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In our search for novel acetylcholinesterase reactivators, we have synthesized a number of 8-azabicyclo[3.2.1]-oximes, 1-phenyl-3-aminopropane oximes, phenylpiperidino oximes and simple pyridinium oximes. Particularly interesting are a-hydroxy oximes, for which a new synthetic method was developed. Our design concept for reactivator molecules focuses on naturally cholinergic molecules which have a binding affinity for the catalytic site on the enzyme. Incorporation of an oximino group in a molecule with an inherent affinity for the active site should lead to effective reactivation. This has been demonstrated for tropyl (8-azabicyclo[3.2.1]) systems. An X ray structure determination on a member of this class, namely, 2a-hydroxy-3-tropanone oxime methiodide (1), has been carried out.

Two sensitive assay procedures have been devised and used in our work for following the reactivation of acetylcholinesterase that has been inhibited by diisopropylfluoro-phosphonate (DFP).

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Bridged Bicyclic Oximes as Acetylcholinesterase Reactivators

Annual and Final Report

Robert M. Moriarty

April 3, 1988

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Table of Contents

Figures

Tables

1. Summary

In our search for novel acetylcholinesterase reactivators, we have synthesized a number of 8-azabicyclo[3.2.1]-oximes, 1-phenyl-3-aminopropane oximes, phenylpiperidino oximes and simple pyridinium oximes. Particularly interesting are α-hydroxy oximes, for which a new synthetic method was developed. Our design concept for reactivator molecules focuses on naturally cholinergic molecules which have a binding affinity for the catalytic site on the enzyme. Incorporation of an oximino group in a molecule with an inherent affinity for the active site should lead to effective reactivation. This has been demonstrated for tropyl (8-azabicyclo[3.2.1]) systems. An X-ray structure determination on a member of this class, namely, 2α-hydroxy-3-tropanone oxime methiodide (1), has been carried out.

Two sensitive assay procedures have been devised and used in our work for following the reactivation of acetylcholinesterase that has been inhibited by diisopropylfluorophosphonate (DFP).

2. Foreword

Acknowledgements

The author thanks Thomas Dougherty, Ph.D., for kinetic measurements, Om Prakash, Ph.D., Pauline Karalis and Cyriac Thachet for synthetic work, V. K. Goswami for chromatographic work, and W. A. Freeman for X-ray crystallographic determinations.

This work was supported by the U.S. Army Medical Research and Development under contract NO. DAMD17-83-C-3107

3. Background

This Annual and Fnal report covers the successful reduction to practice of our basic design concept for acetylcholinesterase reactivators. In our original proposal we presented the hypothesis that molecules which structurally resembled acetylcholine and possessed a nucleophilic oximino group could serve as optimal acetylcholinesterase reactivators. Reactivation refers to the reversal of phosphonylation from the active hydroxyl group on the enzyme. We require the following structural features:

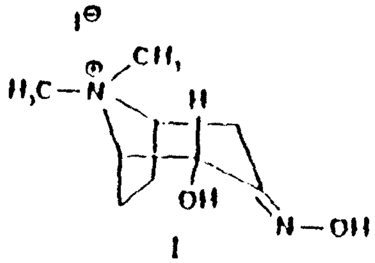
a. A rigid-bridged bicyclic molecule such as 8-azabicyclo[3.2.1]heptane as present in tropane systems.

b. A center of high π-electron density as embodied by the 1-phenyl-3-aminopropane system (suitably substituted)

c. A conformationally hindered oximino ammonium system as exemplified by the phenylpiperdino system

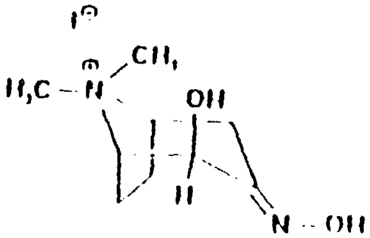
d. The presence of a secondary hydroxyl grouping α to the oximino group in the above structures.

The following structural types fulfill the criteria, and 1, 3, 4, and 5 have been synthesized successfully:



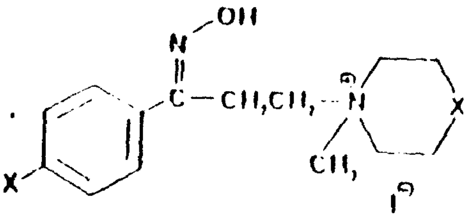
I

2α-Hydroxy-3-tropanone oxime methiodide



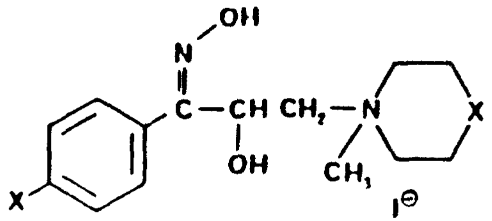
II

2β-Hydroxy-3-tropanone oxime methiodide



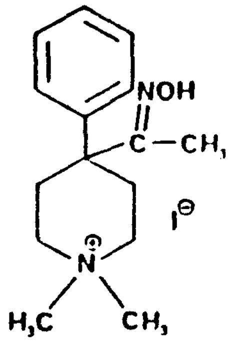
III

Propanone-[1-phenyl-3-amino]oxime methiodide analogs



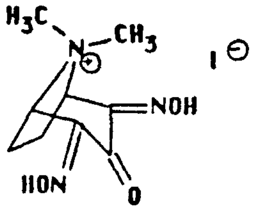
IV

Propanone-[1-phenyl-2-hydroxy-3-amino]oxime methiodide analogs



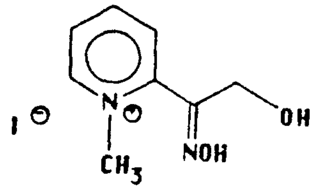
V

4-Acetyl-4-phenylpiperidine methiodide oxime



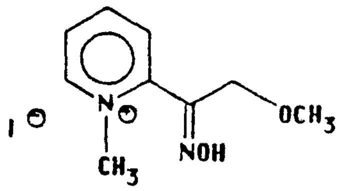
VI

2,4-Bisoximino-tropan-3-one methiodide



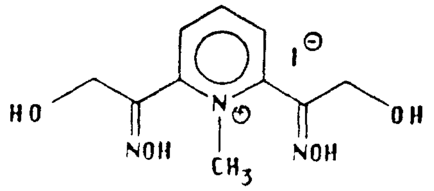
VII

2-(Hydroxymethylcarbonyl) pyridine oxime methiodide and 3-(Hydroxymethylcarbonyl) pyridine methiodide



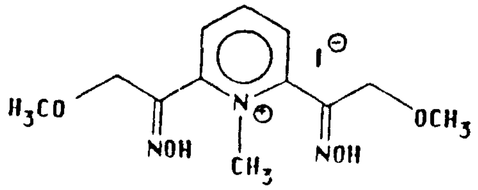
VIII

2-(Methoxymethylcarbonyl) pyridine oxime methiodide



IX

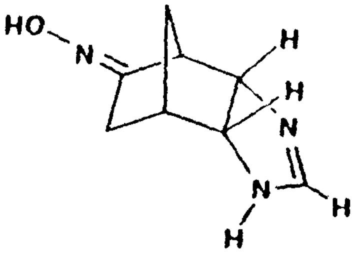
2,6-Bis(Hydroxymethylcarbonyl) pyridine oxime methiodide



X

2,6-Bis(Methoxymethylcarbonyl) pyridine oxime methiodide

The following system was proposed originally and the synthetic approach is being standardized:



XI

Bicycloheptyl dihydroimidazolino system

4. Major Accomplishments During the Two Years

a. 2α-Hydroxy-3-tropanone has been synthesized. This compound has been converted to its oxime methiodide and its structure has been determined by X-ray crystallography.

b. A series of propanone-[1-phenyl-3-amino] oxime methiodides have been synthesized.

c. The above propanone-[1-phenyl-3-amino] derivatives have been oxidized using $C_6H_5I(OAc)_2/CH_3OH/KOH$ to the corresponding propanone-[1-phenyl-2-hydroxy-3-amino] dimethylacetal analogs.

d. In certain cases the above propanone-[1-phenyl-2-hydroxy-3-amino] dimethylacetals were hydrolyzed, converted to the corresponding α-hydroxy oximes and then converted to the methiodide derivatives.

e. 2,4-Bisoximino tropane-3-one has been synthesized. This compound has been converted to its methiodide.

f. Synthesis of α-hydroxyketones, α-methoxy ketones has been achieved using hypervalent iodine oxidation of trimethyl silyl enol ethers of ketones. Thus the synthesis of reactivation was achieved.
    (a) 2-Hydroxymethylcarbonylpyridine oxime methiodide.
    (b) 2,6-Bis(hydroxymethylcarbonyl) pyridine oxime methiodide.
    (c) 2-Methoxymethylcarbonyl pyridine oxime methiodide.
    (d) 2,6-Bis(methoxymethylcarbonyl) pyridine oxime methiodide.

g. A new synthesis of 1,4-diarylbutane-1,4-diones has been developed using hypervalent iodine oxidation for the synthesis of bisoximes.

h. A kinetic procedure has been developed for determining the rates of reactivation of phosphonylated acetylcholinesterase.

i. The percentage reactivation by 20 oxime derivatives synthesized has been determined

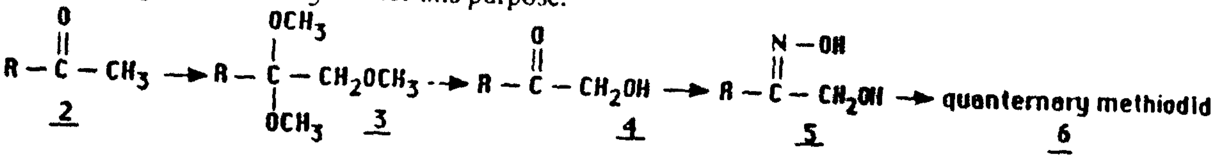
j. The pK$_a$ and binding constants of the structurally related pair of compounds have been determined and compared.

k. Fifteen compounds were submitted to WRAIR for further pharmacological evaluation

l. The fundamental hypothesis of our project, namely, that rigid, bridged bicyclic, ammonium oximes would be effective acetylcholinesterase reactivators, has been substantiated in the case of the 8-azabicyclo[3.2.1] system.

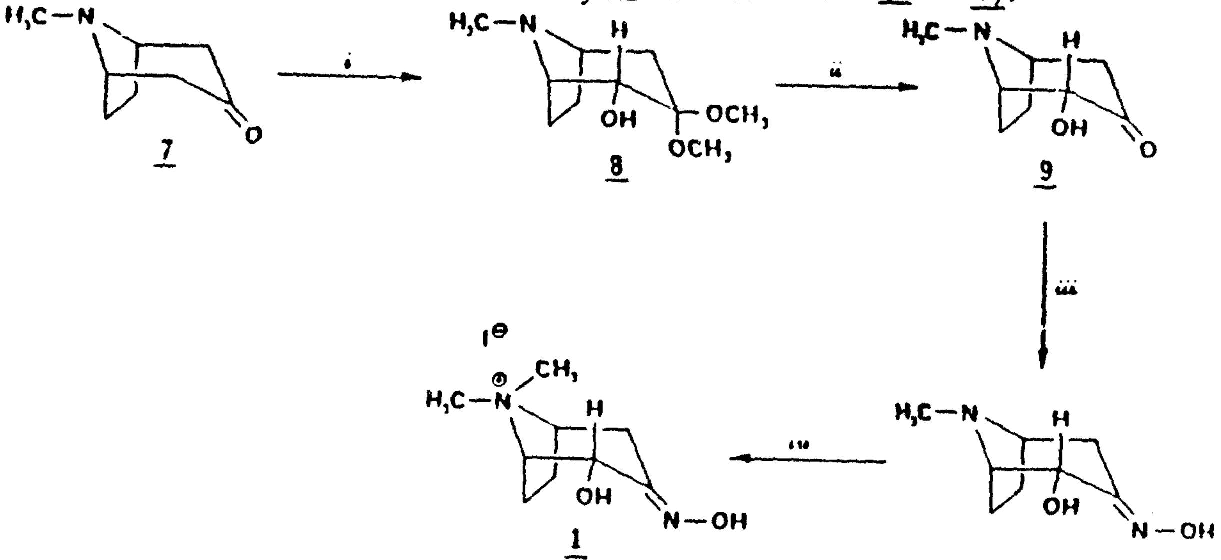
5. Discussion of Syntheses

At the outset of this research a synthetically useful method for the α-hydroxylation of ketones containing amino functionality was not available. Accordingly, we developed the use of $C_6H_5IO/KOH/CH_3OH$ for this purpose.



$$R-\overset{O}{\overset{\|}{C}}-CH_3 \rightarrow R-\underset{OCH_3}{\overset{OCH_3}{C}}-CH_2OCH_3 \dashrightarrow R-\overset{O}{\overset{\|}{C}}-CH_2OH \rightarrow R-\overset{N-OH}{\overset{\|}{C}}-CH_2OH \rightarrow \text{quanternary methiodid}$$

This method was particularly useful in the case of tropanone (7). We were able to carry out the following reaction sequence in excellent yield (7 → 8 → 9 → 10 → 1):



10a = HCl salt

10 = free base

i = $C_6H_5I\text{-}(OAc)_2$, KOH-MeOH, overnight
ii = 3N HCl; 1 hour
iii = NH_2OH HCl, $NaHCO_3$
iv = MeI

A determination of the X-ray crystallographic structure of 1 was undertaken for two reasons. The first was as a structural proof and the second was to obtain molecular parameters for development of structure versus reactivity relationships. The X-ray structure is presented in Fig. 1.

2α-Hydroxy-3-tropanone (9) was described in the literature but the melting point (m.p.) of our material, 65-66°C, was quite different from the reported m.p., 101-103°C.[1] Since we have an X-ray determination, the reported value must be in error. We have done control experiments to show that no inversion of configuration occurs in the sequence 8 → 9 → 10 → 1. A reasonable assumption is that the reported material possesses the epimeric β- and axial configuration at C(2), and is, in fact, 2β-hydroxy-3-tropanone (11):

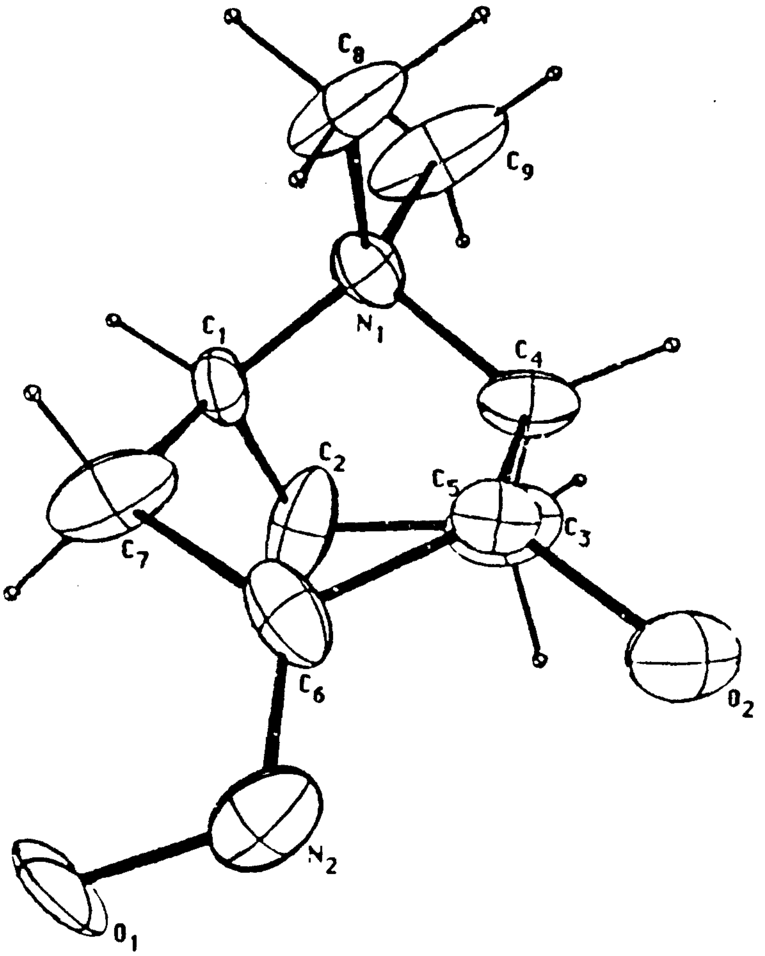
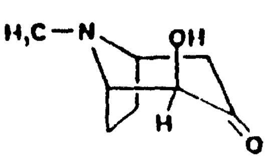


Figure 1. X-ray Structure of 2α-Hydroxy-3-tropanone Oxime Methiodide (1).



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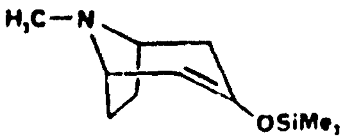
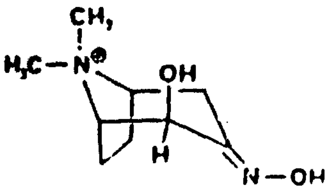
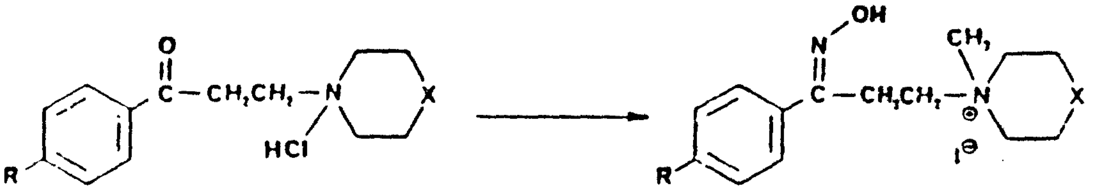


12



We have attempted to synthesize 11 by acid-catalyzed treatment of 8 and 9 but we observed no change in configuration. Tropanone enol silyl ether (12) was synthesized and treatment with OsO$_4$/N-methylmorpholine oxide, OsO$_4$/pyridine, or m-chloroperbenzoic acid did not yield an α-hydroxylated product. Yet to be tried is oxygenation of tropanone lithium enolate and reduction $[(CH_3O)_3PO]$. Failure to yield any α-hydroxylated product, either α or β, in any of these α-hydroxylation procedure. Obtaining authentic 2β-hydroxy-3-tropanone oxime methiodide is important for our studies of reactivation as a comparison with the 2α-analog, namely, 2α-hydroxy-3-tropanone oxime methiodide (1).

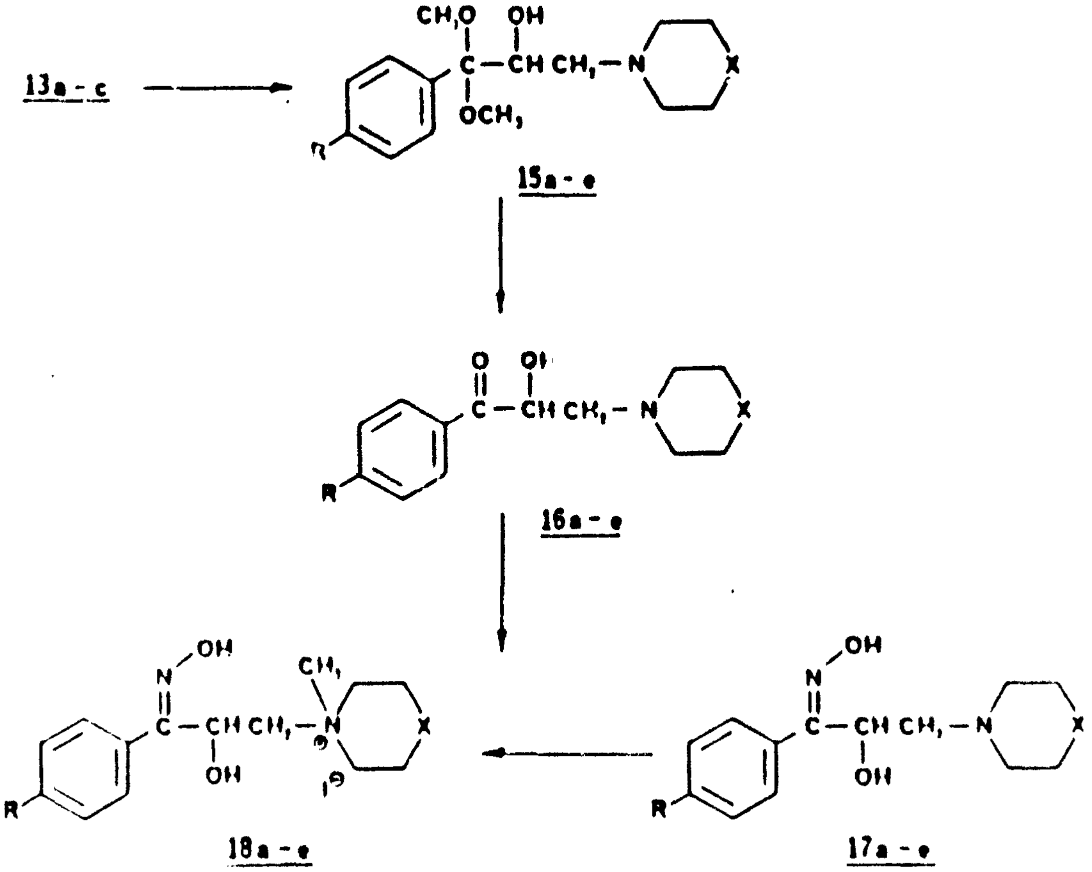
The next series of compounds synthesized were Mannich base derivatives (13a-e) and the derived oximino methiodides (14a-e) via the reaction:



13a; X = CH_2
13b; X = O
13c; X = S
13d; X' = pyrrolidino
13e; X = CH_2; R = OCH_3

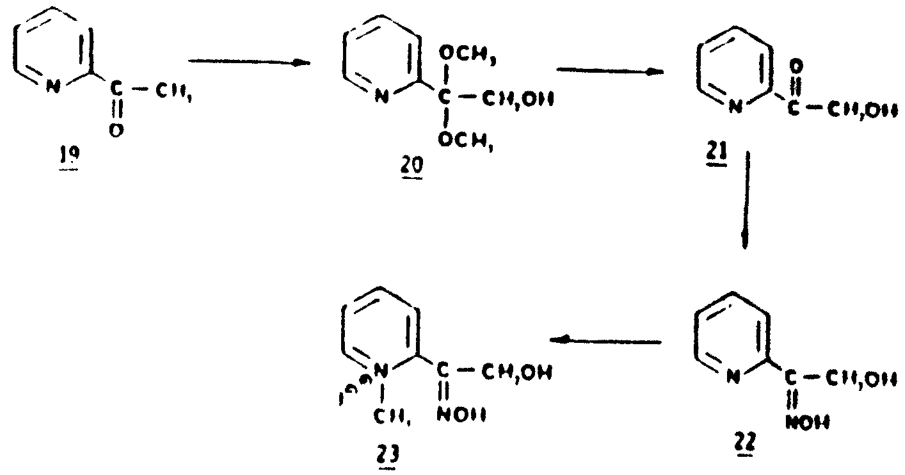
14a; X = CH_2
14b; X = O
14c; X = S
14d; X' = pyrrolidino
14e; X = CH_2; R = OCH_3

Next the Mannich bases, 13a-e, were subjected to the hypervalent iodine oxidative procedure to obtain the α-hydroxydimethylacetal, 15a-e:



Hydrolysis of the dimethylacetal, oximination, quaternization is being actively pursued.

The next series of compounds synthesized are essentially acetyl pyridine derivatives: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22
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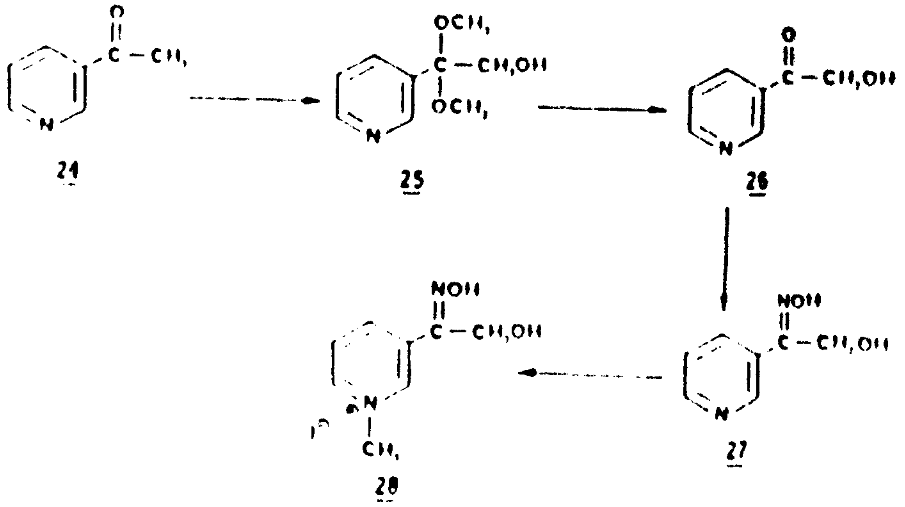
CH2OH
NOH
CH3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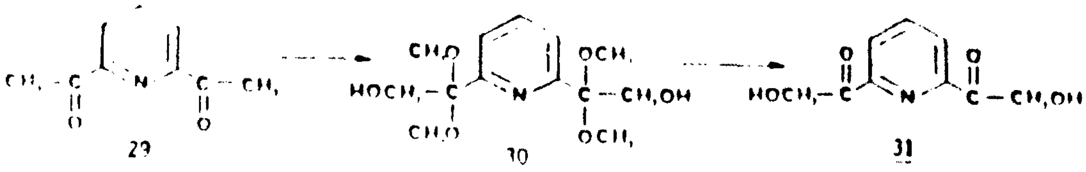
CH2OH
NOH
CH3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31
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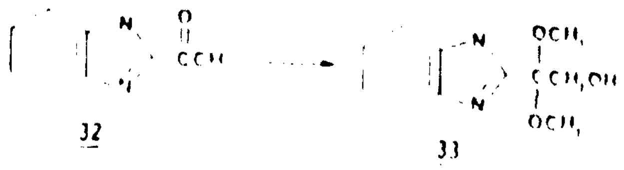
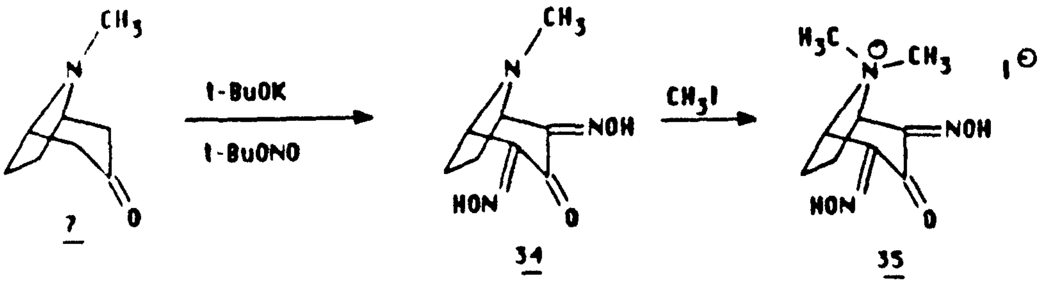
HOCH2
CH2OH


32
33
OCH3
CH2OH

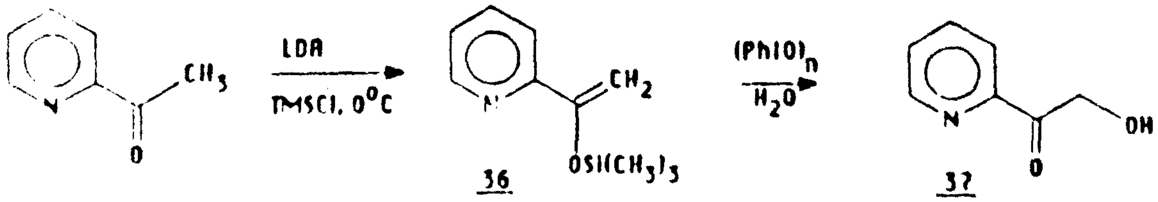
In order to increase the ability of tropane alkaloids to reactive the enzyme by increasing the stability of the oximate anion incorporated with this basic system, we synthesized 2,4-bis oximino-torpan-3-one methiodide (35). Reaction of 3-tropanone with

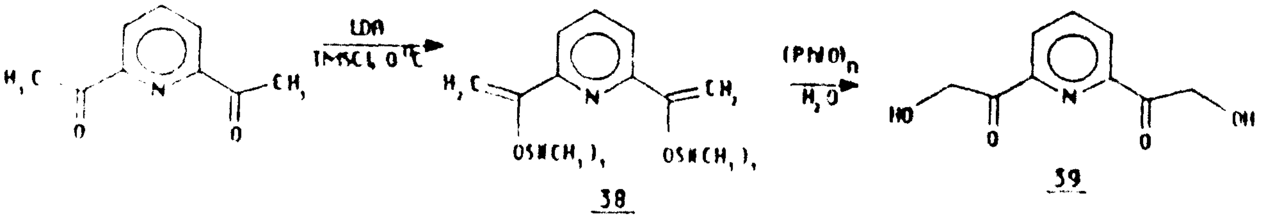


t-butylnitrite and potassium t-butoxide yielded 2,4-bisoximinotropane-3-one (34). 34 on quarternization with methyliodide give 2,4-bisoximinotropane-3-one methiodide in good yields.

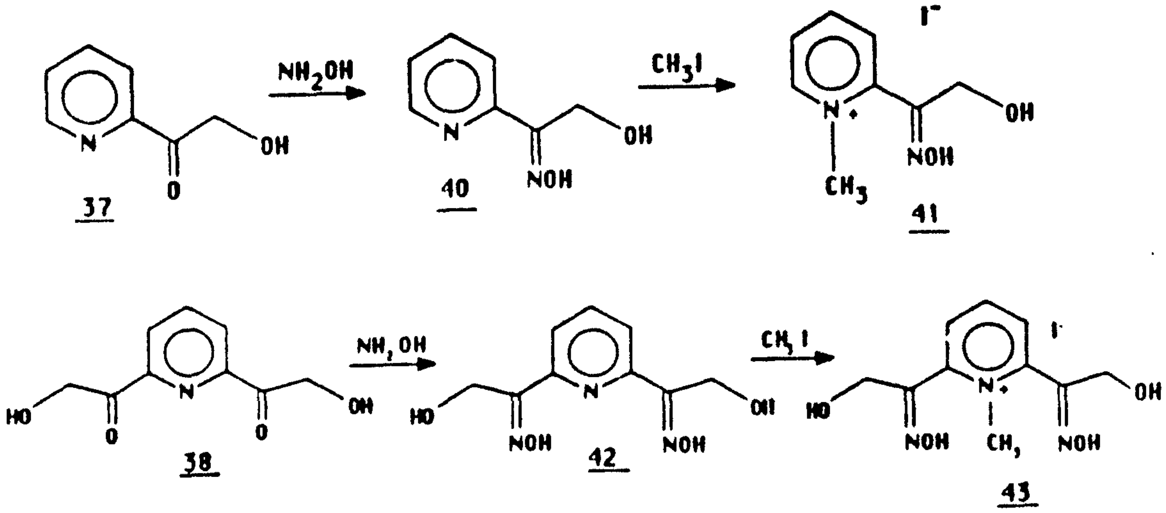
Furthermore, in order to increase the stability of the oximate anion, we synthesized oximes containing α--hydroxy or α-methoxy groups.

(a) This approach includes the treatment of trimethylsilyl enol ethers (36 and 38) of ketones with iodosobenzene in H_2O. Thus treatment of 36 and 38 with iodosobenzene in water at room temperature yielded the α-hydroxy ketones (37) and (39) e.g.:

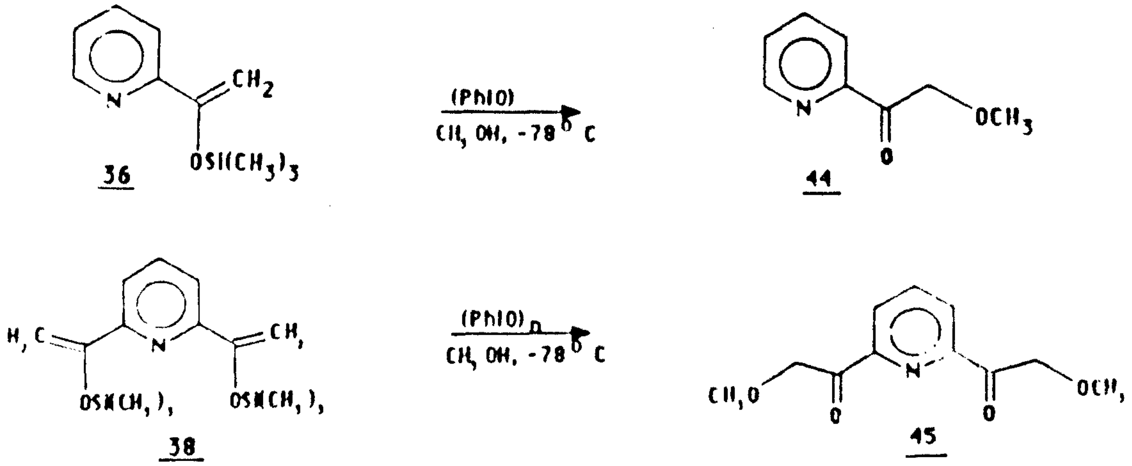




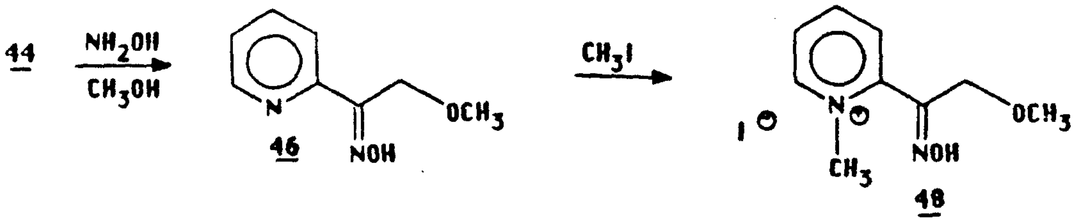
Thus 2-hydroxymethylcarbonyl pyridine (37) and 2,6-bis(hydroxymethylcarbonyl) pyridine (39) so obtained were oximated to corresponding oximes 40 and 42 respectively. Quaternization of 40 and 42 with methyl iodide in dichloromethane or ether yielded 2-hydroxymethylcarbonyl pyridine oxime methiodide (41) and 2,6-bis(hydroxymethylcarbonyl) pyridine oxime methiodide (43) respectively.

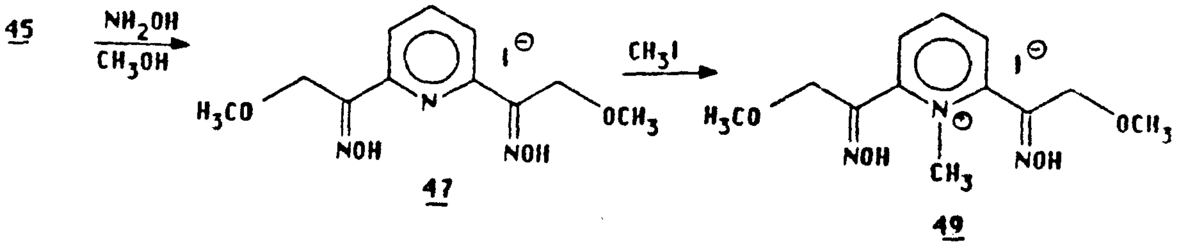


(b) The α-methoxy ketones (44 and 45) respectively were synthesized by the reaction of trimethylsilyl enol ethers (36 and 38) of ketones with iodosobenzene-$BF_3.Et_2O$ in methanol at -78°C.

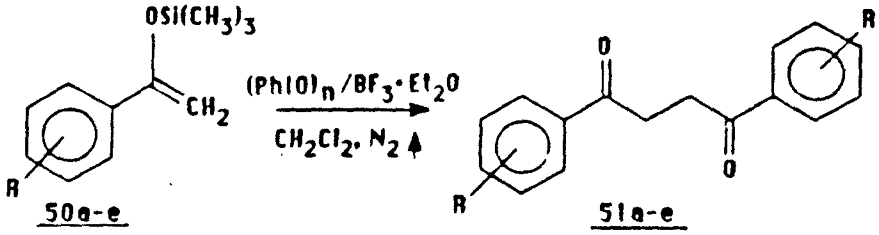


Ketones 44 and 45 were oximated with NH_2OH to 46 and 47 respectively. Quaternization of 46 and 47 with CH_3I in THF or ether resulted in the formation of corresponding methiodides (48 and 49) respectively.



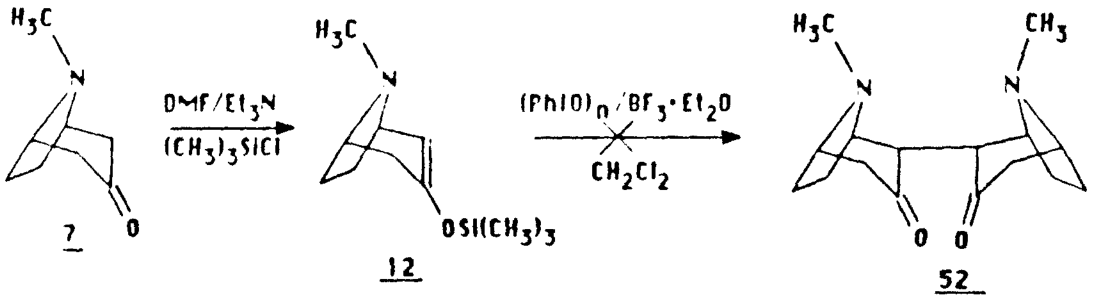


Finally we have developed a synthesis for diaryl 1,4-diketones (51). This synthesis involves the coupling of trimethyl silyl enol ethers (50) of ketones with iodosobenzene in dry dichloromethane under nitrogen.



R = H, OCH_3, Cl, F, CH_3

However the coupling of trimethyl silyl enol ether (18) derived from tropan-3-one 7 under the presently developed carbon-carbon coupling conditions was unsuccessful.



6. Kinetic Studies

Two very sensitive assay procedures have been used in our laboratory for monitoring the activity of acetylcholinesterase. The first assay, with acetylcholine as substrate, is based on coupling away the choline produced from the esterase reaction with choline kinase, which catalyzes the transfer of the γ-phosphate from ATP to choline, producing ADP, and then removed with the pyruvate kinase-lactate dehydrogenase couple, and disappearance of absorbance is monitored at 340 nm.[6]

The second assay procedure uses acetylthiocholine as an alternate substrate for acetylcholinesterase, and involves a chemical reaction between the thiocholine produced from the esterase reaction with dithiobisnitrobenzoate. The product anion of 5-thio-2-nitrobenzoic acid absorbs strongly at 412 nm.

Choline kinase and acetylcholinesterase were purchased from Sigma as the lyophilized powders. Each enzyme was dissolved in enough phosphate buffer, pH 8.0, to make a solution of 5 units/ml for choline kinase and 50 units/ml for acetylcholinesterase. Pyruvate kinase and lactate dehydrogenase were purchased from Boehringer as the glycerol suspensions and were used without further modifications. The potassium salts of phospoenolpyruvate (PEP) and NADH were from Sigma; the sodium salt of ATP was from Boehringer; and acetylthiocholine iodide and dithiobisnitrobenzoic acid were from Aldrich. All other reagents were of the highest quality commercially available.

For the first assay procedure, each cuvette contained 100 mM phosphate buffer pH 8.0 (pH adjusted with KOH), 100 mM KCl, 5 mM $MgCl_2$, 1.0 mM ATP, 1.0 mM PEP, 0.2 mM NADH, 0.1 mM acetylcholine, 5 µl each of the stock solutions of pyruvate kinase and lactate dehydrogenase, 100 µl of choline kinase, and various amounts of acetylcholinesterase and water to yield a total volume of 3.0 ml. For the second assay procedure, each cuvette contained 100 mM phosphate buffer pH 8.0, 0.5 mM acetylthiocholine, 0.5 mM dithiobisnitrobenzoic acid, and various amounts of acetylcholinesterase and water to yield a total volume of 3.0 ml.

Initial velocity studies were run on a Cary 17 spectrophotometer at ambient temperature with a full scale sensitivity of 0.05. For the first assay procedure, the initial velocities were expressed as the µmoles/l of NADH disappearing per minute and were plotted versus the concentration of acetylcholinesterase used. For the second assay procedure, the initial velocities were expressed as the µmoles/l of 5-thio-2-nitrobenzoic acid (TNB) produced per minute and were plotted versus the concentration of acetylcholinesterase used (Fig. 2). It should be noted that a background rate was observed in all cases with both assay procedures. The background rates were subtracted from the acetylcholinesterase rates, however, so the initial velocities reported are the net rates.

Lines A and B demonstrate that both assay procedures are valid for monitoring the activity of acetylcholinesterase, since the measured rate is directly proportional to the concentration of acetylcholinesterase used.

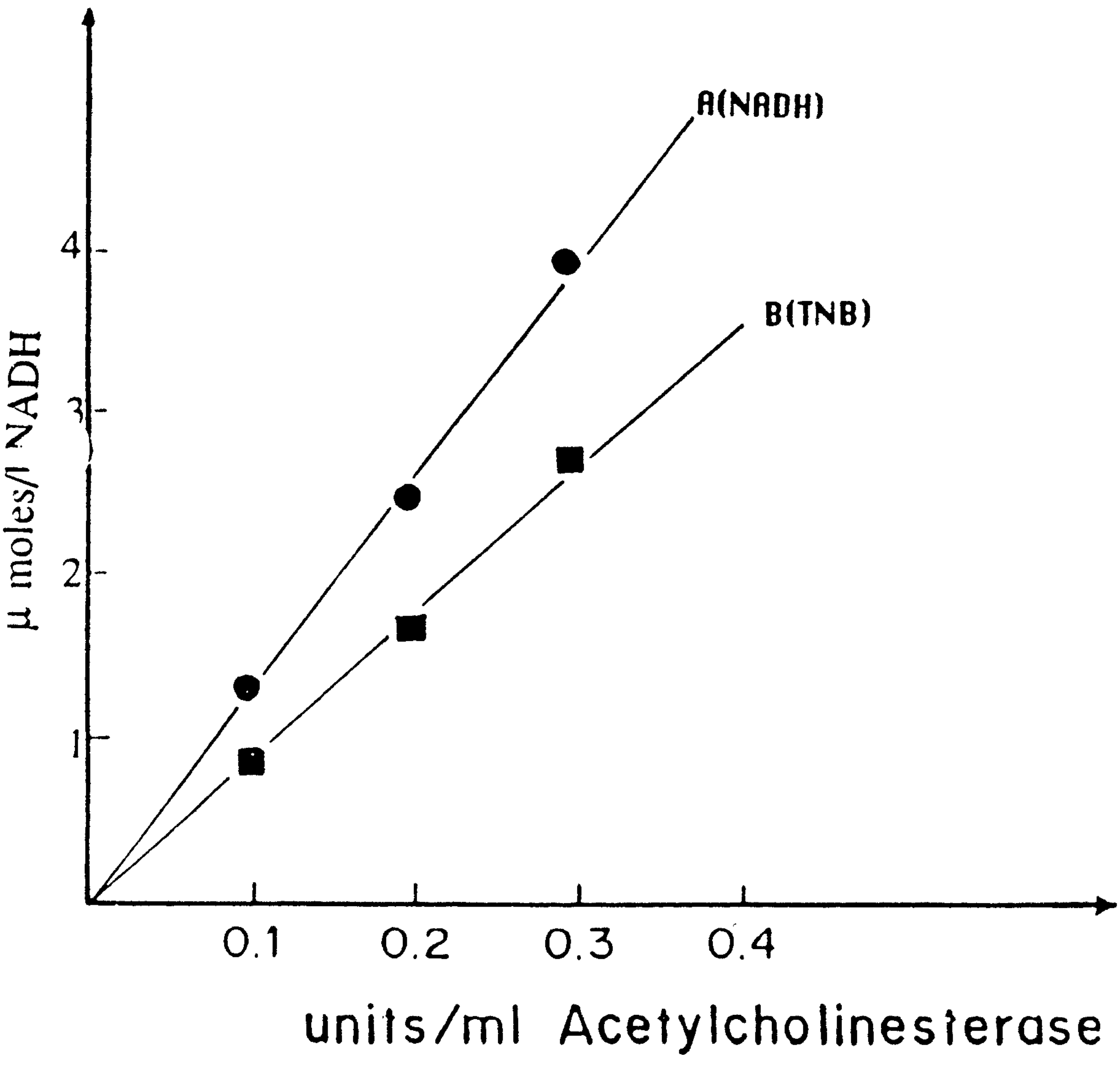


Figure 2. Initial Velocites for NADH and TNB Reactivation of Acetylcholinesterase.

Inactivation Procedure

200 µl of stock acetylcholinesterase was mixed with 5 drops of diisopropylfluorophosphonate (DFP) at 25°C for 30 minutes. The solution was then placed in an Amicon ultrafiltration cell equipped with a Diaflo YM 30 membrane. Two volumes (100 ml) of 0.1 M phosphate buffer, pH 8.0, at 4°C were passed through the cell in order to remove all excess DFP. The acetylcholinesterase was recovered in a volume of 10 ml, and assayed by both procedures previously described. No activity (over background) was demonstrated by either procedure. 200 µl of stock acetylcholinesterase was mixed with 5 drops of water at 25°C for 30 minutes. The resulting solution was treated in the manner described above with less than 5% loss of activity. All procedures described in this section were carried out in a glove box under nitrogen to protect the investigators. Any excess DFP was rendered inactive with concentrated potassium hydroxide.

Reactivation Procedure

Five ml of inactivated acetylcholinesterase from the previous step was mixed with 5 ml of 0.1 mM 2-pralidoxime methiodide (2-PAM) in 0.1 M phosphate buffer pH 8.0 at 25°C for 30 minutes. The solution was then placed in an Amicon ultrafiltration cell equipped with Diaflo YM 30 membrane. Two volumes (100 ml) of 0.1 M phosphate buffer, pH 8.0, at 4°C was passed through the cell in order to remove all excess 2-PAM. The acetylcholinesterase was recovered in a volume of 5 ml, and assayed by both procedures previously described.

The concentrations of the protein in the resulting solution were also determined by standard Biuret assay using stock acetylcholinesterase to construct a standard curve. Comparison of the specific activity of the enzyme treated in this manner with the specific activity of stock acetylcholinesterase (assayed by the same procedures) demonstrated over 40% reactivation.

Table 1. Percentage Reactivation Relative to 2-PAM for Tropanone-Oximes

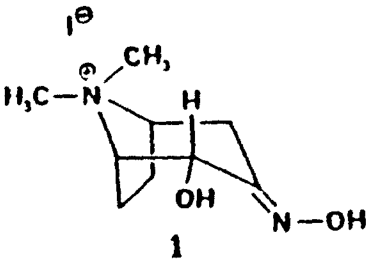
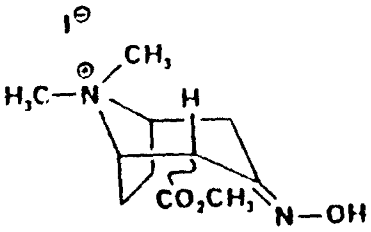
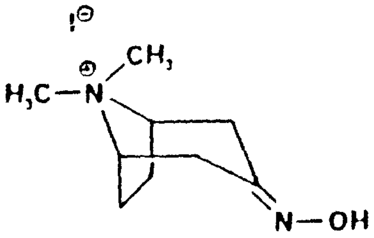
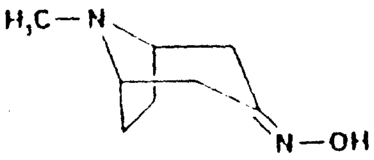
 1	0.75
 33	0.50
 34	0.40
 35	0.05
2-PAM	1.0

Table 2. Percentage Reactivation Relative to 2-PAM for γ-Phenylpropyl Ammonium Oximes.

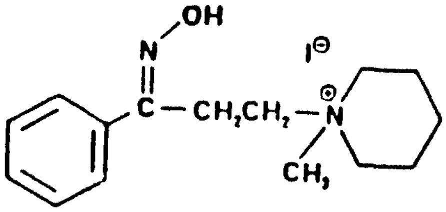
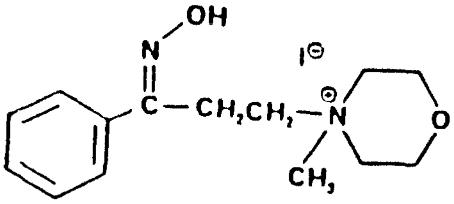
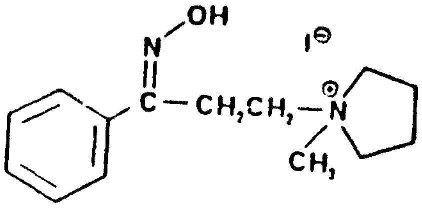
 **14a**	0.05
 **14b**	0.05
 **14**	0.05
2-PAM	1

Table 3. Binding Studies and Percentage Reactivation Relative to 2-PAM for pyridine and tropanone oxime methiodides.

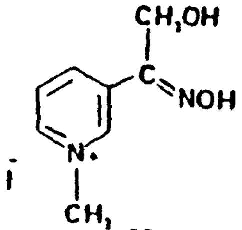
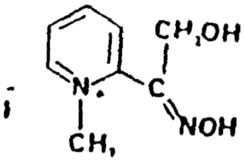
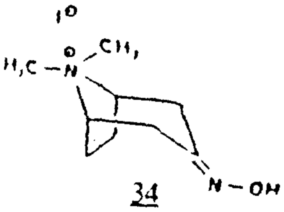
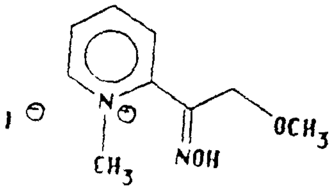
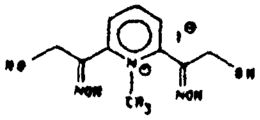
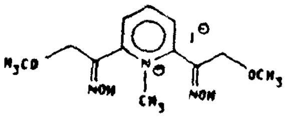
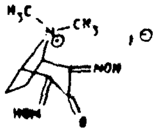
Compounds	pKa		K_i(mM)	% Reactivation
	potentiometric	spectra		
 28	7.5 ± 0.2	7.8 ± 0.1	0.07 ± 0.01	100
 23	8.7 ± 0.2	0.6	0.08 ± 0.02	67
 34	8.4 ± 0.6	9.0 ± 0.1	0.40 ± 0.02	40
 48	8.3 ± 0.2	0.2	0.06 ± 0.01	66

Table 4. **Binding Studies and Percentage Reactivation Relative to 2-PAM for Tropanone Oxime Methiodides.**

Compounds	pKa		K_I(mM)	% Reactivation
	potentiometric	spectra		
 43	9.1 ± 0.2	7.1 ± 0.1	0.15 ± 0.01	53
 49	9.3 ± 0.2	7.1 ± 0.2	0.18 ± 0.02	64
 35	9.8 ± 0.2	10.2 ± 0.2	0.04 ± 0.01	22

7. Discussion of Kinetic Data

First, it should be pointed out that we have in place a standardized and reliable assay for determining percentage reactivation. With the acquisition of the Vacuum Atmospheres Drylab and Guilford spectrophotometer, these studies should move along even more rapidly.

The data presented clearly points to the bridged bicyclic[3] oximes, such as 1, 33, and 34, as valid substrates for further synthetic elaboration in order to improve their reactivation capabilities.

8. Conclusions

We believe we are on the "right track" in this work. Our design for reactivator structure was based upon the accepted model for acetylcholinesterase involving the complement to an onium center and a critical distance between this center and the blocked (phosphorylated) serine hydroxyl group. Our approach emphasizes the binding of the reactivator to the enzyme. Tropane-type systems which are cholinergic offer an ideal "vehicle" to deliver the oximino group to the catalytic active site. It should be emphasized that this approach could also be applied to the design of an inactivator and this is precisely what has been reported recently in Russian acticles.[2,3] They have synthesized a series of alkaloidal phosphates and thiophosphates as acetyl and butyrylcholinesterase inactivators. These workers showed that quaternary bridged nitrogen acetylcholine derivatives of the type we have studied are excellent substrates for butyrylcholinesterase and acetylcholinesterase. As stated in this publication, "large teams of chemists and biochemists at the Institute of Bioorganic Chemistry of the Academy of Sciences of Uzbek SSP, the Institute of Experimental Medicine of the Academy of Medical Sciences of the USSR, and the Sechenov Institute of Evolutionary Physiology and Biochemistry of the USSR Academy of Sciences" have carried out the syntheses and measured the hydrolytic rates of members of this class of compounds [phosphate derivatives of lupane, cytisine and piperidine derivatives].

One could use our approach for the design of a protective acetylcholinesterase by attaching a carbamoyl group to the alkaloid. In a sense, this is the basis of the mechanism of protection afforded by pyridostigmine bromide. The generality of this concept, as applied to diverse alkaloidal structure, is an interesting area of investigation.

Turning to the compounds we have synthesized in the present study, the tropane system looks definitely promising. By varying the ring size and changing the orientation or position of the neighboring hydroxyl group, we believe we can materially improve this system. Also, bridging via a CH_2-O-CH_2 group between two tropanyl units would lead to a potentially interesting compound.

In conclusion, we believe that the vast array of naturally occurring alkaloids of known structure and geometry offer a fertile array for pursuing the concept of delivery of the oximino group to the active site via a vehicle of good affinity for the catalytic site on the enzyme.

9. Synthesis and Characterization of Compounds

Materials: Nuclear magnetic resonance (NMR) spectra were recorded on a Varian A60 or EM360 spectrophotometer; chemical shifts are reported in parts per million (ppm. δ) using tetramethylsilane (TMS) as standard. Unless otherwise mentioned, NMR spectra were recorded on solutions of the compounds in $CDCl_3$. Splitting patterns are designed as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Infrared (I.R.) spectra were obtained using a Unicam SP I.R. spectrophotometer. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Mass spectra (MS) were measured with a Hewlett Packard GC/MS 5985 apparatus at 70 or 20 eV. Microanalyses were obtained from Microan Lab., Skokie, Illinois. All the new compounds gave satisfactory analyses (C, H, N).

Tetrahydrofuran (THF) was dried over $LiAlH_4$, distilled and stored over a 4A molecular sieve. Thin layer chromatography (TLC) was performed on pre-coated TLC sheets, silica gel 60 Fl-254 (layer thickness 0.2 mm, EM reagents). Column chromatography was done on silica gel (60-200 mesh), available from J. T. Baker Chemical Company.

Preparation of Ketones

1-Methyl-4-piperidone, tropan-3-one, 2-acetylpyridine, 3-acetylpyridine, 2-6,-diacetylpyridine and quinuclidione hydrochlorides are commercial products (Aldrich). Other ketones used in these studies ware prepared in the laboratory. Their preparations are given below.

1-Phenyl-3-(1-piperidinyl)propanone hydrochloride[4]

A mixture of 12.2 g. (0.1 mole) of piperidine hydrochloride, 0.25 mL of concentrated HCl, 4.5 g. (0.15 mole) of paraformaldehyde, 30 mL of absolute ethanol, and 12.0 g. (0.1 mole) of paraformaldehyde was added to the solution and refluxing was continued for 2 hours. To the hot mixture was added 250 mL of boiling acetone, and the resulting solution was cooled slowly, finally in ice water. The white crystalline product was collected on a filter; 21.5 g., (85%) m.p. 192-196° C, (literature [Lit.][4]), m.p. (192-193° C).

Using the above procedure, the following were prepared:

1-Phenyl-3-(1-pyrrolidinyl)propanone hydrochloride (13a)

m.p. 148°-152° C

% yield = 65.8

I.R. (mineral oil) cm^{-1}: 1675 (carbonyl stretch)

NMR (D_2O): 1,8-2.4 (6H, m, $-COC\underline{H}_2-$ and $N(CH_2C\underline{H}_2)_2$; 3.0-3.8 (6H, m, $^{+}N-(C\underline{H}_2)_3$); 7.0-8.0 (5H, m, aromatic protons) and (6H, m, 1 $^{+}N-(C\underline{H}_2)_3$).

1-Phenyl-3-(4-morpholinyl)propanone hydrochloride (13b)

m.p. 161-163°C
% yield = 78.0
I.R. (mineral oil) cm^{-1}: 1670 ($>$C=O str).

1-Phenyl-3-(4-thiomorpholinyl)propanone hydrochloride (13c)

m.p. 167-170°C
% yield = 53.5
I.R. (mineral oil) cm^{-1}: 1670 ($>$C=O str)
NMR (D_2O): 2.0-2.3 (6 H m $-\overset{O}{\overset{\|}{C}}-CH_2$ and $\begin{matrix} CH_2 \\ CH_2 \end{matrix}\!\!>\!S$)
3.3-3.4 (6 H m, $\overset{+}{N}-(CH_2)_3$)
7.5-8.3 (5 H m, aromatic protons).

1-(4-Methoxyphenyl)-3-(1-piperidinyl)-propanone hydrochloride (13c)

m.p. 215-216°C (Lit. m.p. 216°C)
% yield = 51.9
I.R. (mineral oil) cm^{-1}: 1680 ($>$C=O str)
NMR (D_2O): 1.4-2.2 (8 H m, $-\overset{O}{\overset{\|}{C}}-CH_2$ + 6 piperidine protons)
2.7-3.7 (6 H m, $^{+}N-(CH_2)_3$)
4.1 (3 H s, $-OCH_3$)
6.7-7.3 (2 H m_2, aromatic)
7.82-8.2 (2 H m, aromatic protons).

1-(4-Methoxyphenyl-3-(1-pyrrolidinyl)propanone hydrochloride

m.p. 186-188°C
% yield = 50.4
I.R. (mineral oil) cm^{-1}: 1660 ($>$C=O str)
NMR (D_2O): 3.2-3.7 (6 H m $^{+}N-(CH_2)_3$).

1-(4-Methoxyphenyl)-3-(1-piperdinyl)-propanone hydrochloride (13c)

m.p. 186-188° C

% yield = 50.4

I.R. (mineral oil) cm^{-1}: 1665 (carbonyl stretch)

NMR (D_2O): 3.4-3.9 [6H, m, $^+N(C\underline{H})(\underline{H})(C\underline{H}_2)(C\underline{H}_2)$]

3.0-3.4 (6H, s, $-COC\underline{H}_2CH_2-$ and $S(C\underline{H}_2)_2$)

4.2 (3H, s, $-OC\underline{H}_3$)

7.0-7.4 (2H, d, aromatic protons)

8.0-8.4 (2H, d, aromatic protons).

Preparation of 2-acetyl-1-methylbenzimidazole

±2-α-hydroxyethylbenzimidazole[5]

A mixture of o-phenylene diamine (0.1 mole), lactic acid (0.12 mole) and 4N HCl (100 mL) was refluxed for 35-60 minutes. The mixture was cooled, basisified with Ag ammonia, washed with water, dried to yield the desired material, m.p. 178-179° C, (Lit.[5] m.p. 178-179° C). Yield = 68%.

2-Acetylbenzimidazole[6]

A solution of chromium trioxide (1.5 g., .015 mole) in water (5 mL) was added dropwise to a solution of (±)2-α-hydroxylethylbenzimidazole (3.24 g., 0.02 mole) in glacial acetic acid (15 mL) at 90° C. The reaction mixture was heated at 100° C for an additional 5 minutes and then poured into 200 mL of water. A flocculent precipitate was discarded. The filtrate was extracted with $CHCl_3$ (3 X 50 mL), and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Crystallization of the residue from benzene (60-80 mL) gave 2-acetylbenzimidazole, 2.1 g, 65%.

m.p. 187-1891° C (Lit.[6] m.p. 188-189° C)

I.R. (Nujol, cm^{-1}): ~1680 (carbonyl stretch)

Yield = 65%

2-Acetyl-1-methylbenzimidazole[6] (32)

Methyl sulfate (1.26 mL, 0.013 mole) was added to a solution of 2-acetylbenzimidazole (1.6g, 0.01 mole) in 2N sodium hydroxide (15 mL). The mixture was cooled to 0° C and stirred. A precipitate formed during 5-10 minutes, was filtered off, washed with cold water and dried to give 2-acetyl-1-methyl-benzimidazole (0.85 g, ~50%) m.p. 73-75° C (Lit.[6] m.p. 74°-75° C). NMR: 2.76 (s, 3H, $-COC\underline{H}_3$), 4.05 (s, 3H, $N-C\underline{H}_3$), 7.25-7.9 (4H, aromatic protons).

General Procedure for Preparation of α-Hydroxyacetals:

Potassium hydroxide (0.15 mole, 3 eq.) was dissolved in 80 mL of methanol with ice-bath cooling, and a solution of the ketone (0.05 mole, 1 eq.) in methanol was added dropwise through a pressure-equalized addition funnel and stirred over a period of 30 minutes. Then solid iodobenzene diacetate (0.055 mole, 11 eq.) was added in portions during a 10 minute period. The reaction mixture was stirred at room temperature overnight. Most of the methanol was evaporated in vacuo, then the residue was added to water and K_2CO_3 to saturate the solution, followed by extraction with $CHCl_3$ or ether,dried ($MgSO_4$), and concentration in vacuo to give the crude product (with iodobenzene). Final isolation/purification of the product was done by column chromatography or crystallization (described in individual cases). These compounds exhibited the properties listed below.

3-Hydroxy-4-piperidone dimethylacetal

This acetal was isolated by addition of hexane to the crude product followed by cooling the solution in a refrigerator overnight. Colorless crystalline solid (recrystallization from hexane) m.p. 109-110° C was obtained in 54% yield. ^{1}H-NMR: 3.24 -3.28 (s, 3H, $C_4\text{-}OC\underline{H}_3$), 3.82-3.90 (m, 1H, $C\underline{H}$). Mass spectrum: m/z 175 (M^+, 22), 143 ($M\text{-}OCH_3$, 45), 126 (55), 112 (43), 86 (100).

2-a-Hydroxytropan-3-one dimethylacetal (8)

This compound was isolated by column chromatography, using ethyl acetate and methanol (75:25) as eluent. Recrystallization from hexane gave pure colorless crystals. M.p. 85-86° C in 33% yield. ^{1}HNMR: 3.24 (s, 3H, $C_3\text{-}OC\underline{H}_3$), 3.29 (s, 3H, $C_3\text{-}OC\underline{H}_3$), 3.88-3.90 (m, 1H, C_2-H); Mass Spectrum: m/z 210 (M^+, 58), 170 (M^+, 22), 143 ($M\text{-}OCH_3$, 45), 126 (55), 112 (43), 86 (100).

1,1-Dimethoxy-1-phenyl-3-(1-piperidinyl)propan-2-ol (15a)

This was isolated in 50% yield by repeated crystallization from hexane, m.p. 80-81° C. ^{1}HNMR: 3.23 (s, 3H, $C_1\text{-}OCH_3$), 3.38 (s, 3H, $C_1\text{-}OCH_3$), 3.95, 4.15 (d, 1H, $C_2\underline{H}$) (J=3Hz); Mass Spectrum: m/z 279 (M^+6), 151 (46), 128 (52), 98 (100).

1,1-Dimethoxy-1-phenyl-3-(1-pyrrolidinyl)propan-2-ol (15 d)

This was isolated in 25% yield by crystallization from hexane m.p. 77°-78° C. ^{1}HNMR: 1.73 (m, 4H, $\text{-}N(CH_2C\underline{H}_2)_2$), 2.4 (m, 6H, $\text{-}N(C\underline{H}_2)_2$), 3.3 (s, 3H, $\text{-}OCH_3$) 3.43 (s, 3H, $\text{-}OCH_3$), 3.55 (s, 1H, $CHO\underline{H}$), 4.04-4.27 (d, 1H, $C\underline{H}OH$), 7.18-7.93 (m, 5H, aromatic protons; MS: m/z 265 (M^+, 0.4), 235 (3), 151 (16.2) 121 (1) 85 (9) 84 (100).

1,2-Dimethoxy-1-phenyl-3-(4-morpholinyl)-propan-2-ol (15 b)

The product was obtained in 60% yield by crystallization from hexane, m.p. 75-76°C. ^{1}H NMR: 3.25, 3.40 (s, 3H, $C_1OC\underline{H}_3$), 4.02-4.20 (dd, 1H, $C_2\underline{H}$)(J = 3 Hz); MS: m/z 281 (M^+, 1) 151 (48) 130 (18), 100 (100).

1,-1-Dimethoxy-1-phenyl-3-(4-thiomorpholinyl)-propan-2-ol (15 c)

A colorless solid separated out when water was added to the residual reaction mixture obtained after evaporation of methanol. Hexane was added and the resulting mixture was stirred for 5 minutes. Filtration followed by washing with cold hexane, followed by water and then drying (under suction) gave pure product in 65% yield, m.p. 129-130° C. ^{1}H NMR: 3.22 (s, 3H, $C_1OC\underline{H}_3$), 3.38 (s, 3H, $C_1OC\underline{H}_3$), 3.98-4.16 (dd, 1D, $C_2\underline{H}$); MS: m/z 297 (M^+, 1) 151 (40).

2,2-Dimethoxy-2-(2-pyridinyl)ethanol (20)

This was obtained in 60% yield from 2-acetylpyridine using CH_2Cl_2: CH_3COCH_3 (95:5) as eluent (R_f = 0.35) m.p. 57°-59° C. ^{1}H NMR: 2.15 (s, 1H, O$\underline{H}$), 3.25 (s, 6H, OC$\underline{H}_3$), 4.00 (s, 2H, C$\underline{H}_2$), 7.25 (m, 1H, C_4-$\underline{H}$), 7.75 (m, 2H, $C_3H_5\underline{H}$), 8.60 (m, 1H, C_6-$\underline{H}$); MS: m/z 183 (M^+), 166, 152, 136, 106, 78.

2,2-Dimethoxy-2-(3-pyridinyl)ethanol (25) or 3-(Hydroxymethylcarbonyl) pyridine dimethyl acetal (25).

This acetal was also prepared according to the general procedure for preparation of α-hydroxyacetals. 3-Acetylpyridine and iodobenzene diacetate were mixed in equimolar ratio. The purification in the final stage was done by precipitaiton with hexane (which dissolves iodobenzene). Recrystallization from hexane-ether gave pure acetal in 38% yield, m.p. 88-89° C. IR: No carbonyl, 3300-3460 (br, OH stretch). NMR: 3.22 (s, 6H, C(C$\underline{H}_3$)$_2$), 3.76 (s, 2H, -C$\underline{H}_2$OH), 7.15-8.5 (m, 4H, 4 pyridinnium protons); MS: m/z 183 (M^+, 0.32), 152 (M-OCH_3, 100), 122 (2.04) 120 (8.6) 106 (16) 78 (4).

2,6-Bis-(hydroxymethylcarbonyl)pyridine tetramethyl diacetal (30)

Potassium hydroxide (5.6 g, 0.1 mole) was dissolved in 50 mL of CH_3OH at 0° C with stirring, and 2,6-diacetyl pyridine (1.63 g, 0.01 mole) was added over a 10 minute period to the solution while immersed in an ice bath. Subsequently iodobenzene diacetate (6.44 g, 0.02 mole) was added in portions during 10 minutes. The reaction mixture was stirred at room temperature overnight. CH_3OH was removed in vacuo. 40 mL of H_2O was added and the resulting solution was directly extracted with chloroform three times. The chloroform extracts were combined, dried with anhydrous Na_2SO_4, and filtered.

After the chloroform was removed, the residue was purified by silica gel preparative TLC, using elution solvent CH_2Cl_2:acetone, 130:20, to get a white solid, $R_f = 0.30$. The solid was crystallized with acetone to obtain white crystals (2.0 g, 72% yield) of 2,6-bis(hydroxymethylcarbonyl)pyridine tetramethyl diacetal, m.p. 153-154°C; ^{1}H NMR ($CDCl_3$), 3.5 (s, 2H, -O$\underline{H}$), 3.9 (s, 4H, -C$\underline{H}_2$-), 7.7 (s, 2H, 3,5 pyridinium protons), 7.95 (s, 1H, 4-pyridinium proton). IR (KBr) n_{max} 3500-3300 (strong), no C=O stretching. Mass spectrum (70 eV) m/z: 287 (M^+), 256, 239, 220, 207, 192, 177, 164, 153, 137, 121, 113, 105, 92, 77.

2-Hydroxymethylcarbonyl-1-methylbenzimidazole dimethylacetal (33)

This acetal was obtained from 2-acetkyl-1-methylbenzimidazole using the same conditions as mentioned in the general procedure. The characteristics are as follows: m.p. 133-134° C; % yield = 60; IR (Nujol cm^{-1}): C=O absent, 3400-3500 (OH stretch); ^{1}H NMR: 3.22 (s, 6H, -C(OC$\underline{H}_3$)$_2$-), 3.83 (s, 3H, -NC$\underline{H}_3$), 3.95 (s, 2H, -C$\underline{H}_2$OH); mass spectrum: m/e 237 (M^+ 1) 236 (M^+, 1%) 205 (M-31, 100%).

Preparation of α-Hydroxyketones:

The hydrolysis of all the acetals described in previous experiments was attempted using various conditions. Only a few cases were successful. The details of these experiments are given in the following description, whereas hydrolysis of other compounds are under study.

2-α-Hydroxy-tropan-3-one (9)

1.0 G of 2-α-hydroxy-tropan-3-one was dissolved in 10 mL of water and to the resulting solution was added 10 mL of 6N HCl. The mixture was stirred at room temperature for 1 hour and then saturated carefully (effervescence occurs) with solid K_2CO_3. Extraction with $CHCl_3$ (5 X 40 mL) followed by drying over $MgSO_4$ and concentration in a vacuum gave crude ketone as an oil which could be crystallized from hexane to give pure product as colorless crystals. M.p.: 65-66° C; % yield = 55; IR ($CHCl_3$) cm^{-1}: 1715 (carbonyl stretch), 3505 (-OH stretch); ^{1}H NMR: 2.52 (s, 3H, NC$\underline{H}_3$), 4.26 (s, 1H, C_2-$\underline{H}$) (J=7Hz), 3.3-3.55 (m, 2H, C_1-$\underline{H}$, $C_5\underline{H}$); MS: m/z 155 (47) 125 (2.15), 124 (1.8), 112 (16) 98 (30) 96 (40), 82(100).

3-(Hydroxymethylcarbonyl)pyridine (26)

1.0 G of the acetal was suspended in 10 mL of water in a 200 mL Erlenmeyer flask and about 30 mL of 6N HCl was added with stirring. The resulting solution was left at room temperature for 20 hours. Aqueous $NaHCO_3$ solution was added until the acetal solution was basic. It was extracted with $CHCl_3$ (5 X 40 mL), dried ($MgSO_4$) and concentrated to yield 0.45 g of 3'-hydroxymethyl carbonyl pyridine (from acetone). M.P. 110-112° C; % yield = 60; ^1H NMR: 4.84 (s, 2H, -COC$\underline{H}_2$OH), 7.25-9.0 (4H, pyridinium protons); IR (KBr): 1715 cm^{-1} (C=O stretch); MS: m/z 137 (M^+, 5), 107 (11), 106 (100) 79 (13), 78 (92).

2,6-Bis-(hydroxymethylcarbonyl) pyridine

1 G of 2,6-bis-(hydroxymethylcarbonyl) pyridine tetramethyl diacetal was dissolved in a solution of 500 mL of acetone and 5 mL of water containing 150 mg of p-toluenesulfonic acid. This mixture was then stirred at room temperature for 6 days with the cap in place. After this period, acetone was evaporated and then water added; the resulting solution was neutralized with dilute aqueous sodium bicarbonate and then extracted with chloroform (4 X 100 mL). The chloroform layers were collected, dried with anhydrous sodium sulfate and filtered, after which the solvent was removed in vacuo. White needle crystals resulted and recrystallization with acetone yielded 400 mg (60% yield) of 2,6-bis-(hydroxymethylcarbonyl) pyridine. M.p. 120-122° C; % yield = 60; IR (KBr): 3500-3300 cm^{-1} (OH stretching), 1710 (C=O stretching); ^{1}H-NMR ($CDCl_3$) δ: 1.25 (s, 2H, O$\underline{H}$), 5.25 (s, 4H, -C$\underline{H}_2$-), 8.10-8.25 (m, 3H, pyridinium protons). Mass (70 eV) m/e: Calculated molecular weight for $C_9H_9NO_4$: 195. Found: 195 (M^+), 164, 137, 121, 105, 91, 84, 77.

Attempted hydrolysis of 2-)hydroxymethylcarbonyl)-1-methylbenzimidazole

The hydrolysis of the 2-(hydroxymethylcarbonyl)-1-methylbenzimidazole dimethylacetal was attempted, using the following conditions:

A: Different Concentrations of HCl and varying reaction times. Only starting material was obtained.

B. p-Toluenesulfonic acid-H_2O/acetone, varying time period from 1-12 days. Starting acetal was obtained.

C. Sulfuric acid. This also gave starting material.

We are still working on this problem and have tried the following alternative method:

Step I: 2-Bromoacetyl-1-methylbenzimidazole hydrobromide[7]

A solution of bromine (.001 mole) in CCl_4 (20 ml) was added dropwise to a suspension of 2-acetyl-1-methylbenzimidazole (.001 mole) in CCl_4 (20 ml). The resulting mixture was refluxed until the color of bromine disappeared. Cooling and filtration gave 2-$\underline{\omega}$-bromoacetyl-1-methylbenzimidazole hydrobromide (80%).

Step II: Reaction of 2-bromoacetyl-1-methylbenzimidazole with potassium hydroxide

The bromoketone hydrobromide obtained in the last step was treated with KOH in EtOH and a little water. A brown solid, which is uncharacterized as yet, separated out. Thus we did not get the desired α-hydroxyketone by this method.

2,4-Bisoximinotropan-3-one Methiodide (35):

2,4-Bisoximinotropan-3-one (34):

To a solution of 3-tropanone ($\underline{1}$, 1.39 g, 0.01 mole) in t-butyl alcohol was added. 0.02 mol of t-Buok and 0.025 mole of t-butylnitrite. The contents were stirred at room temperature for 36 hours. Then solution was neutralized with HCl. Solid so obtained was filtered and crystallized from methanol.

m.p. = 166-168°C
% yield = 40
IR (Nujol) cm^{-1}: 3325 (broad, O-H stretching), 1720 (sharp C=O stretching), 1660 (sharp, C=N stretching).
^1H-NMR (DMSO-d_6) δ: 2.8-3.1 (m, 4H, 2 x $C\underline{H}_2$), 3.12 (s, 3H, N-$C\underline{H}_3$), 5.4 (m, 2H, 2 x $C\underline{H}$).

2,4-Bisoximinotropane-3-one Methiodide (35):

Bisoximinotropane-3-one ($\underline{2}$) was dissolved in 50 ml of dry THF in a 100 ml R.B. flask. To this excess of methyliodide was added and flask was stoppered tightly. The contents were allowed to stir for 36 hours at room temperature. Solid so obtained was filtered and washed with 20 ml of dry THF and was dried.

m.p. = 228-230°C
% yield = 35
IR(KBr) cm^{-1}: 3320 (broad O-H stretching), 1720 (sharp, C=O stretching), 1650 (sharp C=N stretching).
^1H-NMR (DMSO-d_6) δ: 2.8-3.1 (m, 4H, 2x-CH_2-), 3.2 (s, 3H, N-CH_3), 3.4 (s, 3H, CH_3), 5.4 (m, 2H, 2x$C\underline{H}$).
$C_9H_{14}N_3O_3I$: Requires (%)C = 48.73, H = 5.58, N = 21.32. Found: (%)C = 48.44, H = 5.67, N = 21.28.

Silyl Enol Ethers

The silyl enol ethers 36, 38, and 50 were prepared from the respective ketones according to the general method A of House et. al.[8] However, dilute hydrochloric acid was not used in the workup, because acid hydrolysis of the silyl enol ethers occurred to a significant extent in some cases. The ratio of the reactants was the same in the case of monoketones, but a double amount of chlorotrimethylsilane and triethylamine was used in the preparations that start from a diketone, 2,6-diacetylpyridine (7b). All silyl enol ethers were distilled before use.

Preparation of 2,6-Diacetylpyridine Bis(silyl enol ether) (7b)

To a solution of 32.60 g (0.30 mol) of chlorotrimethylsilane and 60.60 g (0.60 mol) of triethylamine in 200 mL of dimethylformamide was added 2,6-diacetylpyridine (5, 20.38 g, 0.125 mol). The resulting mixture was refluxed with stirring overnight and then cooled, diluted with 400 mL of pentane, and washed with three 300 mL portions of ice-cold aqueous sodium bicarbonate. The aqueous layer was extracted with pentane (2 x 150 mL), and the combined organic phase was washed with cold aqueous sodium chloride solution (200 mL). The resulting pentane solution was dried and concentrated in vacuo to yield crude silyl enol ether, 92%. Distillation gave pure product: bp 129-131°C (0.05 mm); 29.5 g (77%); ^{1}H NMR ($CDCl_3$) δ 1.02 (s, 18H), 4.53 (s, 2H), 5.76 (s, 2H), 7.56 (m, 3H).

General Procedure for the Preparation of the α-Hydroxyacetophenones (50).

Boron trifluoride diethyl ether (2.84 g, 20 mmol) and then the silyl enol ether (10 mmol) were added to a stirred and ice-cooled (0-5°C) suspension of iodosobenzene (2.42 g, 11 mmol) in water (50 ml). The mixture was stirred for 2 h, after which the temperature was raised to room temperature; stirring was then continued for a further 2 h, during this time all of the iodosobenzene went into solution indicating completion of the reaction. The solution was neutralized with an excess of solid sodium hydrogen carbonate and then extracted with dichloromethane (5 x 50 ml). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product which contained iodobenzene as a major impurity. Final purification was by column chromatography, distillation, or crystallization. In the cases of solid products addition of hexane generally removed iodobenzene and the crystalline solid separated out of the solution (Table 1).

2-Hydroxyacetylpyridine (37)

A pure colourless crystalline product (62%) m.p. 70-71°C (lit.[9] 68-70°C) was obtained by addition of mixture of hexane and diethyl ether (20 ml each) to the crude product, followed by filtration and cooling of the filtrate at 0°C.

2,6-Bis-(hydroxymethylcarbonyl) pyridine (39)

White needle crystals resulted and recrystallization with acetone yielded 400 mg (60%) yield of 2,6-bis-(hydroxymethylcarbonyl) pyridine. m.p. 120-122°C. IR and NMR characteristics are the same as reported earlier.

2-[(Methoxymethyl)carbonyl]pyridine (44)

Boron trifluoride etherate (17.00 g, 0.12 mol) was dissolved in dry dichloromethane (500 mL), and iodosobenzene (9.68 g, 0.044 mol) was added. The mixture was cooled to -70°C and then silyl enol ether 6 (7.72 g, 0.040 mol) was added. Finally, methanol (10 mL) was added. The reaction mixture was stirred at -70°C for 1 h, and then the temperature was slowly raised to room temperature. Stirring was continued for another 30 min. Water (50 mL) was added, and the mixture was neutralized with a saturated solution of sodium bicarbonate and then transferred to a separatory funnel. The aqueous layer was extracted with dichloromethane (4 x 50 mL). The organic phases were combined, dried with magnesium sulfate, and concentrated in vacuo to yield the crude product which did not show any starting material (by TLC and NMR). Distillation of crude product afforded pure 8: 4.24 g (70%); bp 82-83°C (0.05 mm) (some of the product decomposed during distillation; higher temperatures for distillation are not recommended):

IR (neat) 1720 cm^{-1} (C=O str)
^1H NMR ($CDCl_3$) δ: 3.53 (s, 3H, OCH_3), 5.02 (s, 3H, $C(=O)CH_2$), 7.30-8.05 (m, 3H, pyridine), 8.62-8.80 (m, 1H, pyridine)
MS, m/z 151 ($M^{+\cdot}$, 10), 136 (100).
Anal. Calcd. for $C_8H_9NO_2$: C, 63.58; H, 5.96; N, 9.27. Found: C, 63.29; H, 6.10; N, 9.11.

2,6-Bis[(methoxymethyl)carbonyl]pyridine (45)

Silyl enol ether 7 (6.14 g, 0.020 mol) was treated with iodosobenzene (8.80 g, 0.040 mol), boron trifluoride etherate (11.36 g, 0.080 mol), and 10 mL of methanol in 500 mL of dry dichloromethane. To the crude mixture (obtained as described in case of 8) was added hexane (50 mL), and the resulting mixture was allowed to stand for a few minutes, filtered, and cooled slowly to about 10°C. After 30 min, colorless crystalline product [2.67 g (60%); mp 100-101°C] was collected by filtration and drying. Recrystallization from hexane gave an analytical sample, mp 101-102°C. Filtrates gave more of the product:

total yield 3.16 g (71%);
IR (Nujol) 1720 cm^{-1}
^1H NMR ($CDCl_3$) δ: 3.55 (s, 6H, 2 OCH_3), 5.05 (s, 4H, 2 $CH_3OCH_2C=O$), 8.05-8.40 (m, 3H, pyridine)
MS, m/z 223 ($M^{+\cdot}$, 10), 208 ($M^{+\cdot}$-Me, 100), 192 (8), 176 (18), 134 (27), 105 (20).

General Procedure for Preparation of Oximes

Unless stated differently, the following general procedure was used for preparing the oximes:

The ketones were treated with a slight excess of $NH_2OH{\cdot}HCl$ and $NaHCO_3$ at reflux in EtOH for 1 hour. The reaction mixture was filtered while warm and concentrated under a rotary evaporator, and the residue obtained was recrystallized from an appropriate solvent. These oximes had the following properties:

4-Piperidone oxime:
m.p. 1281-129° C (lit. [8] m.p. 129-130° C); % yield = 87.

Tropan-3-one oxime:
m.p. 112-113° C (lit. [9] m.p. 110-111° C); % yield = 82.

Quinuclidinone oxime:
m.p. 210-215 ° C; % yield = 90; IR (KBr): no carbonyl; $FeCl_3$ test + ve.

1-Phenyl-3-(1-piperidinyl)propanone oxime

This was obtained in 80 % yield on addition of water after evaporating the ethanol; m.p. 146-148° C (lit.[4] m.p. 143° C).

1-Phenyl-3-(1-pyrrolidinyl)propane oxime:

This oxime was isolated on addition of water to the residue, obtained after evaporation of ethanol, m.p. 150-151° C; % yield = 75.

1-Phenyl-3-(4-morpholinyl)-propane oxime

This oxime was also prepared as mentioned in the last experiments; m.p. 146-147°C, % yield = 65.

1(-4-Methoxyphenyl)-3-(1-piperdinyl)propanone oxime:
m.p. 135-136° C (reported 136° C); % yield = 65.

2-α-Hydroxytropan-3-one oxime hydrochloride (10a)

To a solution of NH_2OHHCl (0.011 mol) in MeOH (25mL) was added a solution of 2-hydroxytropan-3-one in MeOH with stirring during 5 minutes. An exothermic reaction occurred and colorless solid separated out of the solution. Cooling, filtration and drying gave oxime hydrochloride, m.p. 190°-195° C (decomposition), % yield = 90.

2-α-Hydroxytropan-3-one oxime (10)

Hydrochloride salt obtained in the last experiment was dissolved in 20 mL of water and then saturated with solid K_2CO_3. Isolation by extraction with $CHCl_3$ (5 X 25 mL) gave pale yellow crystals of oxime, m.p. 165-169° C (decomposition); % yield = 82; IR (Nujol): no carbonyl absorption; $FeCl_3$ test + ve.

2,6-Diacetylpyridine oxime

M. p. 241-242° C (EtOH); % yield = 82; IR (Nujol): no carbonyl absorption.

3-Acetylpyridine oxime

M.p. 115-116° C (lit. [10] m.p. 130-135° C).

3-Hydroxymethylcarbonylpyridine oxime

M.p. 132-134° C; % yield = 60; IR no carbonyl; $FeCl_3$ test + ve.

2-Acetyl-1-methylbenzimidazole oxime

M.p. 218° C (lit. [3] m.p. 218-219° C); % yield = 72.

2-(Hydroxymethylcarbonyl)pyridine oxime (41)

M.p.164-165°C; % yield=60. IR (KBr) cm^{-1}: 3300 (br, OH stretching); 1650 (s, C=N);

^1H NMR ($CDCl_3$) δ: 4.6 (s, 2H, $-C\underline{H}_2-$); 7.3-7.9 (m, 4H, aromatic protons); 12.7 (broad, 2H, 2 x $O\underline{H}$).

2,5-Bis(Hydroxymethylcarbonyl)pyridine oxime (43)

m.p. 170-172°C
% yield = 57
IR (KBr) cm^{-1}: 3300 (broad, O-H stretching), 1650 (sharp, C=N stretching).
^1H NMR ($CDCl_3$) δ: 1.9 (broad, 2H, 2 x $O\underline{H}$); 4.7 (s, 4H, 2 x $C\underline{H}_2$); 7.3-7.5 (m, 3H, aromatic protons); 14.7 (broad, 2H, 2 x $N-O\underline{H}$).

2-(Methoxymethylcarbonyl)pyridine oxime (46):

m.p. 148-150°C
% yield = 63
IR (Nujol) cm^{-1}: 3350 (broad, O-H stretching); 1660 (sharp, C=N stretching).
^1H NMR ($CDCl_3$) δ: 3.3 (s, 3H, $OC\underline{H}_3$); 4.8 (s, 2H, $C\underline{H}_2$); 7.4-7.8 (m, 4H, aromatic protons); 14.2 (broad, 1H, $N=O\underline{H}$).

2,5-Bis(Methoxymethylcarbonyl)pyridine (47b):

m.p. 156-158°C
% yield = 66
IR (KBr) cm^{-1}: 3360 (broad, O-H stretching), 1650 (sharp, C=N stretching).
^1H NMR ($CDCl_3$) δ: 3.25 (s, 6H, 2 x $OC\underline{H}_3$); 4.7 (s, 4H, 2 x $C\underline{H}_2$); 7.3-7.8 (m, 3H, aromatic protons); 14.8 (broad, 2H, 2 x C=N-OH, exchanged with D_2O).

General Procedure for Preparing Oxime Methiodides

Methiodides were prepared by dissolving the oximes in THF or methanol and then adding an excess of iodomethane (3-4 equivalents). The solution was stirred at room temperature for a suitable time; the precipitates were filtered, washed with ether and dried. The following salts were prepared by this procedure:

2-Acetyl-1-methylbenzimidazole oxime methiodide

m.p. 203-207°C (decomposed)
% yield = 90

3-Acetylpyridine oxime methiodide

m.p. 218-220°C
NMR (DMSO δ): 4.39 $(\underset{+}{N}-C\underline{H}_3)$

3-(Hydroxymethylcarbonyl)pyridine oxime methiodide

M.p. 129°-134° C; ^1H NMR (DMSO) δ: 4.38 (s, 3H, $^+N-C\underline{H}_3$); MS: m/z 253.9 (M-30, 7), 152 (L2), 149 (3) 142 (100).

4-Piperidone oxime methiodide

M.p. 213-216° C; % yield - 91; ^1H NMR (D_2O) δ: 3.3 (s, 6H, $^+N(C\underline{H}_3)_2$), 3.55 (m, 4H, $^+N(C\underline{H}_2)_2$).

Tropan-3-one oxime methiodide

M.p. 235-262° C (decomposition); % yield = 86; ^1H NMR (D_2O) δ: 3.13, 3.26 (ss, 6H, $^+N(C\underline{H}_3)_2$), 3.95 (m, 2H, $C_{(2)}\underline{H}_2$).

2-α-Hydroxy-tropan-3-one oxime methiodide

M.p. 189-192° C (decomposition); % yield = 92; ^1H NMR (D_2O) δ: 3.34, 3.2 (ss, 6H, $^+N-CH_3)_2$), 5.05 (d, 1H, C_2-H); X-ray of this compound showed α-configuration at C_2.

1-Phenyl-3-(1-piperdinyl)tropanone oxime methiodide (14a)

M.p. 174-177° C; % yield = 81; ^1H NMR (D_2O) δ: 3.18 (s, 3H, $^+N-C\underline{H}_3$).

1-Phenyl-3-(1-pyrrolidinyl)tropanone oxime methiodide (14a)

M.p. 178-180° C; % yield - 78; ^1H NMR (D_2O) δ: 3.07 (s, 3H, $^+N-C\underline{H}_3$).

Quinuclidinone oxime methiodide

M.p. 258-260° C (decomposition); yield = 89; NMR (D_2O): 3.14 (s, 3H, $^+N-C\underline{H}_3$). ^1H NMR (D_2O) δ: 3.14 (s, 3H, $NC\underline{H}_3$).

2-(Hydroxymethylcarbonyl)pyridine oxime Methiodide (41)

m.p. 150-155°C
% yield = 50
IR (KBr) cm^{-1}: 3300 (broad, O-H stretching), 1660 (sharp, C=N stretching).
^{1}H NMR (DMSO-d$_6$): 3.1 (s, 3H, N-C$\underline{H}_3$); 4.6 (s, 2H, -C$\underline{H}_2$-); 7.4-7.9 (m, 4H, aromatic protons).
$C_8H_{11}N_2O_2$ requires (%)C = 32.65, H = 3.74, N = 9.52. Found (%)C = 32.56, H = 3.66, N = 9.29.

2,5-Bis(hydroxymethylcarbonyl)pyridine oxime Methiodide (43)

m.p. 208-210°C
% yield = 56
IR (KBr) cm^{-1}: 3280 (broad, O-H stretching), 1655 (sharp, C=N stretching).
^{1}H NMR (DMSO-d$_6$): 3.1 (s, 3H, C$\underline{H}_3$); 4.6 (s, 4H, 2 x C$\underline{H}_2$); 7.4-7.8 (m, 3H, aromatic protons).
$C_{10}H_{14}N_3O_4I$: requires (%)C = 32.69, H = 3.81, N = 11.44, I = 34.60. Found (%)C = 32.63, H = 3.68, N = 11.52,
I = 34.34.

2-(Methoxymethylcarbonyl)pyridine oxime Methiodide (48)

m.p. 160-162°C
% yield = 48
IR (KBr) cm^{-1}: 3280 (broad, O-H stretching), 1645 (sharp, C=N stretching).
^{1}H NMR (DMSO-d$_6$) δ: 3.1 (s, 3H, C$\underline{H}_3$), 3.3 (s, 3H, OC$\underline{H}_3$), 4.6 (s, 2H, C$\underline{H}_2$), 7.3-7.8 (m, 4H, aromatic protons).
$C_9H_{12}N_2O_2I$: requires (%)C = 35.17, H = 3.90, N = 9.12, I = 41.36. Found (%)C = 35.20, H = 3.84, N = 9.08, I = 41.29.

2,5-Bis(Methoxymethylcarbonyl)pyridine oxime Methiodide (49)

m.p. = 196-198°C
% yield = 52
IR (KBr) cm^{-1}: 3320 (broad, O-H stretching), 1660 (sharp C=N stretching).
^{1}H NMR (DMSO-d$_6$) δ: 3.1 (s, 3H, N-C$\underline{H}_3$), 3.3 (s, 6H, 2 x OC$\underline{H}_3$), 4.7 (s, 4H, 2 x -CH$_2$-), 7.4-7.9 (m, 3H, aromatic protons).
$C_{12}H_{18}N_3O_4I$ requires (%)C = 36.45, H = 4.55, N = 10.63, I = 32.15. Found (%)C = 36.36, H = 4.48, N = 10.58, I =
32.32.

Attempted Reactions Between Oximes and Chloromethyl Methyl Ether

Four oximes, namely, 4-piperidone, tropan-3-one, 1-phenyl-3-(1-piperidinyl)-, and 1-phenyl-3-(1-pyrrolidinyl) propanones, were treated with chloromethyl methyl ether, but only corresponding hydrochlorides were obtained after the work-up and recrystallization.

Attempts at Making Bis-quaternary Salts

We are trying to prepare bis-oxime quaternary salts. The details are given in the following description:

Preparation of bis-1,3-(4-oximino-1-methylpiperidinium)propane dibromide

Method A consists of the following steps:

Step I: Bis-1,3-(4-piperidone)propane:

4-Piperidone hydrochloride monohydrate (0.02 mole) was put in a 100 ml round bottom flask and 30 ml of methanol was added. Then 0.02 mole of anhydrous potassium carbonate was added and the mixture was stirred. To the stirring mixture was slowly added a solution of 1,3-dibromopropane (.01 mole) in methanol (5 ml) and the mixture was allowed to stir overnight. The next day, methanol was evaporated and water added; the solution was saturated with K_2CO_3 and extracted with $CHCl_3$ to yield about 2.5 viscous oil, which was used without purification in the next step.

MS: m/z 238 (M^+ 1.2), 180 (2.3), 179 (11), 150 (10), 139 (16), 126 (7), 112 (100), 99 (15), 98 (15), 96 (31)

Step II: 1,3 Bis-(4 oximino-1 piperidinyl)propane

Bis-ketone (0.01 mole), obtained in the last step, was dissolved in methanol (5 ml) and added to a solution of hydroxylamine hydrochloride (0.011 mole) in methanol. The mixture was stirred for 2 hours. A solid (oxime hydrochloride) separated out of the solution. This solid was dissolved in water and the solution was saturated with K_2CO_3. The usual work-up using extraction with methanol gave about 45% gummy mass.

I.R.: no carbonyl absorption

MS: m/z 268 (M^+, 1.8), 251 (12), 138 (82), 127 (100), 111 (16.5), 110 (20), 96 (25), 83 (10), 82 (27), 70 (25)

Step III

The last mentioned bis oxime could not yield the corresponding methiodide when treated with methyl iodide. We are still working on this problem and are trying to crystallize bis oxime.

Method B

To a solution of 4 piperidone oxime (.01 mole) in methanol was added an excess of 1,3-dibromopropane and the mixture was stirred at room temperature for several days. After 5-6 days a colorless crystal separated out. Filtering the solid and washing with cold ethanol and recrystallization from ethanol yielded needle-shaped colorless crystals; m.p. 185-187°C. Br test with $AgNO_3$ + ve. NMR does not help in characterization. The mass spectrum does not show any molecular ion or peak which could help in characterization of the product.

The sample of this compound has been submitted for elemental analysis, which can probably tell us about the structure.

Quinuclidinone oxime also gave crystalline solid, m.p. 72-80°C (decomposed).

Attempts at Preparing 2-β-Hydroxytropanone

The following methods using trimethylsilyl and ether as starting material were tried:

Preparation of Trimethylsilyl and Ether (12) from Tropanone[9]

To a solution of 6.52 g. (0.3 mole) of chlorotrimethylsilane and 12.12 g. (16.7 ml, 0.06 mole) of triethylamine (dried over $LiACIH_4$ and distilled) in 20 ml of dimethylformamide was added 7.0 g. (0.05 mole) of tropan-3-one. The resulting mixture, from which some pale yellow solid separated immediately and more separated during the reaction, was refluxed with stirring for 48 hours and then cooled, diluted with 100 ml of pentane, and washed with three 50 ml portions of cold aqueous $NaHCO_3$. The aqueous layer was extracted with pentane. The combined pentane extract was dried ($MgSO_4$) and concentrated under a rotary evaporator to yield crude silyl and ether, which was purified by vacuum distillation and gave an oil.

% yield = 40.
[b.p. 95-100°C/25 mm]
I.R. (Neat) cm^{-1}: 1690 ($C=C-OMe_3Si$)
NMR (without using internal standard TMS): 0 (9H s $(CH_3)_3$-Si)
4.68 (1H d C_2 H)

MS: m/z 207 (M^+).

Oxidation of Silyl Enol Ether (12)

I. Using m-chloroperbenzoic acid (MCPBA)[13]

To a stirred solution of 12 in CH_2Cl_2 (containing a little $NaHCO_3$) was added 1.1 equivalents of 85% MCPBA (Aldrich) in portions over 15-20 minutes. After the resulting mixture was stirred for 1 hour, aqueous Na_2SO_3 was added to destroy the excess of oxide. The solution was saturated with K_2CO_3 and then extracted with ether. The ether extract was dried and concentrated in vacuo. I.R. and NMR spectral data showed the formation of tropan-3-one only.

II. Using Osmium tetroxide/N-methylmorpholine-N-oxide (NMMO•H_2O)[14]

A solution containing 2.0 mmole of 12 in 3 ml of acetone was added at -5°C to a mixture containing 0.04 mmole of osmium tetroxide (added as a solution in 0.91 ml of t-butyl alcohol), 284 mg (2.1 mmole) of NMMO•H_2O, and 4 ml of H_2O in 9 ml of acetone. The resulting mixture was stirred at 0°C for 3 hours, then allowed to warm to 25°C and stirred an additional 6 hours. Sodium hydrosulfite (0.35 g.) and florisil (1.34 g.) were added, and the suspension was stirred and filtered to remove osmium-containing material. The filtrate was acidified with sulfuric acid, diluted with water (10 ml) and then basified with K_2CO_3. Extracting the solution with ether gave tropanone only.

III. Osmium tetroxide/pyridine

To a solution of 12 (2 mmole) in CH_2Cl_2, osmium tetroxide (2 mmole) in pyridine was added dropwise. The mixture was allowed to stir overnight. Work-up gave tropan-3-one.

General Procedure for the Preparation of Butane-1,4-Diones (50a-e)

To a suspension of iodosobenzene (11 mmol) in dry dichloromethane (100 ml) under nitrogen was added boron trifluoride (0.03 mol) with stirring. The mixture was cooled to -40°C and then to the resulting stirred and cold mixture was added silyl enol ether (20 mmol). The reaction mixture was stirred for 1 h at -40°C and then for an additional 1 h at room temperature. During this period the light yellow reaction mixture changed to a dark brown (or light green) solution. This solution was basified with a saturated aqueous solution of sodium hydrogen carbonate and the aqueous layer was extracted with dichloromethane (3 x 25 ml). The organic extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to yield the crude product which contained iodobenzene and small amount of recovered ketone (1) as impurities. Addition of ethanol (5-10 ml) separated the crystalline product. Analytical samples were prepared by recrystallization from a suitable solvent. The results of this reaction on known compounds are summarized in Table 2.

Table 5. Butane-1,4-diones (51a-e) prepared by the hypervalent iodine oxidation of silyl enol ethers.

Compd.	(Yield %)	MP(°C)	[Lit]m.p.(°C)
13a	48	143-144	144[15]
13b	58	150-151	151[6]
13c	62	150-151	150[17]
13d	52	195-197[a]	
13e	64	159-160	158-160[18]

[a] IR (Nujol) cm^{-1}: 1695 (sharp C=O stretching)

^{1}H NMR ($CDCl_3$) δ: 3.40 (s, 4H, 2 x CH_2), 7.81-8.33 (m, 8H, aromatic protons).

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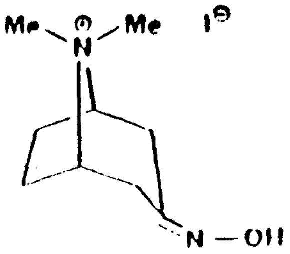
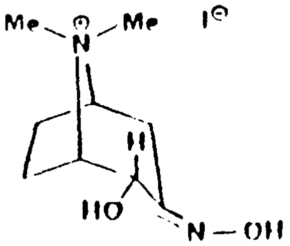
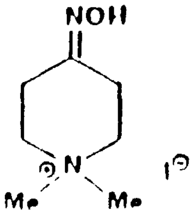
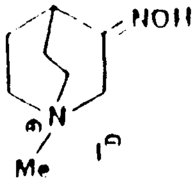
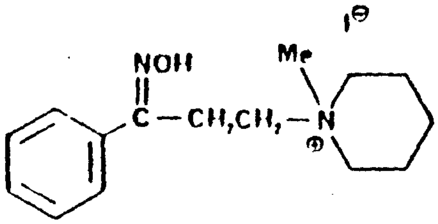
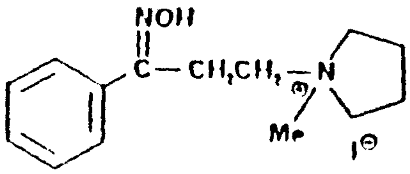
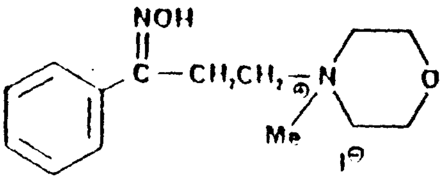
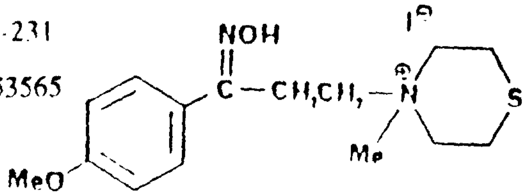
Appendix 1. Compounds Submitted to WRAIR

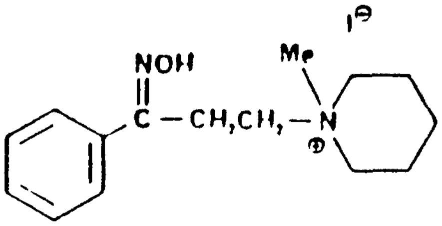
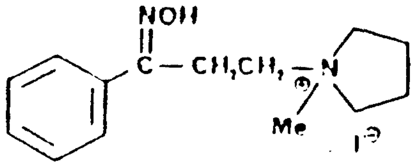
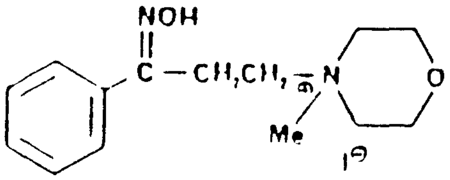
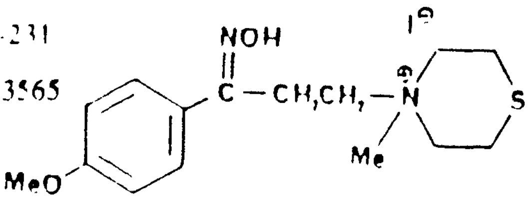
Samples Submitted for Test and Evaluation

UICC Code No.	WRAIR Code No.	Compound Structure	Compound Name	Quantity(2)
OP-51	WR-108591		Tropan-3-one oxime methiodide	2.0 g
OP-28	WR-253574		2-α-Hydroxytropan-3-one oxime methiodide	1.1 g
OP-147	WR-253561		4-Piperidone oxime methiodide	2.1 g
OP-151	WR-253553		3-Quinuclidinone oxime methiodide	1.6 g

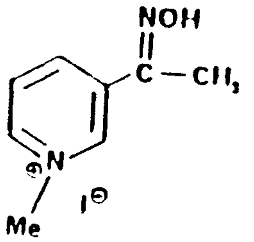
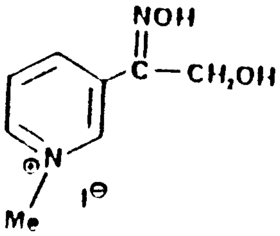
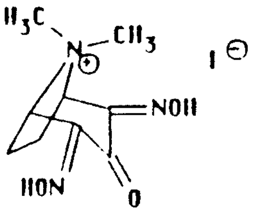
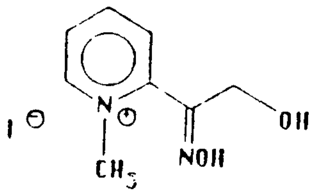
Samples Submitted for Test and Evaluation

UICC Code No.	WRAIR Code No.	Compound Structure	Compound Name	Q
OP-137	WR-253564		Propanone[1-phenyl-3-(1-piperidinyl)] oxime methiodide	
OP-138	WRWR-253560		Propanone[1-phenyl-3-(1-pyrrolidinyl)] oxime methiodide	1
OP-143	WR-2535672		Propanone[1-phenyl-3-(4 morpholinyl)] oxime methiodide	1
OP-231	WR-253565		Propanone[1-p-anisyl 3-(4 thiomorpholinyl)] oxime methiodide	2.0

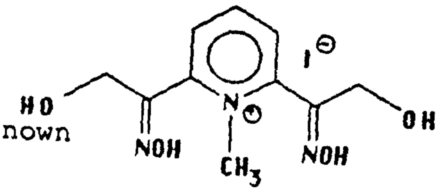
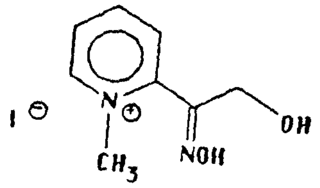
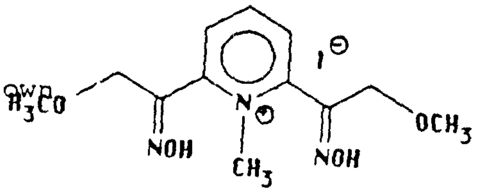
Samples Submitted for Test and Evaluation

UICC Code No.	WRAIR Code No.	Compound Structure	Compound Name	Quantity(2)
OP-137	WR-253564		Propanone[1-phenyl-3-(1-piperidinyl)] oxime methiodide	1.1 g
OP-138	WR-253560		Propanone[1-phenyl-3-(1-pyrrolidinyl)] oxime methiodide	1.2 g
OP-143	WR-253567		Propanone[1-phenyl-3-(4'-morpholinyl)] oxime methiodide	1.0 g
OP-231	WR-253565		Propanone[1-p-anisyl-3-(4-thiomorpholinyl)] oxime methiodide	2.0 g

Samples Submitted for Test and Evaluation

UICC Code No.	WRAIR Code No.	Compound Structure	Compound Name	Quantity(2)
OP-220	WR-253551		Ethanone[1-(3-pyridinyl)] oxime methiodidie	1.0 g
OP-205	WR-253552		Ethanone[1-(3-pyridinyl)2-hydroxy]oxime methiodide	0.5 g
PRV-122	WR-255130		2,4-Bisoximinotropane-3-one methiodide	2.0 g
OP-501	WR-254739		2-(Hydroxymethylcarbonyl)-pyridine oxime methiodide	2.0 g

Samples Submitted for Test and Evaluation

UICC Code No.	WRAIR Code No.	Compound Structure	Compound Name	Quantity(2)
OP-576	WR- Unknown		2,6-Bis(hydroxymethylcarbonyl)-pyridine oxime methiodide	2.0 g
OP-666	WR-Unknown		2-(Methoxymethylcarbonyl)-pyridine oxime methiodide	2.0 g
OP-675	WR-Unknown		2,6-Bis(methoxymethylcarbonyl) pyridine oxime methiodide	2.0 g

11. Publications From the First Year

1. Hypervalent Iodine Oxidation of α,β-Unsaturated Ketones: Chromone, Flavone, Chalcone, and Flavanone: R. M. Moriarty, O. Prakash and W. A. Freeman, J. Chem. Soc. Chem. Comm., 927 (1984).
2. Steric Effects in the Hypervalent Iodide Oxidation of Ketones: R. M. Moriarty and I. Prakash, and H. A. Musallam, Tetrahedron Lett., 5867 (1984).
3. Intramolecular Participation in Hypervalent Iodine Oxidation. The Synthesis of Coumaran-3-one, Aurone and Isoaurone: R. M. Moriarty, O. Prakash, I. Prakash and H. A. Musallam, J. Chem. Soc. Chem. Comm., 1342 (1984).
4. Synthesis of α-Hydroxydimethylacetals from Nitrogen Heterocyclic Ketones using Hypervalent Iodine Oxidation, R. M. Moriarty, O. Prakash, C. T. Thachet and H. A. Musallam, Heterocycles, 23 633 (1985).
5. Hypervalent Iodine Oxidation of Enol Silyl Ethers Using Boron Trifluoride Etherate. A Direct Route to Aryl Hydroxymethylketones, Synthesis, 943 (1985).
6. Hypervalent Iodine Oxidation of Flavone. Synthesis of cis and trans-3-Hydroxyflavanones: R. M. Moriarty and O. Prakash, J. Org. Chem., 50, 151 (1985).
7. Synthesis and Stereochemistry of 2,5-Dimethoxy 3,6-Disubstituted 1,4-Dioxanes obtained from α-Hydroxydimethyl Acetals: R. M. Moriarty and K.-C. Hou, J. Org. Chem., accepted May 1984.
8. Hypervalent Iodine Oxidation of Chromium Tricarbonyl Complexes of Benzocycloalkanones and Acetophenone, R. M. Moriarty, S. G. Engerer, O. Prakash, I. Prakash, U. S. Gill and W. A. Freeman, J. Chem. Soc. Chem. Commun. 1715 (1985).
9. Use of Hypervalent Iodine Oxidation for the C(3)-Hydroxylation of Chromone, Flavone and α-Naphtoflavone, R.M. Moriarty, O.Prakash and H.A. Musallam, J.Heterocyclic Chem, 22, 583 (1985).
10. Solvohyperiodination. A Comparison with Solvothallation, R. M. Moriarty, J. S. Khosrowshahi and Om Prakash, Tetrehedron Letters, 26, 2961 (1985).
11. Carbon-Carbon Bond Formation Using Hypervalent Iodine Under Lewis Acid Conditions: 1,4-Diarylbutane-1,4-diones, J. Chem. Soc. Chem. Commun. 420 (1985).

Papers in Preparation

1. Substituted Tropanone Oximes as Acetylcholine-Esterase Reactivators: R. M. Moriarty, T. Dougherty and O. Prakash.
2. The X-ray Structure of 2α-Hydroxy-3-Tropanone Oxime Methiodide: R. M. Moriarty, W. A. Freeman and O. Prakash.