrolysis of these inhibitors in the presence of other nucleophiles is required. The data presented here provide some information on the linearity of Brönsted plots for the hydrolysis of compounds I and II (k_{OH^-}, k_{H_2O}), by extending the pK_a range to -7

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by including the chloro derivatives in this investigation.

We also present evidence that the chloro compounds do not hydrolyze to any large extent *via* an SN1 pathway, thus minimizing the possibility that the enzyme is inhibited by

$$(RO)_2\overset{O}{\overset{\|}{P^+}}$$
III

a phosphorylium ion III mechanism, when the chloro compounds are the inhibitors.

Experimental Section

Diethyl phosphorofluoridate was prepared according to Saunders and Stacey.[3] Diethyl phosphorochloridate (Aldrich) was redistilled with a Vigreux head as described previously.[1] Diethyl phosphoro(*p*-nitrophenolate), paraoxon, was prepared according to Fagerlind, *et al.*[4]

2-Chloro-, 2-fluoro-, and 2-*p*-nitrophenoxy-1,3,2-dioxaphosphorinane 2-oxides II were prepared according to Lanham[5] and Fukuto, *et al.*,[6] and described by us in an earlier publication.[2]

Kinetic Studies of the Hydrolysis. The rate of the hydrolysis of the various organophosphates was followed by three different methods according to the nature of the leaving group. Table I gives the exact conditions under which each run was conducted.

A. Chloridates were measured by the spectrophotometric method as described before.[1,2] This method is based on the use of *p*-nitrophenol ($1 \times 10^{-4} M$) as an indicator. Two wavelengths were chosen to follow the acid liberation rate: 400 nm for the disappearance of the *p*-nitrophenolate species and 315 nm for the appearance of the corresponding *p*-nitrophenol. The measured rate constants were the same by both techniques. The method was calibrated with benzoic acid. Two equivalents of acid were produced for each mole of the substrate.

The reaction of the chloridates with NaF was carried out by the same technique. The amount of PF (phosphorofluoridate) formation was calculated by subtracting the amount of acid produced in the presence of NaF from the amount of acid liberated under the same experimental conditions without NaF. The hydrolysis of the corresponding phosphorofluoridate at pH 7.0 has a half life of ≅500 min.

B. Fluoridates. The rates of hydrolyses of diethyl phosphorofluoridate and 2-fluoro-1,3,2-dioxaphosphorinane 2-oxide were determined by measuring the production of fluoride ion potentiometrically, using an Orion Model 94-09A fluoride ion electrode and a Type 1230A DC amplifier and electrometer (General Radio Co.). A standard calomel electrode was employed as the reference. The output from the electrometer was automatically recorded as a function of time using a Heath Model IVA-20-26 multispeed recorder.

Reaction with *p*-Nitrophenol. The second-order rate constants for the reaction of diethyl phosphorofluoridate and 2-fluoro-1,3,2-dioxaphosphorinane 2-oxide with *p*-nitrophenol were determined by measuring the production of fluoride ion at pH 8.15 in 0.10 and 0.025 *M* *p*-nitrophenol buffers. In these runs the substrate concentrations were $0.50-1.2 \times 10^{-3} M$, and the reactions were pseudo first order. Moreover, the observed first-order rate constants showed a linear dependence on *p*-nitrophenol concentration indicating the absence of any higher order terms in the catalysis of these substrates by nitrophenol. The general base and nucleophilic components (k_{GB} and k_N) of catalysis by nitrophenol were dissected from the overall second-order rate constant k_T by measuring the amount of paraoxon and 2-*p*-nitrophenoxy-1,3,2-dioxaphosphorinane 2-oxide produced from the corresponding fluoride during the course of the hydrolysis. This was accomplished by extracting these products from the reaction buffer (50 ml) into ether (in two 50-ml portions) under carefully controlled conditions. Separation of the products from any nitrophenol also taken into the ether was accomplished by back extraction with three 50-ml portions of 0.01 *M* NaOH and water, successively. The ether was then removed *in vacuo*, and the residue taken up in 25 ml of acetonitrile. A 100-μl aliquot was then added to 3 ml of 0.10 *M* NaOH and the change in OD was followed to t_∞. From ΔOD_∞ the amount of paraoxon or *p*-nitrophenoxy-1,3,2-dioxaphosphorinane 2-oxide present in the cuvette was calculated. Comparison of this value with that obtained in which known amounts of the nitrophenol derivatives were added to the appropriate buffer and subjected to the identical extraction procedure allowed the calculation of paraoxon or *p*-nitrophenoxy-1,3,2-dioxaphosphorinane 2-oxide formed. The k_N and k_{GB} values were then calculated as shown in eq 1 and 2.

$$k_T = k_{GB} + k_N \quad (1)$$

$$k_N/k_{GB} = \text{paraoxon/diethylphosphoric acid} \quad (2)$$

With paraoxon the extraction procedure was 90 ± 3% efficient, and the ratio of k_N/k_{GB} was 0.53 ± 0.05 for three determinations. For *p*-nitrophenoxy-1,3,2-dioxaphosphorinane 2-oxide only 16 ± 1% of the originally added amount was isolated; however, the procedure was reproducible giving a k_N/k_{GB} of 0.58 ± 0.08.

C. The rate of hydrolysis of the *p*-nitrophenoxy derivatives was measured at 400 nm based on the appearance of the *p*-nitrophenolate anion. For further experimental details see Table I.

Results and Discussion

The biomolecular rate constants for the hydrolysis of I and II in the presence of various nucleophiles are given in Table I at 25° and 0.10 ionic strength. The rates for OH^- and H_2O were plotted in accordance with the Brönsted equation, $\log k = \beta pK_a + C$. In order to construct a plot for at least five different leaving groups, we have taken known rate constants from the literature and corrected them,

Table I. Second-Order Rate Constants for the Hydrolysis of I and II in the Presence of Various Nucleophiles ($T = 25°$, $\mu = 0.10$)[a]

		I: $(C_2H_5O)_2P(O)X$			II: 1,3,2-dioxaphosphorinane 2-oxide P(O)X		
Nucleophile	pH (buffer)	X = Cl	X = F	X = *p*-NP	X = Cl	X = F	X = *p*-NP
OH^-	13.0 (0.10 NaOH)			0.63			1.5
	10.0 (glycine)		110			100	
	7.0–8.3 (phosphate)[b]	1.4×10^5			2.7×10^4		
H_2O	7.0 (Tris)		7.1×10^{-6}			1.6×10^{-6}	
	7.0–8.3 (phosphate)[b]	1.5×10^{-2}			3.0×10^{-3}		
Tris	7.0		1.1×10^{-2}			2.3×10^{-3}	
Phosphate	7.0		9.1×10^{-2}			2.6×10^{-2}	
Glycine	10.0		3.5×10^{-1}			1.7×10^{-1}	
Carbonate	10.0		6.5×10^{-1}			3.6×10^{-1}	
F^-	8.15 (phosphate)	30[c]		1.0×10^{-1}	12[c]		1.1×10^{-2}
p-Nitrophenol	8.15 (phosphate)		9.2×10^{-1}[d]			2.0×10^{-1}[d]	
			$k_N = 4.9 \times 10^{-1}$[e]			$k_N = 1.1 \times 10^{-1}$[e]	

[a]Rates are given in M^{-1} min^{-1}. For further details see the Experimental Section. Rates are not corrected for the actual concentration of nucleophile (ionized species) but correspond to analytical concentrations at the specified pH. [b]k_{OH^-} and k_{H_2O} were separated by plotting k_{obsd} *vs.* $[OH^-]$. The difference in rates for the reported pH range is about 25–30%. [c]Measured at phosphate $\mu = 0.05$, NaF = 0.025 *M*; adjusted to $\mu = 0.1$ with $NaNO_3$. [d]Based on rate of appearance of fluoride ion. [e]k_N based on rate of appearance of the corresponding *p*-nitrophenoxy derivative (see Experimental Section).

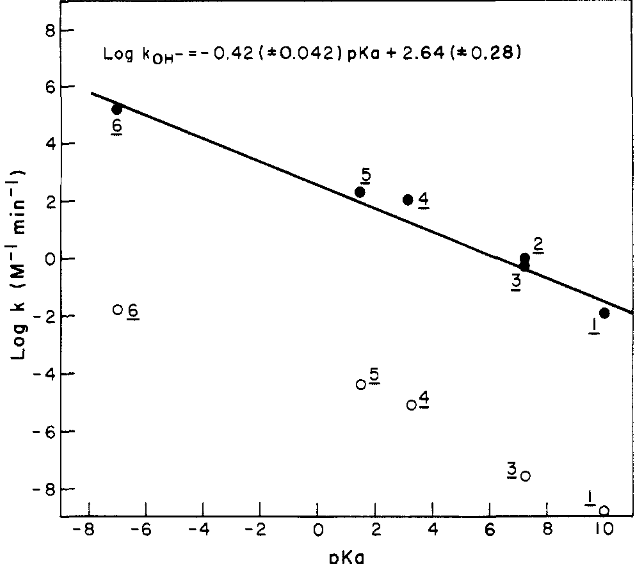

Figure 1. Brönsted plot for the hydrolysis of $(C_2H_5O)_2P(O)X$: open circles, water reaction; filled circles, hydroxide. The numbers refer to various leaving groups (X) as follows: **1**, phenol [J. R. Cox and O. B. Ramsay, *Chem. Rev.*, 64, 317 (1964); W. N. Aldridge and A. N. Davison, *Biochem. J.* **51**, 62 (1952)]; **2**, *p*-nitrophenol; 3, *p*-nitrophenol [H. Coates, *Ann. Appl. Biol.*, 36, 156 (1949)]; **5**, $(C_2H_5O)_2P(O)O^-$ [H. Coates, *ibid.*, 36, 156 (1949)]; 4, F; 6, Cl.

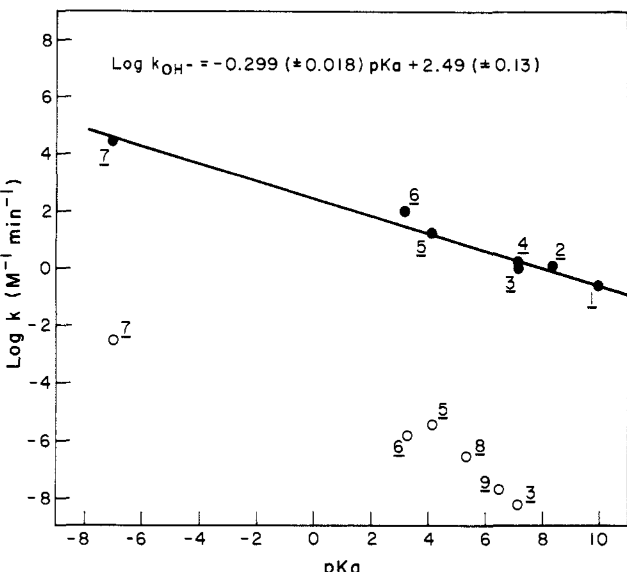

Figure 2. Brönsted plot for the hydrolysis of II: open circles, water; filled circles, hydroxide. The numbers refer to various leaving groups (X) as follows: **1**, phenol;[7] **2**, *m*-nitrophenol;[7] **3**, *p*-nitrophenol;[7] **4**, *p*-nitrophenol; **5**, 2,4-dinitrophenol;[7] **6**, F; 7, Cl.

whenever required, to 25° by using a temperature coefficient of 1.1 per degree. Figures 1 and 2 present the plot of log $k_{(OH^-)}$ and log $k_{(H_2O)}$ *vs.* the pK_a of the leaving group for the I and II series, respectively. These plots demonstrate that when OH^- is the nucleophile, linearity occurs over the entire range of pK_a from 10 to –7. This shows that the Brönsted equation derived by Kahan and Kirby[7] for the attack of OH^- on 2-aryloxy-1,3,2-dioxaphosphorinane 2-oxides can be extended to the pK_a value of –7.0. On the other hand, the data for the water reactions are less conclusive. It is sometimes stated that fluoride is a poor leaving group in P-F compounds but our data suggest that fluoride behaves normally in triesters.

Although it does appear that these Brönsted plots for water, especially for compounds II, may be curved, the curvature is far less sharp than for the reaction of the enzyme with compounds I (Figure 3). The possible curvature in the water reaction does raise the possibility of a pentacovalent intermediate in the hydrolysis of compounds II as favored by Kahan and Kirby.[7] Dostrovsky and Halmann[8] failed to observe ^{18}O exchange during the solvolysis of *O,O*-diethyl phosphorochloridate and suggested that the reaction was a one-stage bimolecular displacement, thus arguing against the rapid reversible formation of an intermediate. However, they pointed out that the negative results obtained with the chloro derivative could not be taken as conclusive, because the lifetime of the intermediate might be too short to result in exchange. Indeed the presumed pentacovalent intermediate would have to undergo a difficult pseudorotation followed by a proton migration in order to obtain oxygen exchange (comment of a reviewer).

The rate constants given for water have been divided by 55.5, *i.e.*, they are formal second-order rate constants. In the case of Tris, phosphate, glycine, and carbonate the second-order constants are given without regard to species of ion and also may be the sum of general base and nucleophilic catalysis or nucleophilic substitution. In the case of *p*-nitrophenol the contributions of general base catalysis and nucleophilic substitution have been separated. At the pH studied, 8.15, almost all (>90%) the *p*-nitrophenol is ionized. The data of Table I enable the calculation of the equilibrium constants for the following reactions.

$$(RO)_2P(=O)F + p\text{-}NO_2C_6H_4O^- \underset{k_{-1}}{\overset{k_N}{\rightleftharpoons}} (RO)_2P(=O)OC_6H_4NO_2 + F^-$$

$K_{eq} = k_N/k_{-1}$ where k_N is the second-order rate constant for the nucleophilic displacement of F^- by *p*-nitrophenol (Table I) and k_{-1} is the rate of the F^- attack on the corresponding *p*-nitrophenoxy derivatives.

K_{eq} I and K_{eq} II were found to be 4.9 and 9.9, respectively, which shows that the ring structure does not introduce any notable distinction in the relative stabilities of the compounds.

In the case of the chloridates, a phosphorylium ion mechanism would seem *a priori* to be a distinct possibility. To test whether such a mechanism (SN1) might be involved in the reaction of the chloridates with nucleophiles (including the enzyme), we studied the rate of reaction of both chloridates (I and II) with NaF. The following schemes (eq 3 and 4) represent the two mechanisms.

$$\text{SN2} \qquad \text{PCl} \xrightarrow{k_{H_2O}} \text{POH}; \quad \text{PCl} \xrightarrow{k_{F^-}} \text{PF} \tag{3}$$

$$\text{SN1} \qquad \text{PCl} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{P}^+ + \text{Cl}^-; \quad \text{P}^+ \rightarrow \text{PF}, \text{POH} \tag{4}$$

Since the phosphorofluoridate (PF) is relatively stable under these conditions, less acid is produced in accordance with the amount of PF that is formed. Thus, we could measure how much phosphorofluoridate was formed and, therefore, evaluate k_{F^-}. In an SN1 mechanism, the rate of disappearance of PCl will not increase even though considerable PF might be formed because the ionization is the slow step. On the other hand, in an SN2 mechanism the rate of disappearance of PCl should increase in the presence of fluoride in accordance with a pseudo-first-order rate constant given by

$$k = k_{H_2O}[H_2O] + k_{F^-}[F^-] = k_{H_2O}[H_2O][1 + k_{F^-}[F^-]/k_{H_2O}[H_2O]]$$

The rates of solvolysis of the chloridates did in fact increase in the presence of fluoride and by the factor expected from the decrease in acid produced. Thus, our results are quantitatively in accord with an SN2 mechanism (Table II). An attempt to find evidence for an SN1 hydrolytic pathway failed in that substitution of Cl^- for NO_3^- did not decrease the rate. A rate decrease would be expected if free ions are formed, as might be expected in water. Thus, we conclude that the formation of a phosphorylium ion does not contribute appreciably to the nucleophilic reactions of these compounds. These results are in agreement with those of Dostrovsky and Halmann.[9] Also, attempts to find evidence for an SN1 pathway in the inhibition of the enzyme by the chloridates I and II failed in that the rates of inhibition were unaffected by replacing 0.5 M Cl^- in the medium with 0.5 M NO_3^-.[1,2]

We found that the inhibition of eel cholinesterase by I and II (including the chloridates) is first order with respect to the inhibitor as well as the enzyme (second-order reaction).[1,2] We can rationalize the break in the Brönsted plot for the inhibition of the enzyme (Figure 3) on the basis of the following two-step reaction sequence (eq 5) if we assume that k_1

$$(C_2H_5O)_2P(O)X + E: \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (C_2H_5O)_2P(O^-)(X)E \xrightarrow{k_2} (C_2H_5O)_2P(O)E + X^- \quad (5)$$

is relatively independent of the pK_a of HX. With the poorer leaving groups, $k_{-1} > k_2$ and the rate constant is approximated by $(k_1/k_{-1})k_2$. Assuming k_1 is relatively independent of the pK_a of HX, it is reasonable to assume that k_2 depends strongly upon the pK_a of the leaving group, and the value of k_{-1} would decrease with increasing electron-withdrawing ability of X.‡ Thus, the rate with relatively poor leaving groups would increase rapidly as the leaving group becomes better. With good leaving groups, $k_2 > k_{-1}$ and the rate constant is approximated by k_1, which we have already assumed is relatively independent of the pK_a of HX. A similar argument might apply to water as nucleophile. However, when OH^- is the nucleophile, k_{-1} is always less than k_2.

Although it is difficult to see why k_1 should be independent of X, since better leaving groups, *i.e.*, those that are more electronegative, would be expected to increase k_1, and in fact the hydroxide ion reaction with the phosphate substrates (I and II) is dependent on the pK_a of the leaving group, one can suggest a reason. The reason is that the enzyme is an extremely good nucleophile in these reactions—one hundred times better than hydroxide ion. In this case k_1 might depend very little upon X.[7] In this illustrative rationalization we have used X^- as the leaving group but a similar rationalization could be made with HX as the leaving group; in this latter case the descending limb of the curve would correspond to k_1 and the horizontal portion to k_1k_2/k_{-1}. The latter part of the curve might be horizontal because as k_1 increases k_2 decreases. However, HX is a less probable leaving group than X^- in these reactions because when HX is a leaving group, as in the acid-catalyzed hydrolysis of phosphate esters, the dependence upon pK_a is small.

Thus, it is difficult to say anything about the details of

‡The value of k_{-1} is either relatively independent of X or decreases as X becomes more electron withdrawing.

Table II. Rates Ratio and Products Ratio[a] for the Reaction of NaF and H_2O with Diethyl Phosphorochloridate and 2-Chloro-1,3,2-dioxaphosphorinane 2-Oxide[b]

Compound	$k_{F^-}(F^-)/k_{H_2O}(H_2O)$[c]	(P – F)/(P – OH)[d]
$ClP(O)(OC_2H_5)_2$	0.71 ± 0.05 (7)[e]	0.64 ± 0.02 (7)
$ClP(O)(OCH_2CH_2CH_2O)$	1.9 ± 0.14 (5)	2.0 ± 0.10 (5)

[a]For an explanation see Results. [b]Phosphate μ = 0.05, NaF, 0.025, $NaNO_3$, 0.025, pH 7.0, T = 25°. [c]From the increase in rate of solvolysis. [d]From the decrease in acid produced. [e]Number in parentheses denotes number of runs.

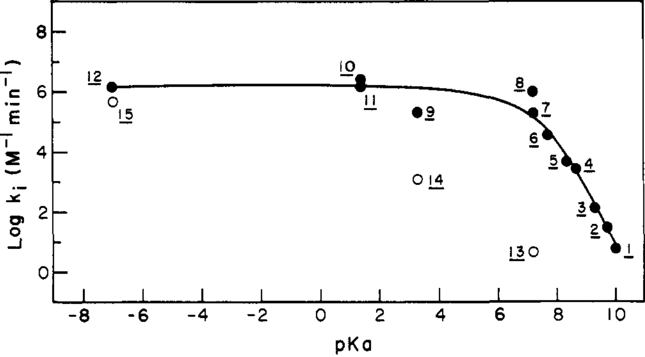

Figure 3. Brönsted plot for the inhibition of eel ChE[2] at pH 7.0, 25°, and μ = 0.1. The solid line represents the diethyl phosphates series whereas the open circles stand for the 1,3,2-dioxaphosphorinane 2-oxides. The numbers refer to various leaving groups: **1**, phenol; **2**, 8-hydroxyquinoline; **3**, *p*-chlorophenol; **4**, 6-hydroxyquinoline; **5**, *m*-nitrophenol; 6, 3-hydroxyquinoline; **7** and **8**, *p*-nitrophenol; **9**, fluoride; **10** and **11**, diethyl phosphate; **12**, chloride. The data for **1**, **3**, **5**, **8**, and **10** are from W. N. Aldridge and A. N. Davison, *Biochem. J.*, **51**, 62 (1952). **2**, **4**, **6**, **7**, and **11** were taken from ref 2 and **12–15** from ref 1 and 2.

the reaction other than that an addition elimination mechanism is supported by these results. The details are hidden in the symbol E.

It is also possible to rationalize these results in terms that are more peculiar to the enzyme. For example, a scheme such as that shown in eq 6 involving reversible enzyme complexes and a slow conformational change before the phosphorylation step could account for the shape of the Brönsted-type plot. The solution for this scheme is given in eq 7.

$$E + I \underset{K_I}{\rightleftharpoons} E{\cdot}I \underset{k_{-c}}{\overset{k_c\ (\text{slow})}{\rightleftharpoons}} E^*{\cdot}I \xrightarrow{k_2} E' \quad (6)$$

$$\frac{d(E^0 - E')}{dt} = \frac{(E^0 - E')}{1 + K_I/I}\,\frac{k_c}{1 + k_{-c}/k_2} \quad (7)$$

The rate becomes second order when $(I) \ll K_I$ and the rate constant becomes

$$k = \frac{k_c}{K_I\left(1 + \frac{k_{-c}}{k_2}\right)} \quad \begin{cases} k_2 > k_{-c} \rightarrow \sim k_c/K_I \\ k_2 < k_{-c} \rightarrow \sim k_ck_2/K_Ik_{-c} \end{cases}$$

If now we assume that the interaction of the inhibitor with enzyme in the reversible complexes has very little to do with X (at least for those compounds where the rate has

leveled off) but involves the other features of the molecule, then K_I, k_c, and k_{-c} will be independent of X. On the other hand, k_2 will be highly dependent upon X and this dependence will only show up when $k_2 \lesssim k_{-c}$. This scheme also might involve a pentacovalent intermediate.

Although this kind of explanation is *ad hoc*, it should be noted that reversible complexes and substrate-induced conformational changes have played a dominant role in enzyme theory for many years.[10,11]

In a previous study,[12] it was found that the curvature that sets in sharply at pK_a = 7.0 did not occur when the leaving group contained a quaternary ammonium function so that these compounds were decidedly more reactive than would be anticipated from the pK_a of their leaving groups. The rationalization offered above would suggest that the conformational change occurs more rapidly when the inducing compound contains a cationic amine function. There is spectral evidence that quaternary amines change the conformation of acetylcholinesterase.[13]

We note that with few exceptions the ring compounds react less rapidly than the open-chain analogs but the distinction is not great enough to account for the poor inhibitory properties of the fluoride and *p*-nitrophenolate in the ring series.

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Synthesis of Some N-Substituted Eleostearic Acid Hydrazides as Potential Monoamine Oxidase Inhibitors†

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The syntheses of five N-substituted eleostearic acid hydrazides are described: *N*-isopropyl-α-eleostearoyl hydrazide, *N*-benzyl-α-eleostearoyl hydrazide, *N*-phenethyl-β-eleostearoyl hydrazide, *N*-α-methylphenethyl-β-eleostearoyl hydrazide, and *N*-β-methylphenethyl-α-eleostearoyl hydrazide. The compounds were investigated for their ability to inhibit monoamine oxidase *in vitro* and to elevate the brain monoamines in mice. The results showed that these compounds were active monoamine oxidase inhibitors with their slightly lower *in vitro* activity but comparable *in vivo* activity in comparison with the corresponding monosubstituted hydrazines.

The monosubstituted hydrazines such as alkyl- and aralkylhydrazines have provided many potent monoamine oxidase (MAO) inhibitors from which phenelzine has emerged as a clinically used antidepressant.[1] Pheniprazine, benzylhydrazine, and isopropylhydrazine are among the most potent MAO inhibitors but are barred from clinical use because of high toxicity.[2-4] Acylation of benzylhydrazine with 5-methyl-3-isoxazolylcarboxylic acid has produced another currently used hydrazine antidepressant, isocarboxazide, with MAO inhibitory activity but reduced toxicity.[5] Iproniazide, the isonicotinic acid acylated isopropylhydrazine, the first MAO inhibitor antidepressant,[6] also possesses an activity comparable to isopropylhydrazine with less toxicity. The present work was to synthesize some N-substituted hydrazides by acylating some of the most potent monosubstituted hydrazines with α-eleostearic acid (9-*cis*-11-*trans*-13-*trans*-octadecatrienoic acid) and β-eleostearic acid (9-*trans*-11-*trans*-13-*trans*-octadecatrienoic acid) and to investigate their MAO inhibitory activity *in vitro* and *in vivo*.

Scheme I

$$\begin{array}{l} CH_2OOCR \\ | \\ CHOOCR \\ | \\ CH_2OOCR \\ \text{I} \end{array} \xrightarrow[\text{ethanol}]{\text{KOH}} \underset{\text{II}}{RCOOH} \xrightarrow[H_2SO_4]{\text{ethanol}}$$

$$\underset{\text{III}}{RCOOCH_2CH_3} \xrightarrow{N_2H_4H_2O} \underset{\text{IV}}{RCONHNH_2} \xrightarrow[\text{or ketones}]{\text{aldehydes}}$$

$$\underset{\text{V}}{RCONHN{=}CHR'} \xrightarrow{LiAlH_4} \underset{\text{VI}}{RCONHNHCH_2R'}$$

R, $CH_3(CH_2)_3(CH{=}CH)_3(CH_2)_7$
R′, alkyl or aralkyl
I, α- or β-eleostearic acid glyceride in tung oil
II, α- or β-eleostearic acid
III, α- or β-ethyl eleostearate
IV, α- or β-eleostearic acid hydrazides
V, acylhydrazones
VI, N-substituted eleostearoyl hydrazides

Chemistry. The type of reaction series chosen for the synthesis of N-substituted hydrazides is summarized as shown in Scheme I.

α- and β-eleostearic acids II were isolated from the domestic tung oil I from kernels of *Aleurites fordii* by the method

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