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(U) Bridged Bicyclic Systems as Acetylcholinesterase Reactivators and Pretreatment Drugs

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Robert M. Moriarty

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19. ABSTRACT (Continue on reverse if necessary and identify by block number)

During the past year, (+) and (-) 2-oximinotropan-3-one methiodides have been synthesized as well as the racemic compound (±) 2-oximinotropan-3-one methiodide. The regioisomeric (+) and (-) 3-oximinotropan-3-one methiodides have also been synthesized. Binding constants to AChE, pKa's and reactivation activities for these compounds have been determined. Atropine-like 3-acetophenyl tropine oxime hydrochloride has been synthesized and submitted for testing. Syntheses of 4-(1-piperidinyl)-4-phenylcyclohexanone oxime methiodide, 1-(1-phenylcyclohexyl)-4-piperidone oxime methiodide and 2-benzylidene-3-quinuclidinone oxime hydrochloride have been achieved. These compounds have been submitted for testing. Several oximes and a-hydroxy oximes containing the thiazole nucleus and the quinoline nucleus have been synthesized and submitted for testing. Similarly, antipyrine-4-aldoxime has been synthesized and submitted for testing. O-(N-Methyl carbamoyl)-3-tropinone oxime methiodide has been synthesized and submitted for testing.

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BRIDGED BICYCLIC SYSTEMS AND PRETREATMENT DRUGS AS ACETYLCHOLINESTERASE REACTIVATORS

Annual Report
July 15, 1986 through July 14, 1987

Robert M. Moriarty

December 15, 1989

Supported by
U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21702-5012

Contract Number DAMD17-85-C-5190

University of Illinois at Chicago
Department of Chemistry
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Chicago, Illinois 60680

1. SUMMARY

During the past year, (+) and (-) 2-oximinotropan-3-one methiodides have been synthesized as well as the racemic compound (±) 2-oximinotropan-3-one methiodide. The regioisomeric (+) and (-) 3-oximinotropan-3-one methiodides have also been synthesized. Binding constants to AChE, pKa's and reactivation activities for these compounds have been determined. Atropine-like 3-acetophenyl tropine oxime hydrochloride has been synthesized and submitted for testing. Syntheses of 4-(1-piperidinyl)-4-phenylcyclohexanone oxime methiodide, 1-(1-phenylcyclohexyl)-4-piperidone oxime methiodide and 2-benzylidene-3-quinuclidinone oxime hydrochloride have been achieved. These compounds have been submitted for testing.

Several oximes and α-hydroxy oximes containing the thiazole nucleus and the quinoline nucleus have been synthesized and submitted for testing. Similarly, antipyrine-4-aldoxime has been synthesized and submitted for testing.

O-(N-Methyl carbamoyl)-3-tropinone oxime methiodide has been synthesized and submitted for testing.

2. FOREWORD

This work was supported by the U. S. Army Medical Research and Development Under Contract No. DAMD17-85-C-5190.

The Principal Investigator thanks Diane E. Clarisse for kinetic measurements and Radhe K. Vaid, Pushpa R. Vavilikolanu, Beena K. Vaid and Thomas E. Hopkins for synthetic work. Invaluable suggestions and guidance in this project were given by H. A. Musallam and R. Engle of USAMRDC.

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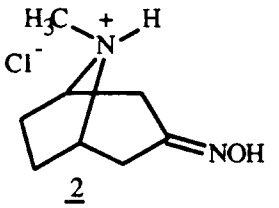
3. BACKGROUND

The aim of our study has been the synthesis of compounds that are structurally related to acetylcholine, modified to incorporate a nucleophilic oximino function. The purpose of these syntheses was to obtain compounds which could be used to reactivate phosphorylated acetylcholinesterase. It has been amply demonstrated that certain classes of compounds possess high affinity for the reactive site of the enzyme. Among the known classes, this study concentrates on those related to atropine, that is, systems containing the azabicyclo[3,2,1]octane system, phencyclidines, heterocyclic systems such as thiazcles, pyrazoles and piperidine analogues. It has been our aim to increase the ability of these compounds to reactivate the enzyme by increasing the stability of the oximate anion. This was done initially by placing an α-hydroxy function adjacent to the ketones. A more powerful stabilizing effect has been achieved using the α-keto group.

The following structural types fulfill these criteria, and 2, 3, 5, 8, 14, 20, 23, 28, 33, 37, 39, 43, 47, 51 and 54 have been synthesized and submitted to WRAIR in the past year.

Reactivators



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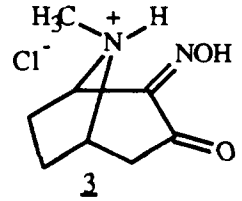

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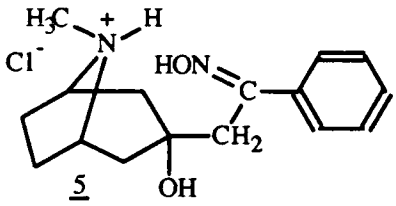

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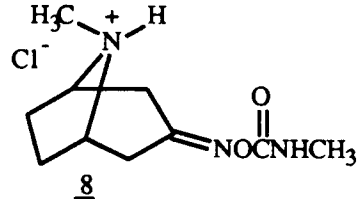

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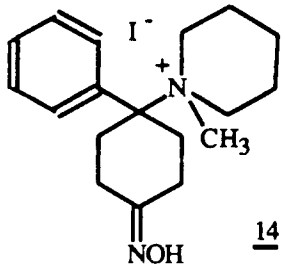
O-(N-Methylcarbamoyl)-3-tropinone Oxime Methiodide



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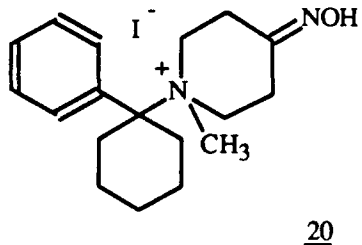

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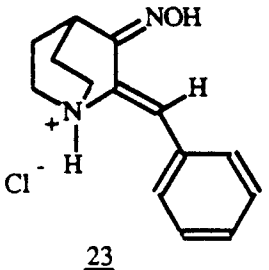
1-(1'Phenyl-1'-cyclohexyl)-4-piperidone Oxime Methiodide



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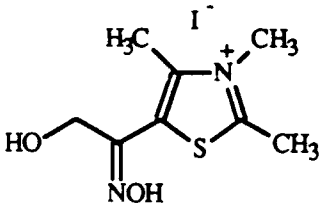
2-Benzylidine-3-Quinuclidinone Oxime Hydrochloride



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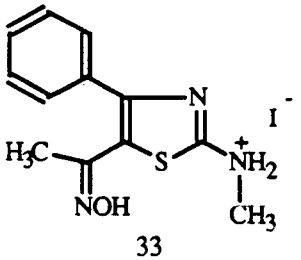
2,4-Dimethyl-5-(α-hyrdoxymethyloximino) Thiazole Methiodide



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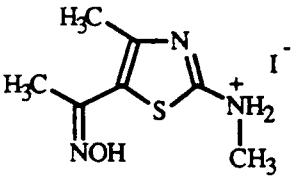

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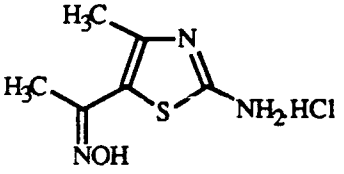
2-Methylamino-4-methyl-5-acetylthiazole Oxime Hydroiodide



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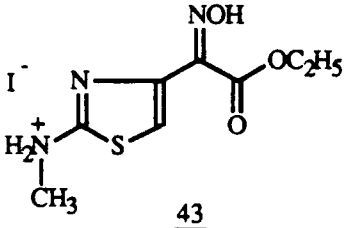
2-Amino-4-methyl-5-acetyloximino Thiazole Hydrochloride



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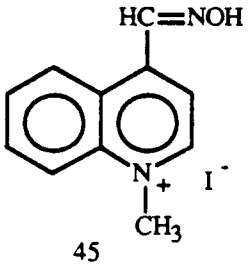
Ethyl-2-amino-α(hydroxyimino)-4-thiazole Acetate Methiodide



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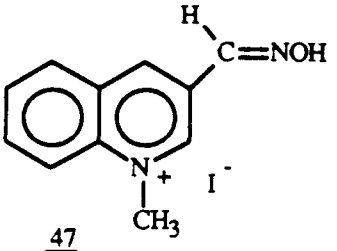
Quinoline-4-aldoxime Methiodide



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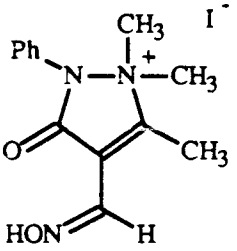
Quinoline-3-aldoxime Methiodide



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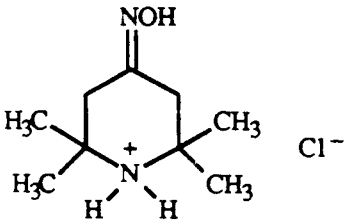
Antipyrine-4-aldoxime Methiodide



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2,2,6,6-Tetrametnyl-4-piperidone Oxime Hydrochloride

4. MAJOR ACCOMPLISHMENTS DURING THE YEAR

a. 2-Oximino-tropan-3-one hydrochloride has been synthesized in its racemic and optically active forms.

b. 3-α-Acetophenyltropine oxime hydrochloride has been synthesized.

c. 4-(1-Piperidinyl)-4-phenylcyclohexanone oxime methiodide and 1-(1-phenylcyclohexyl)-4-piperidone oxime methiodide have been synthesized.

d. 2-Benzylidene-3-quinuclidinone oxime hydrochloride has been synthesized.

e. Several oximes of the thiazole family have been successfully prepared.

f. O-(N-Methylcarbamoyl)-3-tropinone oxime methiodide has been synthesized.

g. Quinoline-3 and 4-aldoxime methiodides have been synthesized.

h. Antipyrine-4-aldoxime methiodide has been synthesized.

i. The pKa's and binding constants of the structurally related pair of compounds have been determined and compared.

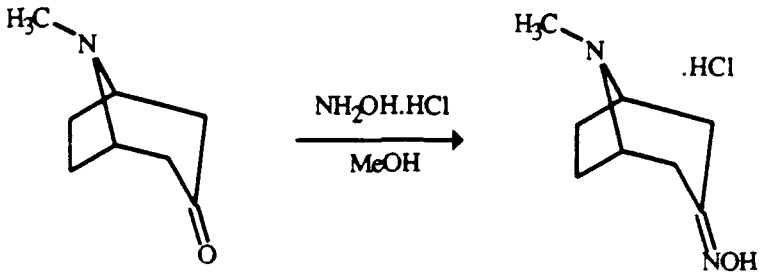
j. It is now possible (i) to gain insight into the stereospecificity of the active site for reactivators, and (ii) to synthesize various derivatives of the phencyclidine family which fit our structural and stereochemical criteria.

5. DISCUSSION OF SYNTHESIS

i) Azabicyclo[3.2.1] Compounds

Tropane-3-Oxime Hydrochloride (2)

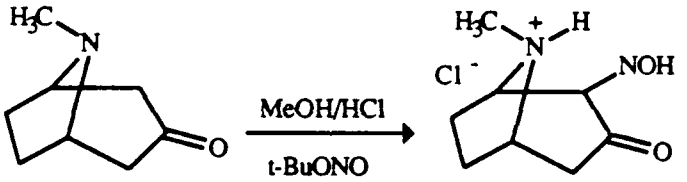
Tropan-3-one, on refluxing with hydroxylamine hydrochloride in methanol, yielded tropan-3-one oxime hydrochloride (2).



1 2

(+)2-Oximino Tropan-3-one Hydrochloride (3)

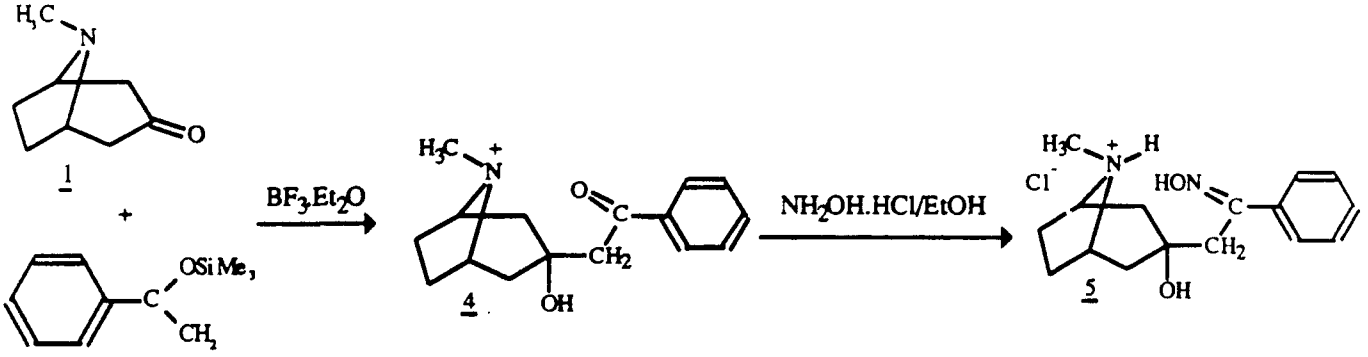
Treatment of tropan-3-one with t-butylnitrite in acidic media yielded 2-oximinotropan-3-one hydrochloride.



1 3

3-Hydroxy-3-phenacyl-8-azabicyclo[3.2.1]octane Oxime Hydrochloride (5)

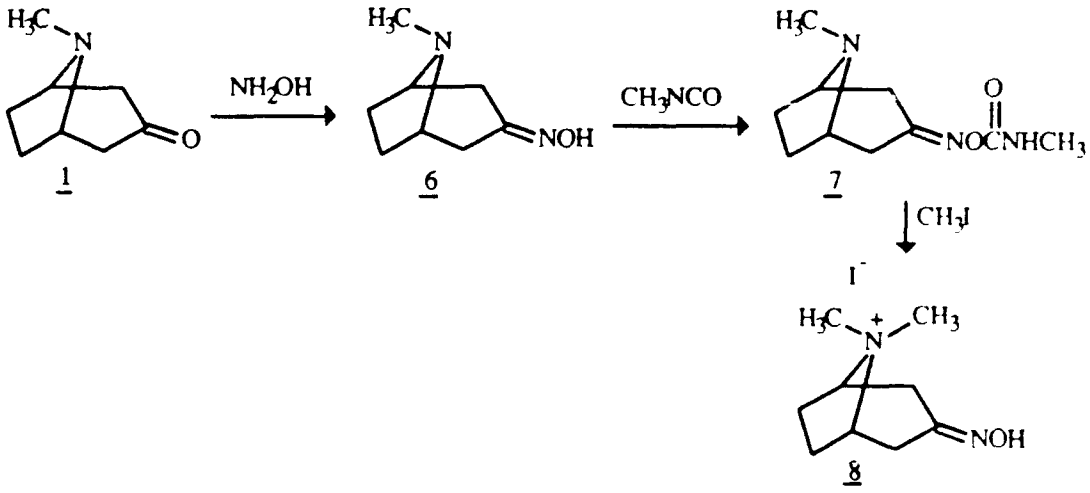
Reaction of tropan-3-one (1) with acetophenone enol silyl ether in the presence boron trifluoride etherate yielded 3-hydroxy-3-phenacyl-8-azabicyclo[3,2,1]octane (4). 4, on treatment with hydroxylamine hydrochloride, yielded 5.



1 4 5

O-(N-Methylcarbamoyl)-3-tropinone Oxime Methiodide (8)

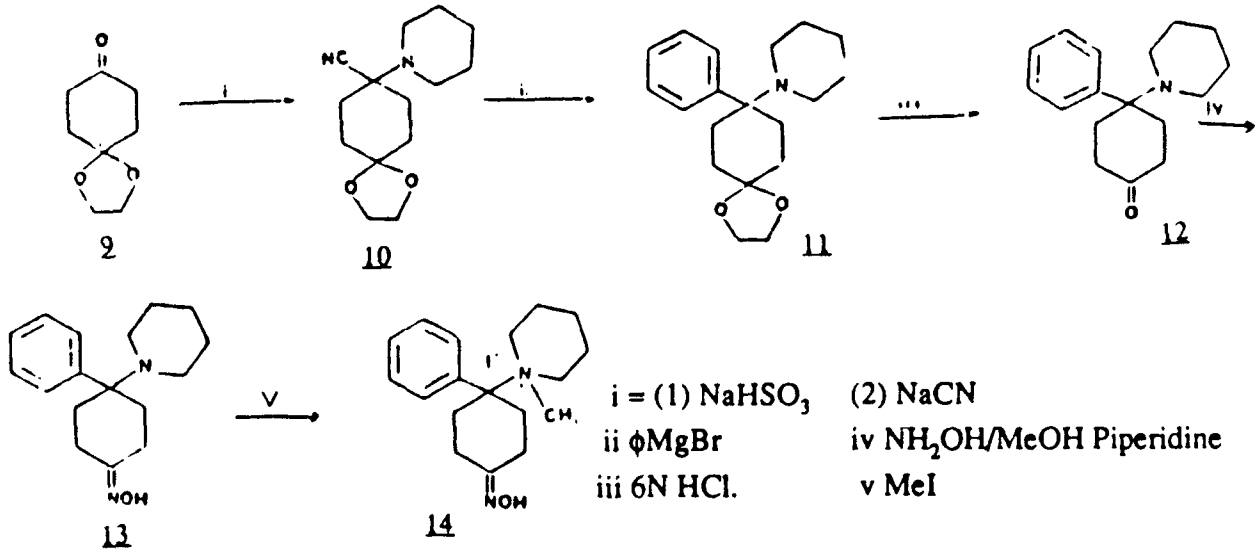
Tropan-3-one (1) on oximation with hydroxylamine yielded tropan-3-one oxime (6), which on reaction with methylisocyanate afforded O-(N-methylcarbamoyl)-3-tropinine oxime (7). 7, on treatment with methyliodide, yielded O-(N-methylcarbamoyl)-3-tropinone oxime methiodide (8).



ii) **Phencyclidine Compounds**

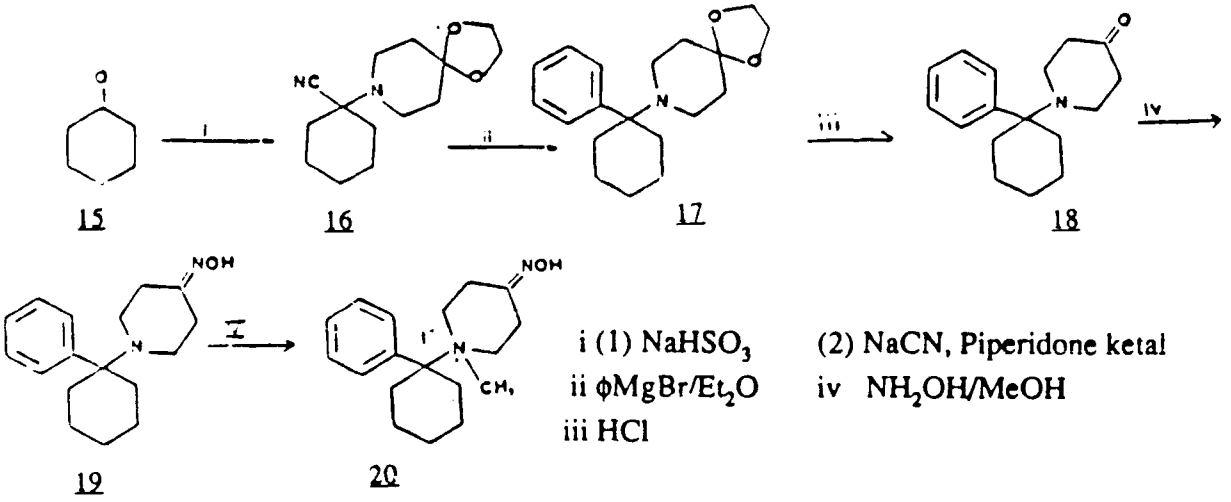
4-(1'-Piperidinyl)-4-phenylcyclohexanone Oxime Methiodide (14)

Treatment of 1,4-cyclohexanedione mono-ethylene ketal (9) with $NaHSO_3$ followed by aqueous solution of NaCN and piperidine yielded 10. 10, on reaction with phenylmagnesium bromide followed by treatment with HCl, yielded 4-(1-piperidinyl)-4-phenyl cyclohexanone (12) which, on oximation followed by quaternization using methyliodide in dichloromethane, yielded 4-(1'-piperidinyl)-4-phenylcyclohexanone oxime methiodine (14).



1-(1'-Phenylcyclohexyl)-4-Piperidone Oxime Methiodide (20)

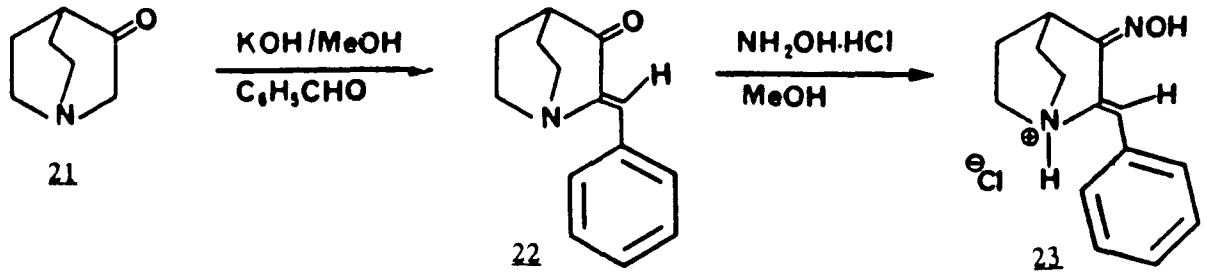
Cyclohexanone (15), on reaction with $NaHSO_3$ followed by a mixture of NaCN and 4-piperidone ketal yielded 16. 16, on reaction with phenylmagnesiumbromide, afforded 17. Hydrolysis of 17 with HCl resulted in the formation of 18. Oximation of 18 followed by quaternization yielded 1-(1'-phenylcyclohexyl)-4-piperidone methiodide (20).



15 16 17 18 19 20

2-Benzylidene-3-Quinuclidinone Oxime Hydrochloride (23)

Treatment of 3-quinuclidone (21) with methanolic KOH followed by the addition of benzaldehyde yielded 22. 22, on reaction with hydroxylamine hydrochloride in methanol, yielded 2-benzylidene-3-quinuclidinone oxime hydrochloride (23).



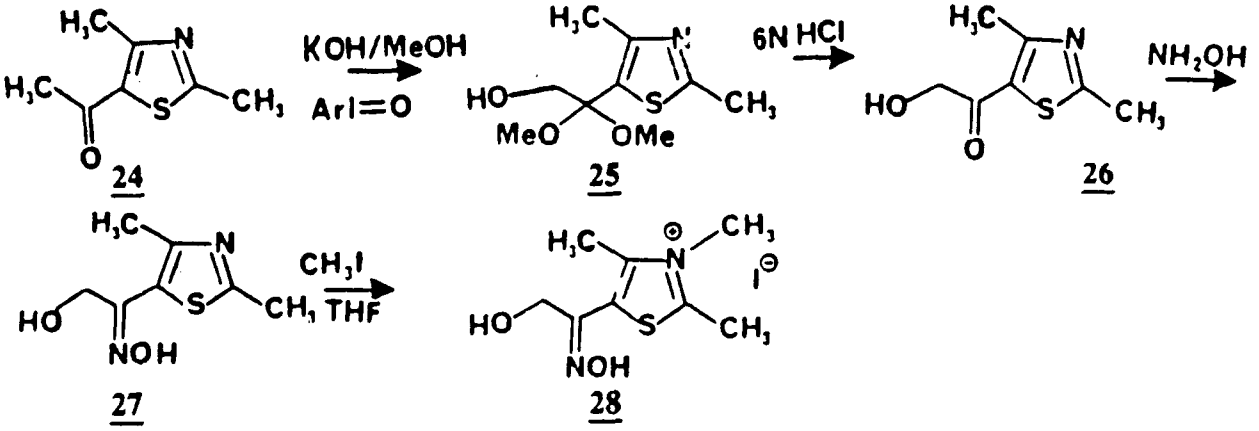
21 22 23

iii) **Heterocyclic Compounds**

Keeping in view the biological importance of various heterocyclic nuclei, anti-inflammatory drugs like fenclozic acid, phenbutazone and oxyphenbutazone contain thiazole and pyrazole nuclei. Similarly, the anti-malarial drugs mephlon and quinine contain quinoline nuclei. It was therefore planned to synthesize various oximes containing these heterocyclic nuclei. The following oximes were synthesized.

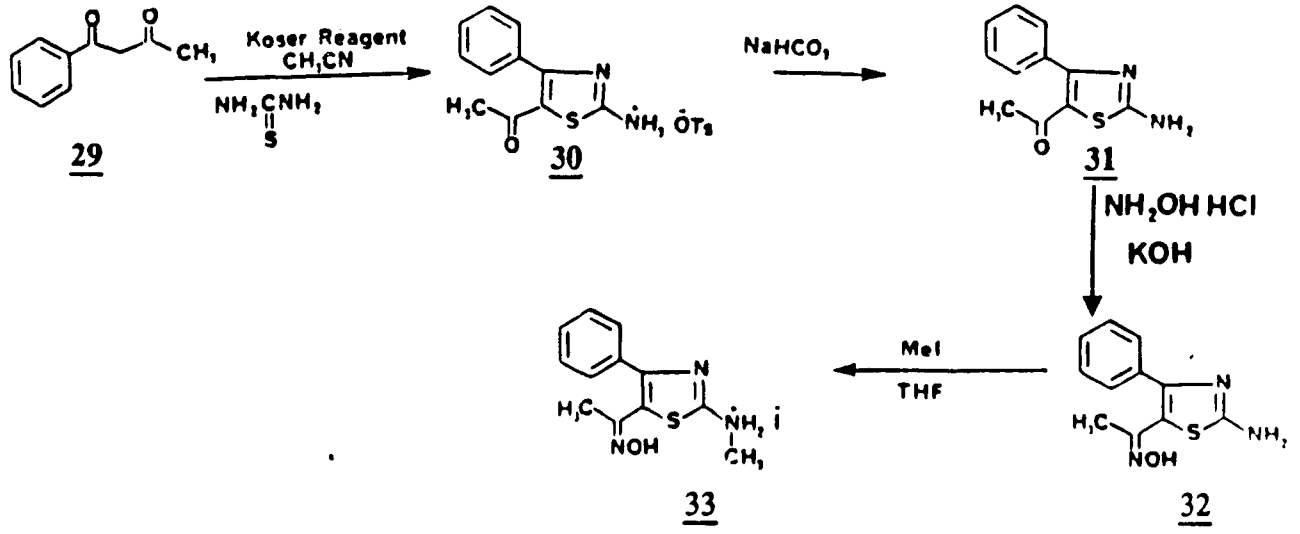
2,4-Dimethyl-5-(α-hydroxymethyloximino)thiazole Methiodide (28)

Treatment of 2,4-dimethyl-5-acetylthiazole (24) with methanolic KOH followed by iodosobenzene yielded 5-(α-hydroxydimethylacetal)-2,4-dimethylthiazole (25) which, on hydrolysis with HCl, afforded α-hydroxyketone (26). Oximination of 26 followed by treatment with methyl iodide in tetrahydrofuran yielded 2,4-dimethyl-5-(α-hydroxymethyloximino)thiazole methiodide (28).



2-Methylamino-4-phenyl-5-acetyl Thiazole Oxime Hydroiodide (33)

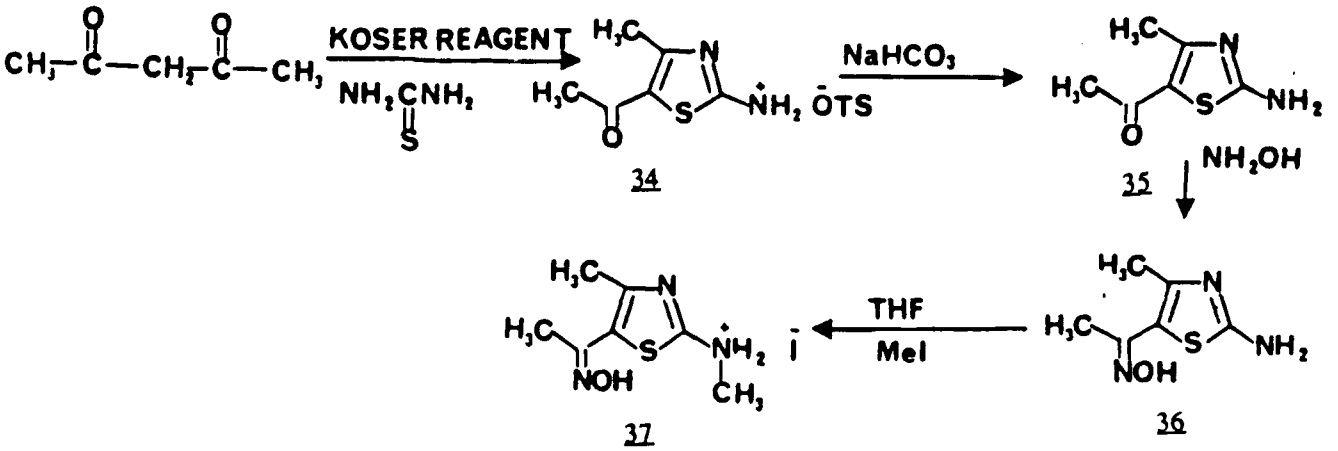
Benzoylacetone (29), on treatment with [hydroxy(tosyloxy)iodo]benzene (Koser Reagent) in CH_3CN followed by thiourea and sodium bicarbonate solution, yielded 2-amino-4-phenyl-5-acetyl thiazole (31). Oximination of (31) with NH_2OH afforded (32) which, on quaternization with methyl iodide in THF, yielded 2-methylamino-4-phenyl-5-acetyloximino hydroiodide (33).



2-Methylamino-4-methyl-5-acetyloximino Hydroiodide (37)

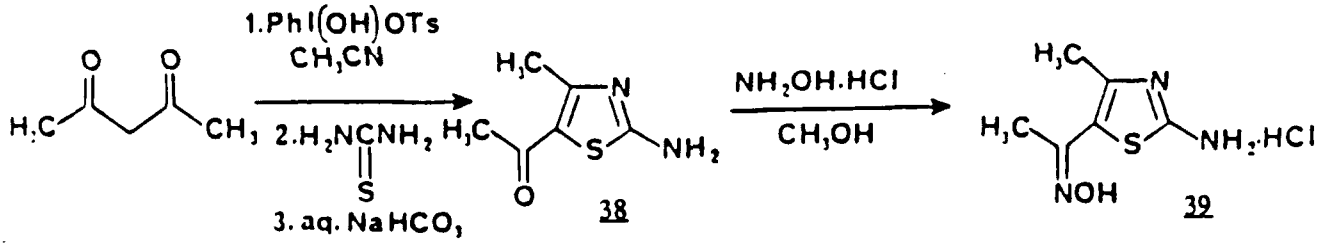
Treatment of 2,4-pentanedione with [hydroxy(tosyloxy)iodo]benzene (Koser Reagent) in CH_3CN, followed by thiourea and sodium bicarbonate, yielded 2-amino-4-methyl-5-acetyl thiazole (35) which, on

reaction with NH_2OH (generated by the reaction of $NH_2OH.HCl$ with KOH in methanol), afforded 2-amino-4-methyl-5-acetyloximino thiazole (36). Quaternization of (36) was achieved using CH_3I in THF to yield (37).



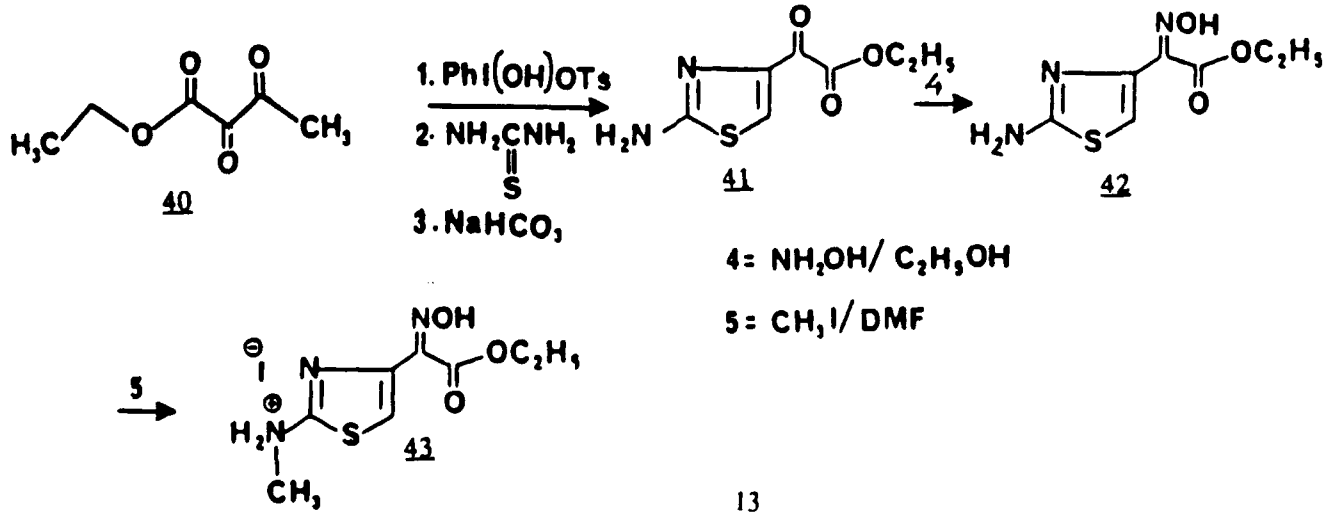
2-Amino-4-methyl-5-acetyl Oximinothiazole Hydrochloride (39)

2,4-Pentanedione, on treatment with [hydroxy(tosyloxy)iodo]benzene in CH_3CN followed by thiourea and sodium bicarbonate solution, yielded 2-amino-4-methyl-5-acetyl thiazole (38) which, on treatment with hydroxyamine hydrochloride in methanol, afforded 2-amino-4-methyl-5-acetyloximinothiazole hydrochloride (39).



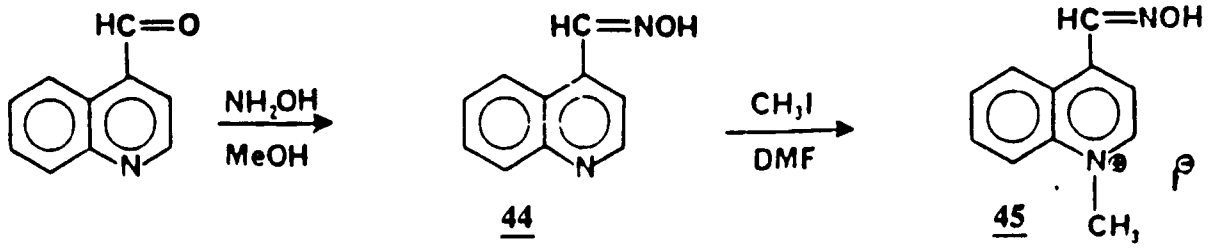
Ethyl-2-amino-α-(hydroxyamino)-4-thiazolacetate Methiodide (43)

Reaction of 40 with [(tosyloxy)iodo]benzene in methanol followed by addition of thiourea yielded tosylate salt of 41, which on neutralization with $NaHCO_3$ yielded ethyl-2-amino-4-thiazole acetate (41). Oximation of 41 followed by quaternization with methyl iodide yielded 43.



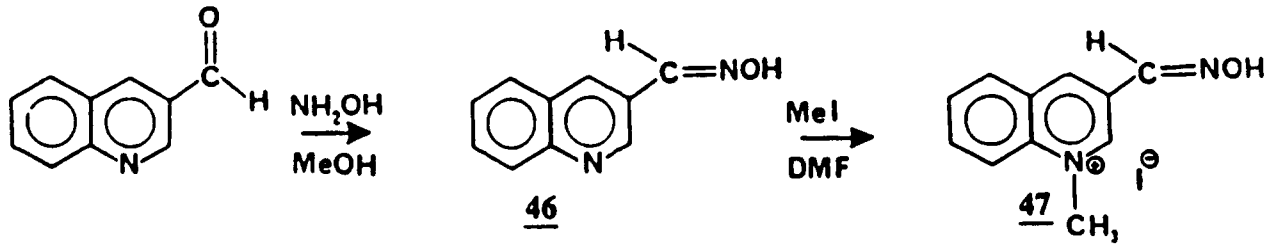
Quinoline-4-aldoxime Methiodide (45)

Quinoline-4-aldehyde, on oximination, yielded the oxime (44) which, on treatment with methyl iodide in DMF, afforded the quaternized quinoline-4-aldoxime methiodide (45).



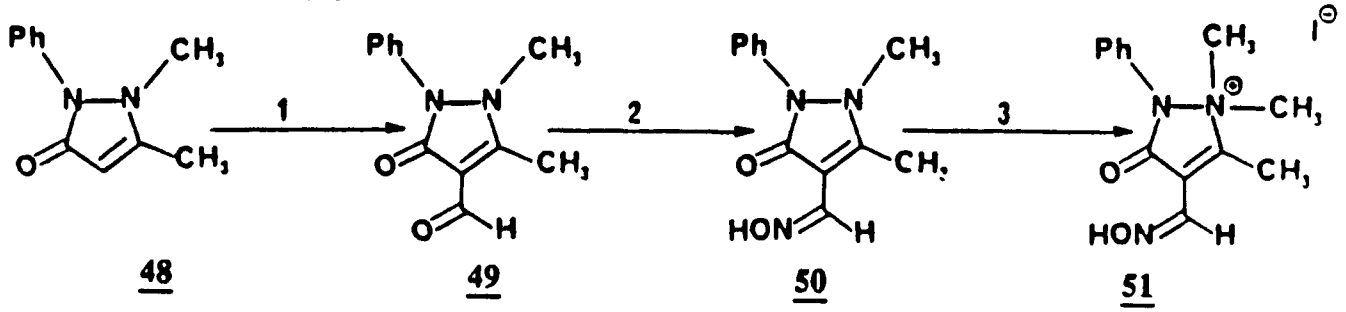
Quinoline-3-aldoxime Methiodide (47)

Treatment of quinoline-3-aldehyde with hydroxylamine (generated by the reaction of $NH_2OH.HCl$ with methanolic KOH) afforded quinoline-3-aldoxime (46). 46, on quaternization with methyl iodide in DMF, yielded quinoline-3-aldoxime-methiodide (47).



Antipyrine-4-aldoxime Methiodide (51)

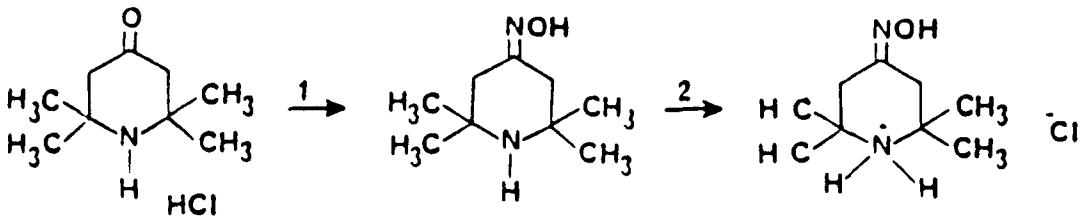
Antipyrine (48), on formylation with DMF/$POCl_3$, yielded antipyrine-4-aldehyde (49) which, on oximation, yielded (50). Quaternization of 50 using methyliodide in dimethylforamide yielded antipyrine-4-aldoxime methiodide (51).



1. DMF/$POCl_3$; 2. NH_2OH•HCl/MeOH-CH_3CO_2Na; 3. DMF/CH_3I

2,2,6,6-Tetramethyl-4-piperidone Oxime Hydrochloride (54)

This compound was synthesized by oximation of 2,2,6,6-tetramethyl-4-piperidone (52) followed by quaternization using dry HCl gas in methanol.



52 53 54

1. NH_2OH/MeOH/NaOAc
2. MeOH/HCl

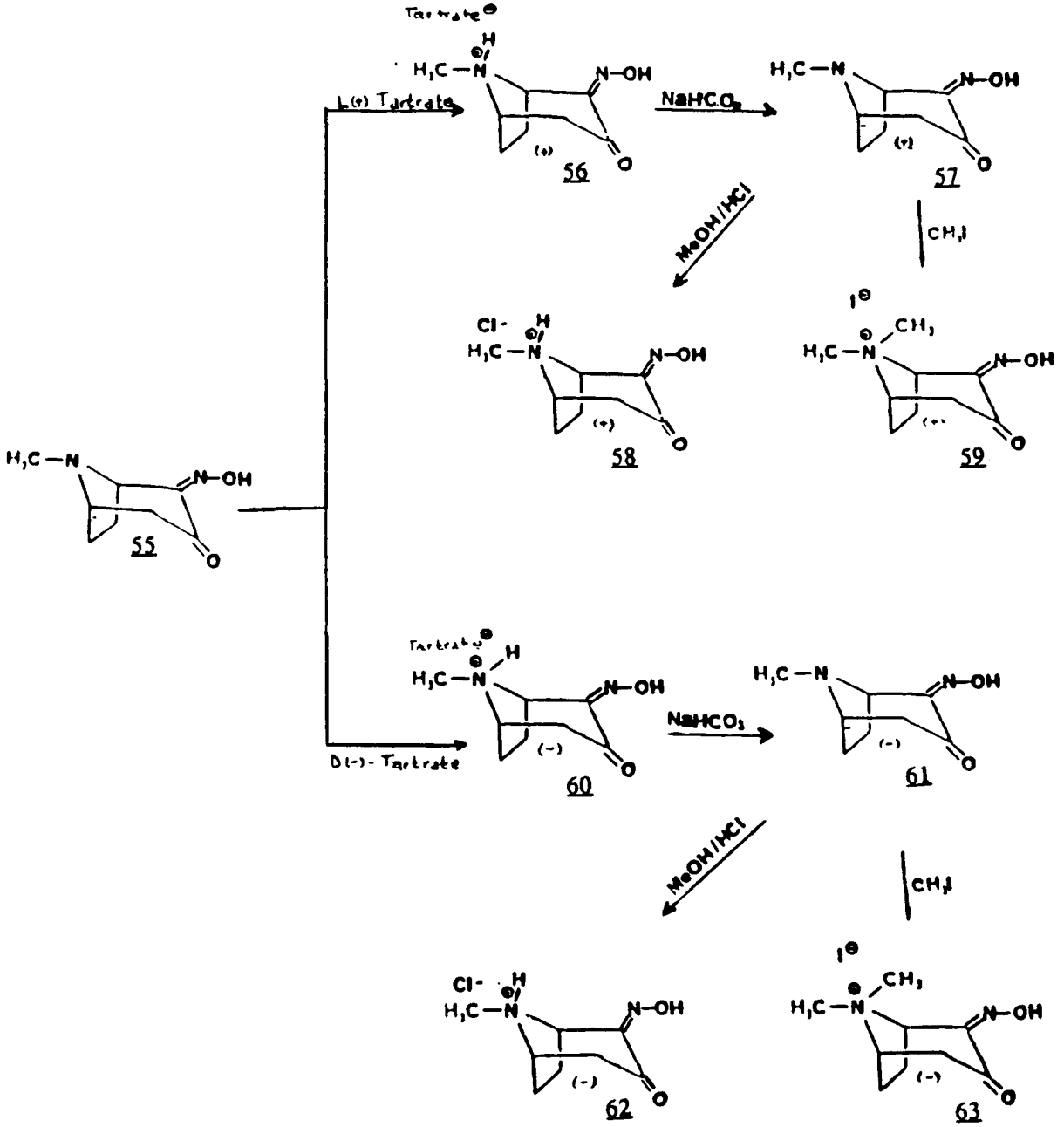
iv) **Optically Active Azabicyclic Compounds**

The best approach to prepare the desired optically active azabicyclic compounds is by using the method of α-nitrosation in acidic medium. This proved to be an excellent method. Use of concentrated HCl and t-BuONO in methanol gave good yields (66%) of the hydrochloride of the α-ketooxime (3). The product precipitated out of the methanol solution and had only to be filtered. The free base, 55 in this case, was obtained as a solid on treatment of an aqueous solution of the HCl salt (3) with bicarbonate. The oxime precipitated out of solution as pH approached 6.0.

The accessibility of 2-oximino 3-tropinone made the resolution of the racemate a conceivable problem to solve. Initially, the racemic oxime (55) was reacted with (+) camphor sulfonyl chloride in hopes of obtaining the O-camphorsulfonate and separating the diastereomers formed. This method did not meet with success and an alternative solution had to be found. The failure of this attempt might be linked to the relative stability of the oximate anion. It is the anion that must react with the sulfonyl chloride. Later attempts to derivatize the oxime with isocyanates also gave unstable products. The relative unfavorability of reaction at the oximate is altered in the biochemical scenario by the enzyme.

In 1971, Atkinson and McRitchie synthesized (±) 2-tropinone using the Bell and Archer sequence and reduced the ketone to the racemic alcohols. The (+) 2-tropanol and (-) 2-tropanol were isolated using (+) tartaric acid and (-) tartaric acid.[1] Using the same methodology (Scheme 1), the D and L-tartaric acids were employed to resolve (±) 2-oximino 3-tropinone (55). Similarly, the (+) isomer (57) was isolated using L-(+) tartaric acid to make tartrate, and by taking advantage of the difference in solubilities for the diastereomers. The optical purity was determined by using a Eu(III) shift reagent (Figure 1).

The spectrum of the Eu(III) complex of 57 shows no splitting, particularly of the N-methyl which normally appears as a sharp singlet. With the shift reagent, one expects a separation of this signal into two peaks of differing intensities depending on the relative amounts of the two isomers. Since this is not seen, one may infer that only one isomer is present in any appreciable amount. The (-) isomer (60), was isolated in a similar manner using (-) tartaric acid. The optical rotations of the two, when measured, were found to correspond closely. Then, in the standard manner, the methiodides 59 and 63 were prepared. In addition, to allow comparision to the racemic hydrochlolride (64), the HCl salts 58 and 62 were made by adding HCl to methanolic solution of the free bases.



Scheme 1: Resolution of (±) 2-Oximino-3-tropinone (55)

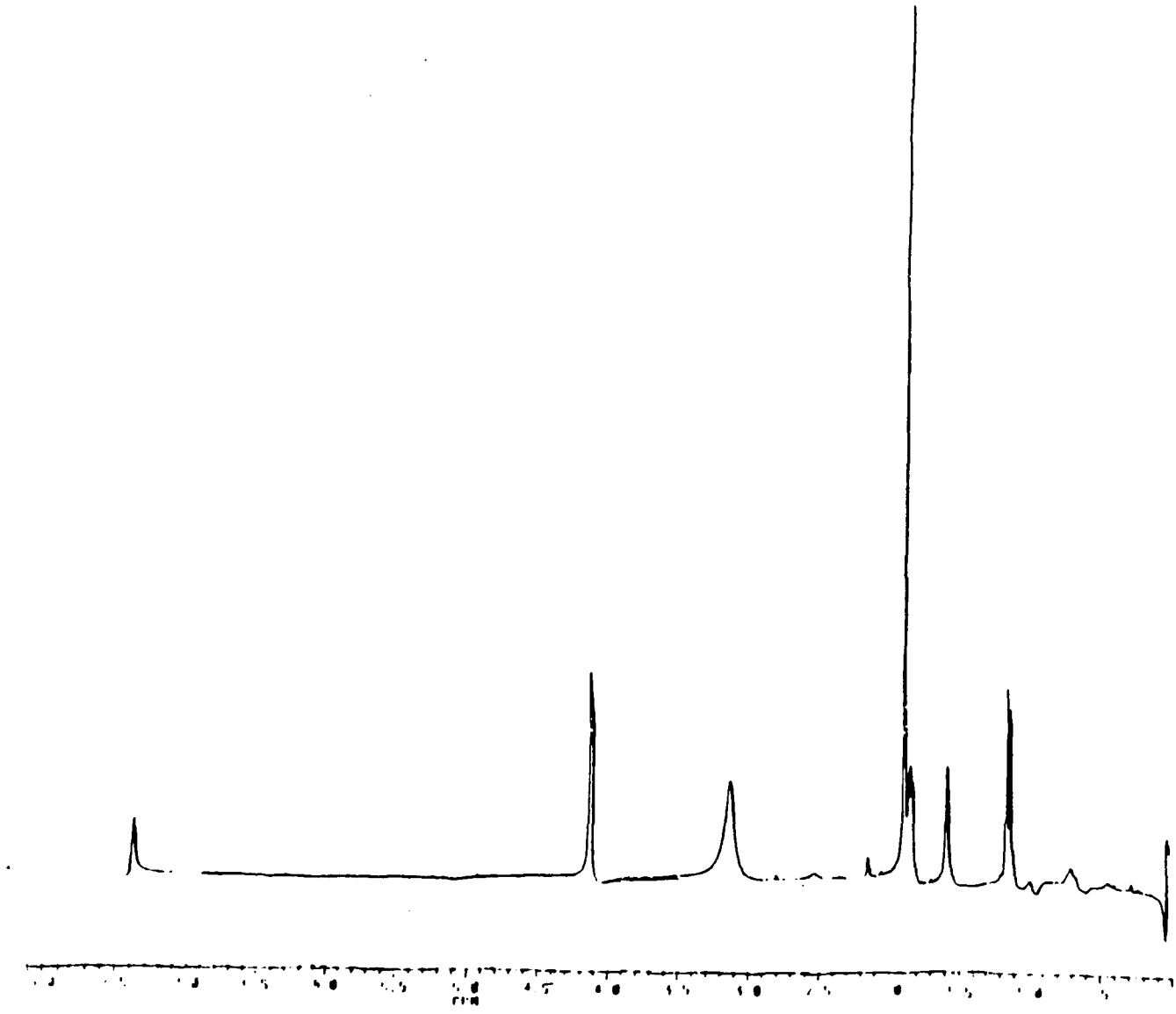
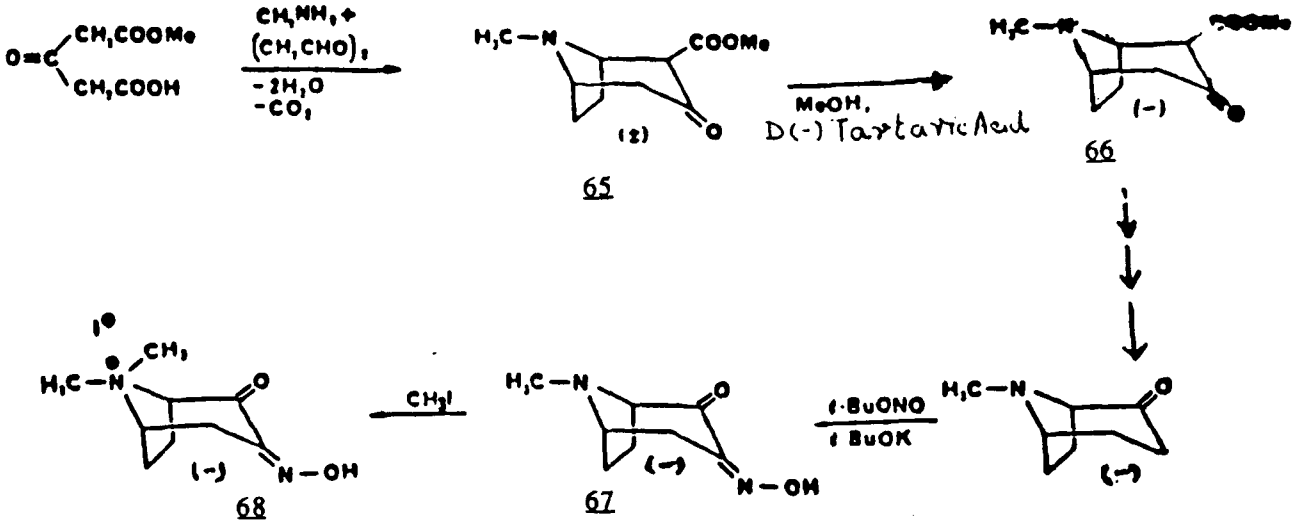


Figure 1: NMR Spectrum of (+) 2-Oximino-3-tropinone (57) and Eu(III) Complex

Synthesis of (-) 3-Oximino 2-Tropinone Methiodide (68)

The synthesis of (-) 3-oximino 2-tropinone methiodide (68) was achieved using the racemic intermediate 2-carbomethoxy tropinone (65). The key step was the resolution of 65 to give (-) 2-carbomethoxy tropinone (66).[2] Using the difference in solubilities of the diastereomeric salts, a solution of the racemate was treated with D(-) tartaric acid. The resulting salt was then broken up with aqueous sodium bicarbonate. The (-) 2-carbomethoxy tropinone was then subjected to the same degradation sequence as the racemate. By resolving the mixture at the outset, the yields of each of the steps were somewhat better. The isolated yield of the ketooxime was raised from 8% to 16.8%. The methiodide (68) was then prepared in the usual manner.



6. KINETIC STUDIES

Experimental: Assays

Acetylcholinesterase from the electric eel was purchased from Sigma Chemical Co.; dithio-bisnitrobenzoic acid (DTNB), acetylthiocholine, and 2-PAM were purchased from Aldrich Chemical Co.; Sephadex G-25 resin and TRIS buffer were also purchased from Sigma Chemical Co.; Bio-Rad Dye was purchased from Sigam Chemical Co., and Boehringer-Mannheim Biochemicals.

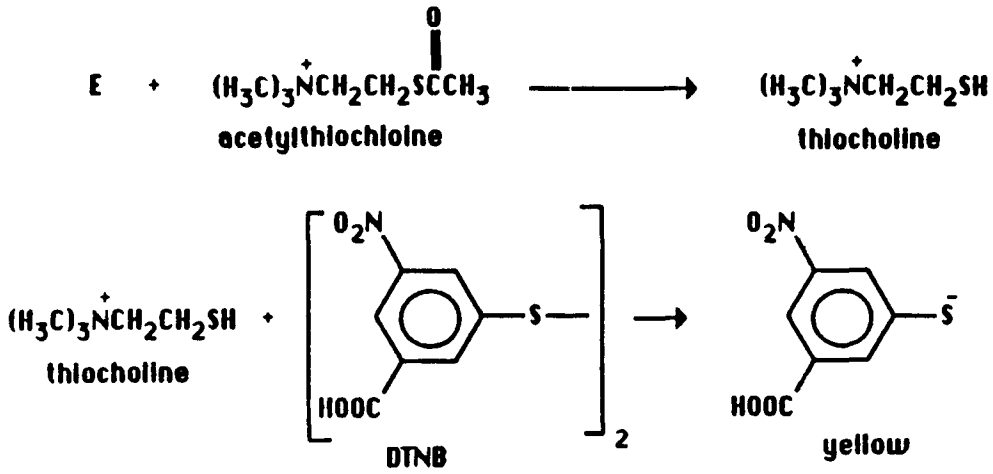
i) pKa Determinations

A 25 mM aqueous solution of the oxime was titrated with 100 mM potassium hydroxide solution at 100λ increments. The change in pH with each volume of base added was determined using the Henderson-Haselbach equation to calculate the pKa. The pKa is defined as the pH at which the species is 50% ionized. Simple calculations of pKa are in Tables 1-2.

ii) KI Determination

Acetylcholinesterase stock solution was prepared by mixing 10λ of electric eel acetylcholinesterase (Sigma Chemical Co.) having a specific activity of 1300 U/mg, and containing 0.46 mg Protein/ml in 1.99 ml of 100 mM TRIS buffer at pH 7.4. The rate of hydrolysis of the substrate, acetylthiocholine, was

monitered at various concentrations (50, 100, and 300λ of 50 mM solution). The production of free thiocholine was determined by following change in O.D. at 412 nm using DTNB as a coupler.



Each assay was then repeated using 50 liter and 100 liter of 50 mM oxime solution, 10 liter of the enzyme and the same series of acetylthiocholine concentrations in 100 mM TRIS buffer at a pH of 7.4. The volume in each cuvette never exceeded 3 ml total. In addition, blank experiments were performed to determine the interaction between substrate and the oxime at identical concentrations without enzyme.

The data was subjected to standard Michaelis-Menton kinetics for competitive inhibition. The Lineweaver-Burke (1/v vs. 1/S) plots were made and the slopes of these lines were replotted in slope vs. [I]. KI's were determined from this plot and are listed in Tables 1-2.

iii) **Inactivation Procedure**

Acetylcholinesterase stock solution was prepared by a ten-fold dilution of commercial enzyme solution. Simultaneously, a DFP solution was prepared by adding 10λ of DFP to 990λ of absolute EtOH. This was diluted once more by adding 100λ to 400λ EtOH. The enzyme stock solution was incubated with 75λ DFP-EtOH solution for 5-10 minutes. After checking for enzyme activity, the solution was passed through columns packed with Sephadex G-25 resin in 100 mM TRIS buffer at pH 7.4, to remove excess DFP. The inactivated enzyme was collected and pooled to ensure homogeneity.

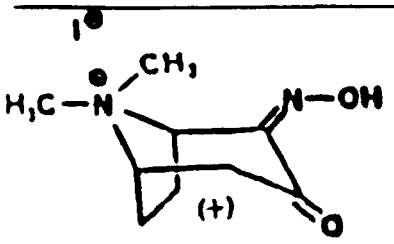
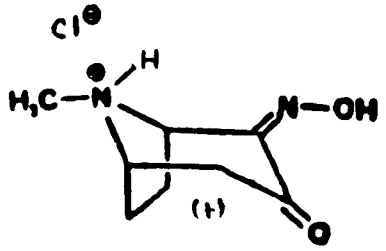
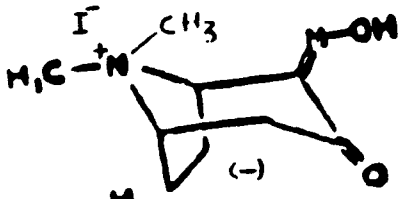
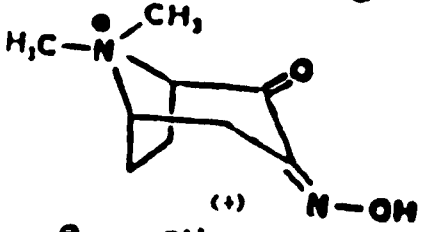
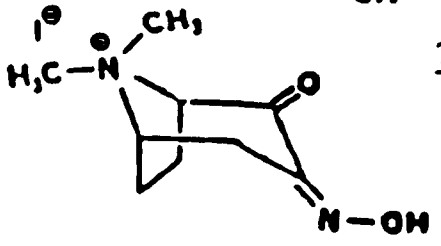
iv) **Reactivation Procedure**

The inactivated enzyme, 200λ, was incubated with 100λ of 25 mM solutions of reactivator at room temperature and pH 7.4. After 2 hours, the solution was passed through a column packed with Sephadex G-25 resin to remove the reactivator from the solution. The enzyme was collected and assayed for activity using acetylthiocholine and DTNB. The formation of thiocholine was monitered as the change in O.D. at 412 nm.

v) **Bradford Assay**

Each enzyme sample was treated with a 200λ aliquot of Bio-Rad dye to determine the exact amount of enzyme present. The dye contains Coomassie G-250 which gives a characteristic blue color that is proportional to the amount of protein present. The O.D. was measured at 595 nm in a quartz cuvette. The measurements were converted to μg/ml using a standard curve lyophilized acetylcholinesterase having a specific activity of 1000 U/mg, at specific concentrations.

Table 1. Binding Constants and Reactivation Data of Tropanone Analogues Relative to 2-PA

COMPOUND	NO.	pKa	Ki	REACTIVATION
	59	6.20	----	27%
	58	6.20	----	22%
	63	5.40	----	22%
	62	5.40	----	23%
	69	7.20	0.214	113%
	70	7.20	0.351	98%

contd.

Table 1. Binding Constants and Reactivation Data of Tropanone Analogues Relative to 2-PA

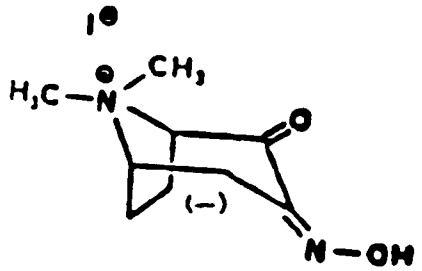
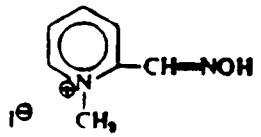
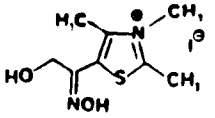
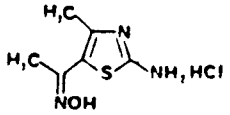
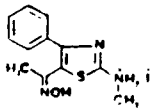
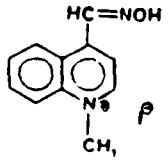
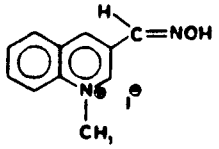
COMPOUND	NO.	pKa	Ki	REACTIVATION
	68	7.20	1.36	27%
	2-PAM	7.80	0.070	100%

Table 2. Reactivation and Binding Data of Heterocyclic Analogues Relative to 2-PAM.

COMPOUND	% RELATIVE RATE OF REACTIVATION	K_I(BINDING CONSTANT) mM
 1	25.56	0.083
 2	7.62	0.027
 4	4.42	0.0092
 7	92.56	0.0077
 8	7.74	----

The reactivating potency of the compounds were evaluated with respect to their relative ability to reactivate electric eel AChE (acetylcholinehydrolase, EC 3.1.1.7) inhibited by diisopropyl phosphorofluoridate. These results are expressed as percent reactivation relative to pyridine-2-aldoxime methiodide.

(Diisopropylphosphoryl)acetylcholinesterase was incubated with each compound (8.33 mM for 2 hrs. at pH 7.4 and 25°C).

In this manner, changes in the activity of the enzyme could be attributed directly to the ability of the oxime to reactivate the enzyme. Control experiments to determine the effect of column chromatography, incubation time, and reactivator on enzyme activity were performed concurrently. 2-PAM was studied in an identical fashion and all oximes were compared directly to it as the standard.

The oximes that were prepared and studied are summarized in Table 1. The compounds of interest, namely the 3-keto 2-oximino tropane salts (59, 58, 63, and 62) and the 2-keto 3-oximino tropane salts (69, 70, and 68), gave two contradicting answers to the question of stereoselectivity.

The 3-keto 2-oximino salts (both hydrochlorides and methiodides) showed that the inactivated enzyme did not exhibit any preference for one enantiomer over the other. Both stereoisomers proved to have essentially identical reactivating ability. In other words, the enzyme could not differentiate between the ethano bridge and the positively charged nitrogen bridge. This is a consequence of the fact that the difference between the enantiomers lies in the oximino function "changing sides" so to speak. Since the inhibited enzyme is unable to differentiate between (+) and (-), in effect, a plane of symmetry has been created making the concave and convex faces of the molecule "identical". This seems to support the idea that a quaternary nitrogen is not essential for binding to the active site, and the anionic site is actually a "trimethyl site" or a region of hydrophobic interaction.[4-6] The range of 29-26% reactivation for the methiodides and 23-22% for the hydrochlorides, places the differences well within experimental error, so that they cannot be considered as differences at all.

The answer to the question of stereoselectivity changes for the 2-keto 3-oximino tropane methiodides (69, 70, and 68). In this series, the blocked enzyme exhibited a decided preference for the (+) isomer (69), which was able to regenerate enzyme activity to a greater extent than 2-PAM. The (-) isomer (68), could only restore 27% of enzymatic activity. This means that the inhibited enzyme could differentiate between the enantiomers. This is significant in that the active site of the enzyme is already masked to a certain extent by the phosphate ester. Even with this restriction, the enzyme is able to exhibit a large degree of stereoselectivity.

Since all of the oxime methiodides synthesized in the phencyclidine series were very poorly soluble in water, it was not possible to perform the standard pKa and competitive inhibition studies. The relative ability of these oximes to reactivate may only be determined by testing the compounds in live organisms. Based on previous experience with tropane alkaloids, it seems quite likely that the oximes may not be nucleophilic but the binding constants may be quite good. Previous binding studies for PCP with rat brain tissue gave a binding constant of 0.25vM. Keeping in view the studies done by Kammeka et al. in 1982, even if the substitution decreases the binding capacity of the oximes by a factor of 100, the value would still be on the order of 10^{-5}. This is the same order of magnitude as 2-PAM and not entirely unacceptable. As in the case of the atropine analogs, the only real way to determine if the ability of this class of compounds to penetrate the blood-brain barrier may be combined with the ability of oximes to restore enzyme activity, would be to perform experiments *in vivo*.

Preliminary test results from the U.S. Army Research Institute proved promising but did not specifically address the question of CNS activity. The change in the survival rate of mice that had been treated with various doses of 71, 15 and 60 minutes before treatment with the agent Soman and treatment with predetermined doses of a combination of atropine and 2-PAM 10 seconds after Soman administration,

were determined. A minimum of four additional survivors were required before an improvement was identified.

From the data collected, it appears that 71 has some beneficial effect when used in the pre-treatment mode. It has the same effect as a dose of pyridostigmine that is 1000 times smaller. It is important to note that the lethal dose, or LD_{50}, of pyridostigmine is much smaller than that determined for 71, so administration of 100 mg/kg of 71, LD_{50}=206.3 mg/kg, would not have the same effect. In order to assess CNS effectiveness, however, more specific experiments must be performed, perhaps with brain tissue as in the case of the binding studies done on PCP.

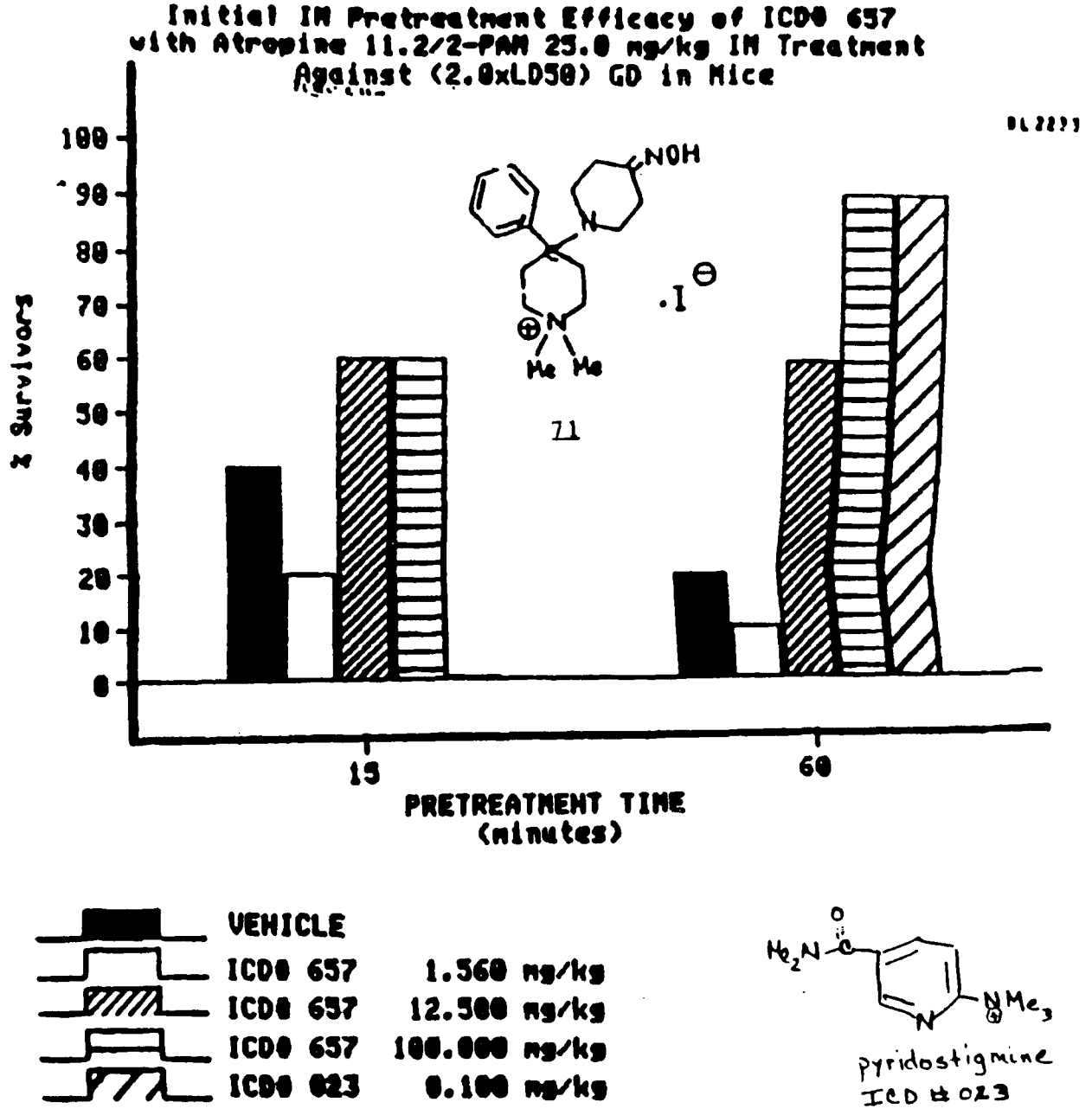


Figure 2: Test Data from USAMRICD of 4-(1'-Piperidinyl)-4-phenylcyclohexanone Oxime Methiodide (14)

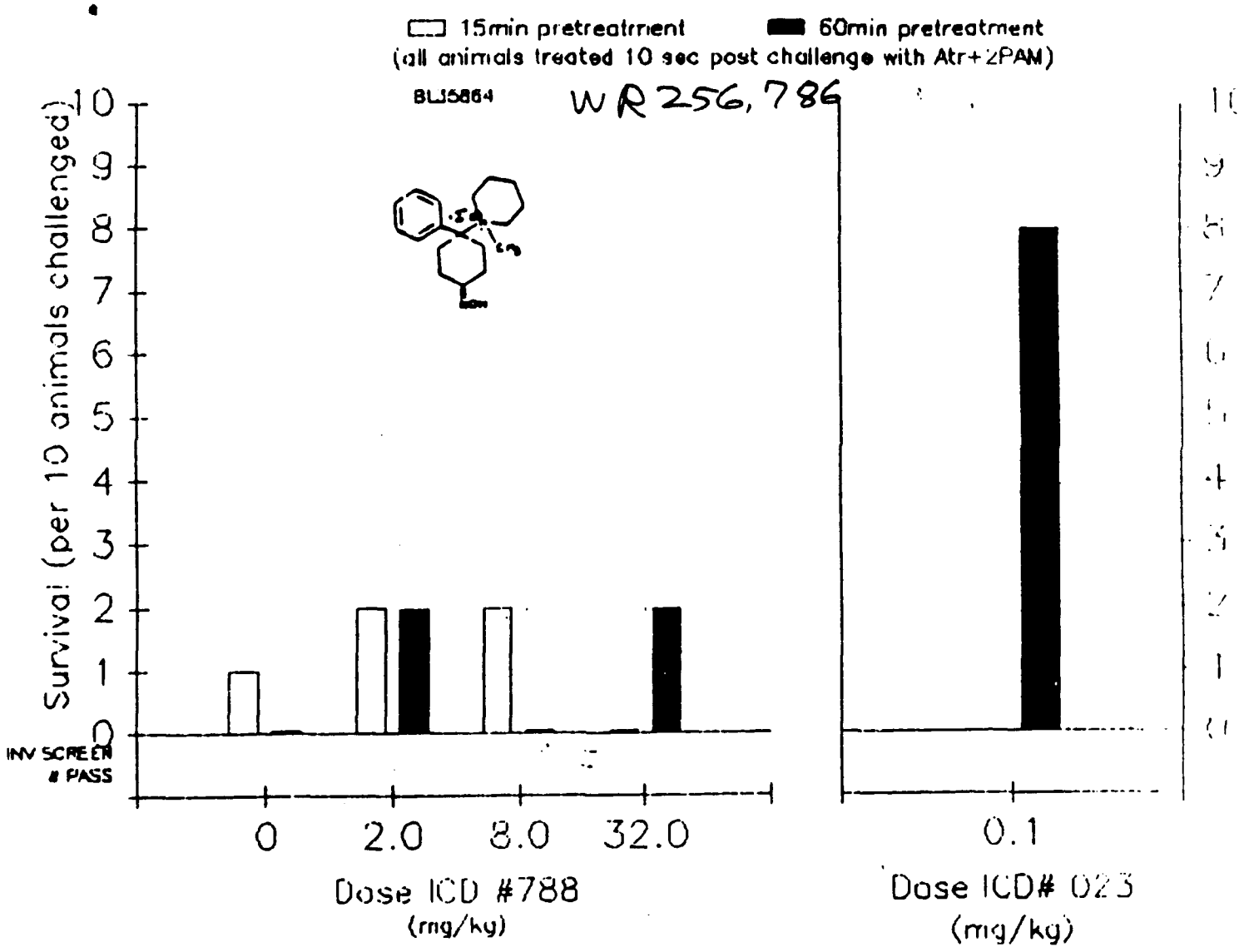


Figure 3: Test Data from USAMRICD of 1-(1'-Phenyl-1'-cyclohexyl)-4-piperidone Oxime Methiodide (20)

7. SYNTHESES 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 in 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 (IR) spectra were obtained using a Unicam SP 1000 IR spectrophotometer. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Mass spectra (MS) were obtained with a Hewlett Packard G/C/MS 5985 apparatus at 70 or 20 eV. Microanalyses were obtained from Micron Lab in 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 F-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.

3-Tropinone Oxime Hydrochloride (2)

3-Tropinone (1, 3.0 g, 0.0215 mole) was dissolved in 60 ml of absolute methanol and stirred with hydroxylamine hydrochloride (1.49 g, 0.0215 mole) at room temperature overnight. Vacuum assisted filtration allowed isolation 3.81 g of a white solid.

m.p.	207-209°C (decomposition)
% yield	91
NMR (D_2O)δ	1.8-2.8 (m, 8H, 4 x CH_2), 2.98 (s, 3H, CH_3), 4.1-4.35 (m, 2H, 2 x CH)
IR(Nujol)cm^{-1}	3406 (O-H stretching), 1653 (C=N stretching)
Analysis	$C_8H_{15}N_2OCl$, % Calc.: C = 50.39, H = 7.87, N = 14.69, Cl = 18.64.
	% Found: C = 50.13, H = 7.99, N = 14.81, Cl = 18.53

(±) 2-Oximino 3-tropinone Hydrochloride (3)

3-Tropinone (1, 6.95 g, 0.05 mole) was dissolved in methanol (100 ml) and conc. HCl (5 ml) was then added with stirring. After 15 minutes, t-butyl nitrite (20.5 ml) was added cautiously to the yellow solution. The solution lost some of its color and bubbled vigorously. Stirring was contiued at room temperature and filtration after five days gave 6.75 g of the hydrochloride.

m.p.	230-232°C
% yield	66
^1H NMR (D_2O) δ	1.8-2.4 (m, 6H, 3 x CH_2), 3.1 (s, 3H, N-CH_3), 4.0 (m, 2H, 2 x CH)
IR (Nujol) cm^{-1}	3300 (br, O-H stretching), 1713 (sh, C=O sretching), 1615 (sh, C=N stretching)
Analysis	% Calc.: C = 46.94, H = 6.36, N = 13.69, Cl = 17.36.
	% Found: C = 46.41, H = 6.08, N = 14.01, Cl = 16.98

Synthesis of 3-Hydroxy-3-phenyl-8-azabicyclo[3.2.1]octane Oxime Hydrochloride (5)

Acetophenone Enol Silyl Ether:

Acetophenone (19.42 g, 0.162 mole) was added slowly to a stirring solution of 50 ml triethyl amine (TEA) and 50 ml of chlorotrimethylsilane in 200 ml of dry DMF. The reaction mixture was heated at reflux for fifteen hours. After cooling, an equal volume of pentane was added and the biphasic solution was treated first with crushed ice and then carefully with cold sodium bicarbonate solution. The mixture was then transferred to a separatory funnel and pentane was evaporated, leaving a mixture of the ketone and silyl ether. The crude mixture was distilled under vacuum.

b.p.	78-80°C/10 mm, [Lit][7] b.p. 78-80°C/10 mm
^{1}H NMR	0.2 (s, 9H, 3 x CH_3), 5.4 (d, 2H, CH_2), 7.3-7.5 (m, 5H, aromatic protons)

3-Hydroxy-3-phenacyl-8-azabicyclo[3.2.1]octane (4)

3-Tropinone (1, 10.0 g, 0.072 mole) dissolved in dry methylene chloride (60 ml) was added dropwise to a stirred solution containing one equivalent of acetophenone enol silyl ether in 150 ml of dry methylene chloride. Two equivalents of boron trifluoride etherate solution were then added *via* syringe. The reaction mixture slowly darkened from yellow to deep brown. Stirring was continued overnight at room temperature. The reaction was quenched carefully with saturated sodium bicarbonate solution until the bubbling subsided. A solid appeared in the two-phase solution and was filtered to give 9.52 g of a buff colored solid, m.p. 188-192°C. This borate complex was dissolved with difficulty in aqueous sodium bicarbonate. The clear solution turned brown. The aqueous solution was then extracted with methylene chloride. The organic layers were combined, dried and evaporated to give 2.06 g of the free condensation product.

mp.	104°-106°C
% yield	15
^{1}H NMR	1.75-2.25 (m, 8H, 4xCH_2), 2.35 (s, 3H, CH_3), 3.1 (m, 2H, 2xCH), 3.1-3.3 (m, 2H, 2xCH), 4.05 (br, 1H, OH), 7.8-8.2 (m, 5H, aromatic protons)
IR (Nujol) cm^{-1}	3489 (-OH), 1666 (C=O)
MS	m/e 241 M^+ (18), 212 M^+ (29), 136, 105, 77, 28
Analysis	$C_{16}H_{21}NO_2$, % Calc.: C = 74.13, H = 8.11, N = 5.41. % Found: C = 74.07, H = 7.83, N = 5.20

3-Hydroxy-3-phenacyl-8-azabicyclo[3.2.1]octane Oxime Hydrochloride (5)

The above ketone (4, 2.0 g, 0.0077 mole) was dissolved in absolute methanol (75 ml) and hydroxylamine hydrochloride (0.53 g, 0.0077 mole) was added. The solution was stirred overnight at room temperature. The solvent was evaporated and the slightly gummy residue was swirled in acetone. The resulting white solid was filtered, giving 2.12 g of the hydrochloride.

m.p.	155-158°C
% yield	88.6
^{1}H NMR (D_2O) δ	2.2-2.8 (m, 8H, 4xCH_2), 3.0 (s, 2H, CH_2), 3.0 (s, 3H, N-CH_3), 3.9 (m, 2H, 2xCH), 7.3-7.5 (m, 5H, aromatic protons)
IR (Nujol) cm^{-1}	3300 (br N-H, O-H stretchings), 1660 (sh, C=N stretching)

Analysis	$C_{16}H_{23}N_2O_2Cl$, % Calc.:C = 61.84, H = 7.41, N = 9.01, Cl = 11.43.
	% Found: C = 61.57, H = 7.63, N = 9.23, Cl = 11.09

Preparation of O-(N-Methylcarbamoyl)-3-tropinone Oxime Methiodide (8)

3-tropinone Oxime (6)

Hydroxylamine hydrochloride (4.99 g, 71.8 mmole) and potassium hydroxide (4.03 g, 71.8 mmole) were dissolved in separate 75 ml aliquots of anhydrous methanol. The solutions were cooled to 0-5°C and combined with stirring. The temperature of the solution was maintained at 0-5°C for one hour so that the precipitation of potassium chloride would be complete. The resulting solution of free hydroxylamine was gravity-filtered into a 250 ml round bottom flask containing tropinone (1, 5.00 g 35.9 mmol). The filter cake was washed with 10 ml of cold anhydrous methanol to ensure complete transfer of free hydroxylamine. The flask was stoppered and the reaction mixture was stirred overnight. The methanol and excess hydroxylamine were removed under vacuum, giving 5.15 g of 3-tropinone oxime (6).

m.p.	110°C, [Lit][8] m.p. 111°C
% yield	94

O-(N-Methylcarbamoyl)-3-tropinone Oxime (7)

3-Tropinone oxime (6, 2.45 g, 15.9 mmole) was dissolved in 25 ml of dry benzene. Methylisocyanate (1.36 g, 23.8 mmole) was added and the reaction stirred for 12 hours. The reaction mixture was filtered to remove any insoluble material and the solvent removed under vacuum. 3.02 g O-(N-methylcarbamoyl)-3-tropinone oxime (7) was isolated as a viscous amber oil.

% yield	89
^{1}H NMR	1.8-2.6 (m, 8H, 4xCH_2), 2.7 (s, 3H, CH_3), 3.0 (s, 3H, CH_3), 3.8 (m, 2H, 2xCH)
IR (Neat) cm^{-1}	1740 (sh, C=O stretching), 3150 (sh, N-H stretching)

O-(N-Methylcarbamoyl)-3-tropinone Oxime Methiodide (8)

O-(N-Methylcarbamoyl)-3-tropinone oxime (1.25 g, 5.9 mmol) was dissolved in 15 ml dry benzene. Iodobenzene (1.68 g, 11.8 mmol) was added and the flask stoppered. The reaction mixture was stirred for 12 hours, during which time the formation of a white solid was observed. The solid was filtered and washed with a few mm of dry benzene. The filter cake was then dried in a warm oven. 1.40 g of O-(N-methylcarbamoyl)-3-tropinone oxime methiodide was isolated.

m.p.	140-143°C (decomposition)
% yield	67
^{1}H NMR (D_2O) δ	1.82-2.7 (m, 8H, 4xCH_2), 2.8 (s, 3H, CH_3), 3.0 (s, 3H, CH_3), 3.15 (s, 3H, CH_3), 3.8 (m, 2H, 2xCH)
IR (KBr) cm^{-1}	1740 (sh, C=O stretching), 3200 (sh, N-H stretching)
Analysis	$C_{11}H_{20}N_3O_2I$, % Calc.: C = 37.41, H = 5.71, N = 11.90, I = 35.93.
	% Found: C = 36.98, H = 5.63, N = 11.04, I = 34.73

Synthesis of 4-(1-Piperidinyl)-4-phenylcyclohexanone Oxime Methiodide (14)

4-Cyano(1'-piperidinyl) Cyclohexanone Ethylene Ketal (10)

1,4-Cyclohexandione monoethylene ketal (9, 10.92 g, 0.070 mole) was added to a solution of $NaHSO_3$ (7.98 g, 0.077 mole) in 30 ml of H_2O. The mixture solidified within minutes of vigorous swirling. Piperidine (6.93 g, 0.070 mole) was added to solution of NaCN (3.76 g, 0.077 mole) in 20 ml H_2O. The aqueous cyanide mixture was added to a cooled slurry of the bisulfate addition product. The solution was stirred overnight at room temperature. Filtration gave 14.20 g of the carbonitrile (10) as a white crystalline product.

m.p.	90°C
% yield	81

4-(1'-Piperidinyl)-4-phenylcyclohexanone Ethylene Ketal (11)

The crude carbonitrile 10 (12.0 g, 0.048 mole) was dissolved in 250 ml of a 1:1 benzene:ether mixture and was added dropwise to a stirred solution containing 2 equivalents of phenylmagnesium bromide in 100 ml dry ether. The reaction mixture was allowed to stir overnight at room temperature. The reaction was quenched carefully with 200 ml of cold water. Subsequent extraction with ether gave, after drying and evaporation , 12.2 g of 11 as an oil.

% yield	84

4-(1'-Piperidinyl)-4-phenylcyclohexanone (12)

Ketal 11 (12.0 g, 0.048 mole) was dissolved in 500 ml of 6N HCl and stirred at room temperature for one week. The acid solution was neutralized cautiously with cold aqueous ammonium hydroxide and extracted with ether. The ethereal layers were combined, dried and evaporated to give 4.05 g of the product as an oil.

% yield	41
IR (Nujol) cm^{-1}	1710 (sh, C=O stretching)

4-(1'-Piperidinyl)-4-phenylcyclohexanone Oxime (13)

Ketone 12 (3.0 g, 0.012 mole) was dissolved in methanol and treated with one equivalent of NH_2OH (in methanol) at room temperature for 4 hours. Filtration gave 2.38 g of the oxime 13.

m.p.	110°C
IR (KBr) cm^{-1}	3280 (br, O-H stretching), 1660 (sh, C=N stretching)

4-(1'-Piperidine)-4-phenylcyclohexanone Oxime Methiodide (14)

Oxime 13 (2.0 g, 0.007 mole) was dissolved in 250 ml CH_2Cl_2, and then treated with a five-fold excess of MeI. After one week at room temperature, filtration gave 2.23 g of 14.

m.p.	206°-208°C (decomposition)
% yield	77
IR (KBr) cm^{-1}	3318 (br., O-H stretching), 1651 (sh., C=N stretching)
NMR (DMSO-d_6)	9.1-9.3 (1H, -OH), 7.0-7.5 (5H), 0.6-3.7 (21H)

Analysis % Calc.: C = 52.17, H = 6.52, N = 6.76, I = 30.67.
% Found: C = 51.85, H = 5.98, N = 6.20, I = 30.18.

Synthesis of 1-(1'-Phenyl 1'-cyclohexyl)p4-oximino Piperidone Methiodide (20)

1-(1'Cyanocyclohexyl)-4-piperidone Ethylene Ketal (16)

Cyclohexanone (6.84 g, 0.070 mole) was swirled in a solution of sodium bisulfate (7.98 g, 0.077 mole) in 30 ml of H_2O. With vigorous stirring, the mixture solidified within minutes. 4-Piperidone ethylene ketal (10.0 g, 0.070 mole) was added to a solution of sodium cyanide (3.76 g, 0.077 mole) in 20 ml H_2O. The aqueous cyanide mixture was added to a cooled slurry of the bisulfate addition product. The solution was stirred overnight at room temperature. The resultant crystalline solid was filtered, giving 13.38 g of the carbonitrile 16.

m.p. 94-96°C

1-(1'-Phenylcyclohexy')-4-piperidone Ethylene Ketal (17)

The crude carbonitrile 16 (12.0 g, 0.048 mole) was dissolved in 150 ml of a 1:1 benzene:ether mixture and added dropwise to a stirring solution of 1.5 equivalents phenylmagnesium bromide in 100 ml dry ether. The reaction mixture was stirred overnight at room temperature. The excess Grignard reagent was carefully destroyed with 150 ml of cold water. Subsequent extraction with ether gave, after drying and evaporation, 10.52 g of the crude product as an oil. The oil crystallized on standing.

m.p. 56-58°C

1-(1'Phenylcyclohexyl)-4-piperidone (18)

Ketal 17 (15.0 g, 0.049 mole) was heated at reflux with 40% formic acid for 4 hours. After the solution was cooled, it was neutralized carefully with 1N NaOH. Repeated extraction with ether gave, after drying and evaporation, 9.2 g of the desired ketone (18).

m.p. 80-82°C

% yield 72

IR (Neat) cm^{-1} 1720 (sh, C=O stretching)

1-(1'-Phenylcyclohexyl)-4-oximino Piperidone (19)

Ketone 18 (2.0 g, 0.0078 mole) was dissolved in 50 ml CH_3OH and treated with 20 ml of methanolic hydroxylamine solution. After six hours, the solution was concentrated to 10 ml and filtered, giving 1.83 g of a pale yellow solid.

m.p. 156-158°C

% yield 86

IR (KBr) cm^{-1} 3500 (br, O-H stretching)

MS m/e 272 (M^+), 255 (M^+ 17), 178, 83

1-(1'-Phenylcyclohexyl)-4-oximino Piperidone Methiodide (20)

Oxime 19 (1.8 g) was dissolved in 200 ml dry THF and treated with a five-fold excess of methyl iodide.

The flask was stoppered and allowed to sit at room temperature. After three days, a fine crystalline solid began to line the walls of the flask. The solution was allowed to stand for another four days. Scraping and filtering gave 1.2 g of fine tan crystals. The filtrate was allowed to sit an additional 2 days, and subsequent filtration recovered an additional 0.2 g of product, thus a total of 1.40 g of 20 was collected.

m.p.	210-211°C (decomposition)
% yield	51
^{1}H NMR (DMSO-d_6) δ	1.3-2.4 (m, 14H, 7xCH_2), 2.8 (m, 4H, 2xCH_2), 3.0 (s, 3H, N-CH_3), 7.4-7.7 (m, 5H, aromatic protons)
IR (KBr) cm^{-1}	3279 (br, O-H stretching), 1668 (sh, C=N stretching)
Analysis	$C_{18}H_{27}N_2OI$, % Calc.: C = 52.17, H = 6.52, N = 6.76, I = 30.67. % Found: C = 51,98, H = 6.60, N = 6.62, I = 30.58

Synthesis of 2-Benzylidine-3-quinuclidinone Oxime Hydrochloride (23)

2-Benzylidine-3-quinuclidinone (22)

3-quinuclidinone (21, 1.26 g, 0.01 mole) was added to a solution of KOH (0.56 g, 0.01 mole), dissolved in 100 ml of methanol and cooled to 0°C. Benzaldehyde (1.06 g, 0.01 mole) was added and the contents stirred at 0°C for 8 h, and then at room temperature for 2 h. Methanol was evaporated and 100 ml of H_2O was added. Extraction was done with dichloromethane (3 x 100 ml). The dichloromethane layer was dried over $MgSO_4$ (anhydrous). Evaporation of dichloromethane yielded crude 2-benzylidine-3-quinuclidinone which was crystallized from methanol to give 1.4 g.

m.p.	130°C, [Lit][9] m.p. 128°-130°C
% yield	66

2-Benzylidine-3-quinuclidone Oxime Hydrochloride (23)

2-Benzylidine-3-quinuclidinone (22, 2.0 g, 0.0093 mole) was dissolved in 70 ml of methanol. To this was added $NH_2OH.HCl$ (0.6417 g, 0.0093 mole). The solution was refluxed for 6 h and then allowed to cool at room temperature. The resulting solid was filtered and crystallized from water to yield 1.4 g.

m.p.	193-194°C
% yield	57
^{1}H NMR (D_2O) δ	1.6-2.3 (m, 4H, 2xCH_2), 3.2-4.0 (m, 5H, 2xCH_2, CH), 7.1-7.6 (m, 6H, 5 aromatic and one C-H protons)
IR (KBr) cm^{-1}	3092 (br, O-H, N-H stretching), 1676 (sh, C=N stretching)
Analysis	$C_{14}H_{17}ClN_2O$, % Calc.: C = 63.51, H = 6.43, N = 10.59, Cl = 13.42. % Found: C = 63.05, H = 6.55, N = 10.42, Cl = 13.25

2,4-Dimethyl-5-(α-hydroxymethyloximino)thiazole Methiodide (28)

2,4-Dimethyl-5-(α-hydroxydimethylacetal)thiazole (25)

To powedered potassium hydroxide (8.4 g, 0.15 mole) was added 80 ml of anhydrous methanol. The solution was cooled to 5-10°C. While stirring, 2,4-dimethyl-5-acetylthiazole (1, 7.75 g, 0.05 mole) was added over a 15 minute period. After the solution was stirred for an additional 10 minutes, iodosobenzene

(12.1 g, 0.055 mole) was added over a period of 30 minutes. The ice bath was removed and the resulting yellow-colored slurry was stirred overnight at room temperature resulting in a clear red solution. The mixture was concentrated, after which 50 ml of water was added, followed by extraction with dichloromethane (4x100 ml). The combined dichloromethane extracts were washed with water and dried over anhydrous $MgSO_4$ for 1 h. After filtration, the dichloromethane was removed to give 7 g of 2,4-dimethyl-5-(α-hydroxydimethylacetal)thiazole (25).

m.p.	95-96°C
% yield	65
^{1}H NMR	2.3 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 3.3 (s, 6H, 2xOCH_3), 3.9 (br, 3H, 2H of CH_2 and 1H of OH)
IR (Nujol) cm^{-1}	3270 (br, O-H stretching)
Analysis	$C_9H_{15}NSO_3$, % Calc.: C = 49.76, H = 6.91, N = 6.45, S = 14.75.
	% Found: C = 49.66, H = 6.85, N = 6.35, S = 14.85

2,4-Dimethyl-5-(α-hydroxyacetyl)thiazole (26)

25 (7 g, 0.0322 mole) was placed in a 500 ml round-bottom flask equipped with a magnetic stirrer. To this was added 6N HCl (70 ml) in 3 portions and the solution was stirred overnight. A saturated solution of $NaHCO_3$ was used to free the base (3), followed by extraction with CH_2Cl_2 (3x100 ml). The organic layer was dried over anhydrous $MgSO_4$, and subsequent evaporation afforded 3.5 g 2,4-dimethyl-5-(α-hydroxyacetyl)thiazole (26).

m.p.	82-83°C
% yield	63.4
^{1}H NMR	2.35 (s, 6H, 2xCH_3), 3.75 (br, 1H, OH), 4.3 (s, 2H, $COCH_3$)
IR (Nujol) cm^{-1}	3280 (br, O-H stretching), 1700 (sh, C=O stretching)
Analysis	$C_7H_9NSO_2$, % Calc.: C = 49.12, H = 5.26, N = 6.35, S = 18.71.
	% Found: C = 49.03, H = 5.15, N = 8.18, S = 18.65

2,4-Dimethyl-5-(α-hydroxyacetyl)thiazole Oxime (27)

A mixture of 26 (3 g, 0.0175 mole) and hydroxylamine (0.726 g, 0.022 mole) in methanol (10 ml) was stirred at room temperature for 24 h. Methanol was removed to yield the oxime which was then washed with water to yield 2.8 g of 2,4-dimethyl-5-(α-hydroxyacetyl)thiazole oxime (27).

m.p.	135°C
% yield	85
^{1}H NMR	2.3 (s, 6H, 2xCH_3), 4.3 (s, 2H, CH_2), 6.7 (br, 1H, OH)
IR (Nujol) cm^{-1}	3280 (br, O-H stretching), 1601 (sh, C=N stretching)
Analysis	$C_7H_{10}N_2SO_2$, % Calc.: C = 45.16, H = 5.37, N = 15.05, S = 17.20.
	% Found: C = 44.98, H = 5.30, N = 15.03, S = 17.20

2,4-Dimethyl-5-(α-hydroxyacetyl)thiazole Methiodide (28)

Oxime 27 (2.9 g, 0.156 mole) was dissolved in 60 ml of THF. Methyl iodide (7 ml) was added and the

mixture was left at room temperature for 15 days. 2.5 g of solid was collected by filtration.

m.p.	135-141°C
% yield	49
^{1}H NMR (D_2O)δ	2.5 and 2.6 (ss, 3H, CH_3), 3.0 (s, 3H, CH_3), 4.0 (s, 2H, CH_2)
IR (Nujol) cm^{-1}	3177 (br, O-H stretching), 1601 (sh, C=N stretching)
Analysis	$C_8H_{13}N_2SIO_2$, % Calc.: C = 29.33, H = 4.01, N = 8.56, S = 9.75, I = 38.01.
	% Found: C = 29.26, H = 3.96, N = 8.53, S = 9.75, I = 38.71

Synthesis of 2-Methylaminoo-4-phenyl-5-acetyltiozole Oxime Hydroiodide (33)

2-Amino-4-phenyl-5-acetylthiazole hydrotosylate (30)

To a solution of benzoylacetone (29, 1.61 g, 0.01 mole) in CH_3CN (50 ml) was added [hydroxy(tosyloxy)iodo]benzene (3.92 g, 0.01 mole). Contents were refluxed for 1 h, thiourea (0.76 g, 0.01 mole) was added and refluxing continued for 4 h. Contents were then cooled and after filtering and crystallization from water, 2.8 g solid were obtained.

m.p.	172°C
% yield	71
^{1}H NMR (DMSO-d_6)δ	2.2 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 7.1-7.9 (m, 9H, aromatic protons), 9.8 (broad N-H protons)
IR (KBr) cm^{-1}	2880 (br, N-H stretching), 1690 (sh, C=O stretching)

2-Amino-4-phenyl-5-acetylthiazole (31)

To a standard solution of $NaHCO_3$ (100 ml) was added 2.8 g of 2-amino-4-phenyl-5-acetylthiazole hydrotosylate (30). The contents were stirred for 6 hrs and filtered to give 1.5 g of 2-amino-4-phenyl-5-acetylthiazole (31).

m.p.	150° C, [Lit][10] m.p. 150° C
% yield	95

2-Amino-4-phenyl-5-acetyloximinothiazole (32)

To a methanolic solution (100 ml) of 2-amino-4-phenyl-5-acetylthiazole (31) (4.55 g, 0.0208 mole) was added (1.46 g, 0.0208 mole) of $NH_2OH.HCl$ and (1.66 g, 0.0208 mole) of CH_3COONa. The contents were refluxed for 6 hrs. After refluxing the volume is reduced to half. To this, water was added and left overnight. 3.8 g solid was obtained after filtration.

m.p.	132°C, [Lit][10] m.p. 132°C.
% yield	78

2-Methylamino-4-phenyl-5-acetyloximinothiazole hydroiodide (33)

2-Amino-4-phenyl-5-acetyloximinothiazole (32) (1.5 g, 0.0064 mole) was dissolved in 100 ml of THF. To this wass added excess of methyliodide, and the contents were refluxed for 4 hr and then allowed to sit for 6 days. Solid so obtained was filtered and crystallized from hot water to give 1.8 g.

m.p.	266-268°C

% yield	75
^{1}H NMR (DMSO-d_6)δ	2.3 (s, 3H, CH_3), 3.8 (s, 3H, CH_3), 7.7-8.3 (m, 5H, aromatic protons), 10.1 (b, 2H, NH_2)
IR (KBr) cm^{-1}	3455 (br, OH), 3196 (br, N-H stretching), 1645 (sh, C=N stretching)
Analysis	$C_{12}H_{14}N_3SOI$, % Calc.: C = 38.40, H = 3.64, N = 11.12, S = 9.20, I = 34.12
	% Found: C = 38.40, H = 3.64, N = 11.12, S = 9.20, I = 34.12

2-Methylamino-4-Methyl-5-Acetyloximino Hydroiodide (37)

2-Amino-4-Methyl-5-Acetylthiazole Hydrotosylate (34)

To acetylacetone (3 g, 0.03 mole) in acetonitrile (60 ml) was added [hydroxy(tosyloxy)iodo]benzene (11.76 g, 0.03 mole), contents were refluxed for 1 hr, then thiourea (2.28 g, 0.03 mole) was added. Contents were refluxed for 5 hr. The solid obtained was filtered to give 6.8 g of 2-amino-4-methyl-5-acetylthiazole.

m.p.	257°C
% yield	69
^{1}H NMR (DMSO-d_6)δ	2.3 (s, 3H, CH_3), 2.37 (s, 6H, CH_3 & $COCH_3$), 7.2 (d), 7.7 (d, 2H each, aromatic protons)
IR (KBr) cm^{-1}	2973 (br, N-H stretching)

2-Amino-4-Methyl-5-Acetyl Thiazole (35)

To a saturated solution of sodium bicarbonate (100 ml) was added 5 g of 2-amino-4-methyl-5-acetylthiazole hydrotosylate (34). The contents were stirred for 2 hr. Filtration yielded 2.1 g of 2-amino-4-methyl-5-acetylthiazole (35).

m.p.	270°C, [Lit][10] m.p. 270-272°C
% yield	85
^{1}H NMR (DMSO-d_6)δ	2.3 (s, 3H, CH_3), 2.4 (s, 3H, 5-$COCH_3$), 7.7 (b, 2H, NH_2)
IR (KBr) cm^{-1}	3350 (sh, NH_2 stretching), 1680 (sh, C=O stretching)

2-Amino-4-methyl-5-acetyloximino thiazole (36)

2-Amino-4-methyl-5-acetyloximino thiazole hydrochloride (2.8 g, 0.0137 mole) was suspended in 100 ml of saturated solution of sodium bicarbonate. The contents were stirred for 4 hr and filtered to give crude product, which was crystallized from methanol, yielding 2.05 g of 2-amino-4-methyl-5-acetyloximino thiazole.

m.p.	166-168°C, [Lit][10] m.p. 167-169°C
% yield	86.9

2-Methylamino-4-methyl-5-acetyloximino Thiazole Hydroiodide (37)

2-amino-4-methyl-5-acetyloximino thiazole (2.05 g, 0.01198 mole) was dissolved in tetrahydrofuran. To this was added iodomethane (3.38 g, 0.0239 mole). Contents were allowed to sit at room temperature for

a week. The solid that separated was filtered and crystallized from hot water, yielding 2.2 g of 2-methylamino-4-methyl-5-acetyloximino thiazole hydroiodide .

m.p.	248°C
% yield	59
^{1}H NMR (D_2O)δ	2.15 (s, 3H, 4-CH_3), 2.3 (s, 3H, CH_3), 3.4 (s, 3H, -CH_3)
IR (KBr) cm^{-1}	3256, 3113 (br, N-H, O-H stretching), 1530 (sh, C=N stretching)
Ms	M^+ 313 $C_7H_{12}N_3SOI$ Mol. Wt. 313
Analysis	$C_7H_{12}N_3SOI$, % Calc.: C = 26.85, H = 3.76, N = 13.07, S = 10.68, I = 39.99
	% Found: C = 26.83, H = 3.83, N = 13.41, S = 10.22, I = 40.57

2-Amino-4-methyl-5-acetylthiazole (38)

2,4-Pentanedione (1.0 g, 0.01 mole) was added to a refluxing solution of [hydroxy(tosyloxy) iodo]benzene (3.92 g, 0.01 mole) in 60 ml of CH_3CN. After refluxing for 45 minutes, thiourea (0.76 g, 0.01 mole) was added and refluxing was continued for an additional 4 hr. The contents were cooled and the resulting solid was then filtered to remove iodobenzene and washed thoroughly with water. The solid was stirred in aqueous $NaHCO_3$ solution (100 ml) for 2 hr, then filtered to yield 1.25 g of 2c.

m.p.	270°C, [Lit][10] m.p. 270-272°C
% yield	80
^{1}H NMR (DMSO-d_6)δ	2.3 (s, 3H, -CH_3), 2.4 (s, 3H, 5-$COCH_3$), 7.7 (b, 2H, NH_2)
IR (KBr) cm^{-1}	3350, 3330 (sh, NH_2 stretching), 1680 (sh, C=O stretching)

2-Amino-4-methyl-5-acetyloximinothiazole Hydrochloride (39)

To a methanolic solution (100 ml) of (1.56 g, 0.01 mole) of 2-amino-4-methylthiazole was added (0.69 g, 0.01 mole) of hydroxylamine hydrochloride. The contents were refluxed for 6 hr and the volume was concentrated to half and then allowed to sit at room temperature. The solid so obtained was filtered and washed with methanol and crystallized from water to yield 1.5 g of 2-amino-4-methyl-5-acetyloximino thiazole hydrochloride.

m.p.	216-218°C
% yield	74
^{1}H NMR (DMSO-d_6)δ	2.1 (s, 3H, CH_3), 4.8-6.5 (b, 3H, NH_3), 9.5 (b, 1H, NOH)
IR (KBr) cm^{-1}	3254 (br, O-H stretching), 1622 (sh, C=N stretching)
Ms	M^+207, $C_6H_{10}N_3SClO$ calculated Mol. Wt. = 207
Analysis	$C_6H_{10}N_3SClO$, % Calc.: C = 35.06, H = 4.81, N = 19.80, S = 15.66, I = 16.09
	% Found : C = 34.78, H = 4.83, N = 20.28, S = 15.45, Cl = 16.90

Ethyl-2-amino-α-(hydrozyimino)-4-thiazolacetate methiodide (42)

Ethyl-2-amino-4-thiazoleglyoxylate (41)

To (2.88 g, 0.01 mole) of 40 in 60 ml of acetonitrile was added [hydroxy(tosyloxy)iodo]benzene (7.86 g, 0.02 mole). Contents were refluxed for 1 hr, then thiourea (1.52 g, 0.02 mole) was added and refluxing was continued for 3 hrs. After this, the volume was concentrated to half and cooled to room temperature. The tosylate salt obtained was filtered to remove iodobenzene and washed thoroughly with water. The solid was stirred in aqueous $NaHCO_3$ for 2 hrs, then filtered to give 2.80 g of ethyl-2-amino-4-thiazoleglyoxylate (41).

m.p.	150°C, [Lit][10] m.p. 150-152°C
% yield	70

Ethyl-2-amino-α-(hydroxyimino)-4-thiazoleacetate (42)

To an ethanolic solution (80 ml) of ethyl 2-amino-4-thiazoleglycoylate (4 g, 0.02 mole) was added hydroxylamine (0.99 g, 0.03 mole). The solution was stirred for 10 hrs by which time solid precipitate out. The precipitate was filtered; evaporation of ethanol yielded 2.8 g of ethyl-2-amino-α-(hydroxyimino)-4-thiazoleacetate (42).

m.p.	204°-206°C, [Lit][10] m.p. 204-206°C
% yield	65

Ethyl-2-amino-α-(hydroxyimino)-4-thiazoleacetate Methiodide (43)

Oxime (42) (2.5 g, 0.011 mole) was dissolved in DMF and solution was allowed to warm at 150°C. To this solution was added methyl iodide (4 ml) through a water condenser very slowly. After half an hour a solid precipitated out, which was filtered, washed with Et_2O and crystallized from hot water to yield 43 (2.3 g).

m.p.	188-189°C
% yield	56
^1H NMR (DMSO-d_6)δ	1.3 (t, 3H, CH_3), 4.2 (q, 2H, CH_2CH_3), 6.9 (s, 1H, 2-thiazole proton), 7.1 (broad, 1H, NOH)
IR (KBr) cm^{-1}	3090 (br, O-H stretching), 1730 (sh, C=O stretching)
Analysis	$C_8H_{12}N_3SO_3I$, % Calc.: C = 26.89, H = 3.36, N = 11.76, S = 8.96, I = 35.57. % Found: C = 26.93, H = 3.43, N = 11.68, S = 9.22, I = 35.81

Synthesis of Quinoline-4-aldoxime Methiodide (45)

Quinoline-4-aldoxime (44)

To quinoline-4-aldehyde (1.57 g, 0.01 mole) in 50 ml of methanol was added hydroxalamine hydrochloride (1.035 g, 0.015 mole) and 4 drops of pyridine. The contents were refluxed for 4 hr, then methanol was evaporated and 50 ml of water was added. The solid obtained was filtered and crystallized from methanol., giving 1.4 g of quinoline-4-aldoxime (44).

m.p.	183-185°C, [Lit][11] m.p. 185°C
% yield	81.39

Quinoline-4-aldoxime Methiodide (45)

Quinoline-4-aldoxime (44, 1 g, 0.0081 mole) was dissolved in 10 ml of DMF. The contents were warmed to 90° and excess of methyliodide was added over 5 minutes. Then contents were allowed to cool overnight. The solid so obtained was filtered, washed with ether and crystallized from hot water, yielding 1.3 g of quinoline-4-aldoxime-methiodide (45) was obtained.

m.p.	236-238°C
% yield	71
^{1}H NMR (DMSO-d_6)δ	4.1 (b, 1H, NO<u>H</u>), 4.4 (s, 3H, C<u>H</u>$_3$), 7.7-9.3 (m, 6H, aromatic protons)
IR (KBr) cm^{-1}	3144 (br, O-H stretching), 1612 (sh, C=N stretching)
Analysis	$C_{11}H_{11}N_2OI$, % Calc.: C = 42.42, H = 3.46, N = 8.90, I = 40.60. Found (%): C = 42.03, H = 3.50, N = 8.91, I = 40.44

Synthesis of Quinoline-3-aldoxime Methiodide (47)

Quinoline-3-aldoxime (46)

To quinoline-3-aldehyde (1.57 g, 0.01 mole) in 50 ml of methanol was added $NH_2OH.HCl$ (1.035 g, 0.015 mole) and 4 drops of pyridine. The contents were refluxed for 4 hr, methanol was evaporated and 50 ml of water was added. The solid obtained was filtered and crystallized from methanol, giving 1.35 g of quinoline-3-aldoxime (46).

m.p.	226-228°C, [Lit][11] m.p. 228°C
% yield	78

Quinoline-3-aldoxime Methiodide (47)

Quinoline-3-aldoxime methiodide (46, 1 g, 0.0081 mole) was dissolved in 10 ml of DMF. The contents were warmed to 90° and then excess of methiodide was added. Then contents were allowed to cool overnight. The solid so obtained was filtered , washed with ether and crystallized from hot water. Thus 1.2 g of quinoline-3-aldoxime methiodide (47) was obtained.

m.p.	262°C
% yield	66
^{1}H NMR (DMSO-d_6)δ	3.2 (s, NO<u>H</u>), 4.5 (s, 3H, C<u>H</u>$_3$), 7.8-8.5 (m, 5H), 9.2 (s, 1H), 9.8 (s, 1H)
IR (KBr) cm^{-1}	3200 (br, O-H stretching), 1630 (sh, C=N stretching)
Analysis	$C_{11}H_{11}N_2OI$, % Calc.: C = 42.05, H = 3.63, N = 8.87, I = 40.67 % Found: C = 42.03, H = 3.50, N = 8.91, I = 40.44

Antipyrine-4-aldoxime methiodide (51)

Antipyrine-4-aldehyde (49)

To antipyrine (49), 5 g, 0.0266 mole) was added 10 ml of $POCl_3$ and 4 ml of dimethyl formamide.

The contents were allowed to reflux for 4 hr. After this the $POCl_3$ was removed and water (100 ml) was added to flask. Extraction with chloroform (4 x 100 ml), followed by drying and evaporation of chloroform afforded 4 g antipyrine-4-aldehyde (49).

m.p.	161°C, [Lit][12] m.p. 160-162°C
% yield	69

Antipyrine-4-aldoxime (50)

To a methanolic solution (100 ml) of antipyrine-4-aldehyde (49, 4.5 g 0.0208 mole) is added $NH_2OH.HCl$ (1.46 g, 0.0208 mole) and CH_3COONa (1.66 g, 0.0208 mole). The contents were refluxed for 4 hr. After refluxing the volume was reduced to half. To this wass added water and left overnight. 3.5 g of solid was obtained after filtration.

m.p.	192°C, [Lit][7] m.p. 192-193°C
% yield	72

Antipyrine-4-aldoxime methiodine (51)

Antipyrine-4-aldoxime (50, 3 g, 0.0129 mole) was dissolved in 15 ml of DMF. The contents were warmed to 150°C, 5 ml of methiodidewas added and temperature was maintained for 15 minutes. After this, the solid started to precipitate and the contents were cooled to room temperature. The solid obtained was filtered and washed with ether and crystallized from hot water to provide 2.5 g of 3.

m.p.	223-225°C
% yield	52
^1H NMR (DMSO-d_6)	δ 2.3 (s, 3H, CH_3), 3.2 (s, 3H, CH_3), 3.5 (s, 3H, CH_3), 7.35 (s, 5H, aromatics), 8.5 (s, 1H, CH)
IR (KBr) cm^{-1}	3400 (br, O-H stretching), 1641 (sh, C=O stretching), 1551 (sh, C=N stretching)
Analysis	$C_{13}H_{16}N_3O_2I$, r% Calc.: C = 41.82, H = 4.28, N = 11.26, I = 34.04. % Found: C = 41.39, H = 4.30, N = 6.76, I = 30.67

Preparation of 2,2,6,6-Tetramethyl-4-Piperidoneoxime Hydrochloride (54)

2,2,6,6-Tetramethyl-4-piperidone oxime (53)

To 2,2,6,6-tetramethyl-4-piperidone hydrochloride (52, 1.91 g, 0.01 mole) in methanol was added $NH_2OH.HCl$ (0.690 g, 0.01 mole) and CH_3COONa (1.62 g, 0.02 mole). Contents were refluxed for 3-4 hr, and filtered immediately to remove inorganic salt. The filtrate was concentrated and left at room temperature overnight, giving 1.2 g of solid after filtration.

m.p.	148-150°C, [Lit][13] m.p. 151-153°C
% yield	70.6

2,2,6,6-Tetramethyl-4-piperidoneoxime Hydrochloride (54)

2,2,6,6-Tetramethyl-4-piperidone oxime (1.2 g, 0.007 mole) was dissolved in dry methanol (60 ml). To this solution dry HCl was passed for 15 minutes and contents were left overnight at room temperature. The solid was filtered and crystallized from water, yielding 1 g of 2,2,6,6-tetramethyl-4-piperidone oxime

hydrochloride.

m.p.	295-298°C
% yield	69
^{1}H NMR (D_2O)δ	1.1 (s, 12H, 4 x CH_3), 2.1 (s, 2H, CH_2), 2.3 (s, 2H, CH_2)
IR (KBr) cm^{-1}	2791 (br, O-H stretching), 1659 (sh, C=N stretching)
Analysis	$C_9H_{19}N_2OCl$, % Calc.: C = 52.14, N = 13.53, Cl = 16.99
	Found: C = 52.30, H = 9.20, Cl = 17.19

Synthesis of Optically Active Compounds

(±) 2-Oximino-3-tropinone (55)

The above hydrochloride (53, 2.0 g) was dissolved in 30 ml of water and sodium bicarbonate was added in small portions until the pH reached 6. Free base precipitated out of solution, and filtration gave 1.55 g of the free base as a yellow solid.

m.p. 170-173°C (decomposition)

Resolution of (±) 2-Oximino-3-tropinone (55)

(+),(+) 2-Oximino-3-tropinone Tartrate (56)

Racemic 2-oximino-3-tropinone (55, 2.0 g, 0.012 mole) was dissolved in 25 ml of absolute MeOH. (+) Tartaric acid (1.80 g, 0.012 mole) was dissolved in 20 ml MeOH. Both solutions were warmed and then were allowed to cool after mixing. The mixture was stoppered and allowed to stand overnight. Filtration of the mixture gave 1.78 g of the tartrate as a pale yellow crystalline solid.

m.p. 172-177°C

^{1}H NMR (D_2O)δ 4.70 (2H, tartrate methine), 3.0 (3H, N-Me)

(+) 2-Oximino-3-tropinone (57)

The above tartrate (56) was suspended in 20 ml of distilled water and basified with small portions of sodium bicarbonate until the solid went into solution and a small excess caused the free base to precipitate out of solution. Filtration gave 0.80 g of the free base as a yellow solid. The optical purity of the free base the Eu(III) complex was obtained using tris-[3-(trifluoromethylhydroxymethylene)-(+)camphorato]Eu(III) as a shift reagent. The NMR is depicted in Figure 1. Based on the 400 MHz spectrum, the free base was greater than 98% pure.

m.p. 212-214°C

$[\alpha]^{25}D$ +16.88 (MeOH, c = 13.5 mg/ml)

(-),(-) 2-Oximino-3-tropinone Tartrate (60)

Racemic 2-oximino-3-tropinone (55), (2.0 g, 0.012 mole) was dissoved in 25 ml of absolute MeOH. (–) Tartaric acid (1.80 g, 0.012 mole) was dissolved in 20 ml MeOH and both solutions were mixed after warming. The mixture was allowed to cool in a closed flask after addition of 5 ml ethyl acetate. The cloudy solution was allowed to sit overnight. Filtration gave 1.82 g of the tartrate.

m.p. 171-174°C

^{1}H NMR (D_2O)δ 4.70 (2H, methine), 3.0 (3H, N-Me)

(-) 2-Oximino-3-tropinone (61)

The above salt (35), 1.80 g, was suspended in 20 ml of distilled water and basified slowly with sodium bicarbonate. The solution cleared and with addition of excess bicarbonate, the free base precipitated out of solution. Filtration gave 0.68 g of an orange solid.

m.p. 210°-212°C

$[\alpha]^{25}D$ 16.78 (MeOH, c = 15 mg/ml)

(+) 2-Oximino-3-tropinone Methiodide (59)

The free base (32, 0.150 g) was dissolved in MeOH and stirred with excess MeI. After concentration of the solvent to 5 ml, filtration gave 160 mg of the quarternary salt.

m.p. 224-226°C

Analysis % Calc.: C = 34.84, H = 4.84, N = 9.03, I = 40.96

% Found: C = 34.79, H = 4.97, N = 9.19, I = 40.71

(+) 2-Oximino-3-tropinone Hydrochloride (58)

The free base (32, 70 mg) was dissolved in 4 ml of MeOH and 3 drops of conc. HCl were added. The yellow solution turned clear and a white solid precipitated out. Filtration gave 60 mg of white fluffy crystals.

m.p. 242-250°C

Analysis % Calc.: C = 46.94, H = 6.36, N = 13.69, Cl = 17.36

% Found: C = 47.17, H = 6.70, N = 13.88, Cl = 17.69

(-) 2-Oximino-3-tropinone Methiodide (63)

The free base (36, 100 mg) was dissolved in 8 ml of MeOH and allowed to sit overnight at room temperature with an excess of MeI in a stoppered flask. After concentrating the solution to one half the original volume, filtration gave 135 mg of crystalline yellow product.

m.p. 218-220°C

Analysis % Calc.: C = 34.84, H = 4.84, N = 9.03, I = 40.96

% Found: C = 34.99, H = 4.98, N = 8.96, I = 41.04

(-) 2-Oximino-3-tropinone Hydrochloride (62)

The free base (36, 60 mg) was dissolved in 4 ml of absolute methanol. Three drops of conc. HCl was added, the solution lost its yellow color and a white solid precipitated out. Filtration gave 45 mg of the HCl salt.

m.p. 235-245°C

Analysis % Calc.: C = 46.94, H = 6.36, N = 13.69, Cl = 17.36

% Found: C = 46.77, H = 6.52, N = 13.57, Cl = 17.44

(-) 3-Oximino-2-Tropinone Methiodide (68)

(-) 2-Carbomethoxy-3-Tropinone (66)

Racemic 2-carbomethoxy-3-tropinone (65, 1.51 g, 0.768 mole) was dissolved in 400 ml absolute methanol with warming. D(-)Tartaric acid (115.3 g, 0.768 mole) dissolved on warming in 400 ml of absolute methanol. The two solutions were combined while still warm. The diastereomeric salt was isolated by filtration and was dissolved in 750 ml of water. The aqueous solution was made alkaline with an excess of sodium bicarbonate. At pH 8, the solution was exhaustively extracted with chloroform. After drying and evaporation at reduced pressure, the crude oil was swirled with acetone and allowed to crystalline. Filtration gave 72.3 gof the desired (-) isomer.

% yield	95.2
$[\alpha]^{25}D$	-20.35 [Lit. $[\alpha]^{25}$ = -20.15] [65]

(-) 3-Oximino-2-tropinone (67)

The ketone (55a), prepared using the degradation scheme used to prepare (+) 2-tropinone, (4.0 g, 0.0288 mole) was dissolved in 100 ml absolute methanol. To this solution was added 3 ml of conc. HCl. After 15 minutes, 12 ml of t-butyl nitrate was added dropwise to the stirring solution. The solution was kept at room temperature overnight. Filtration gave the hydrochloride, which was immediately dissolved 75 ml of water. The aqueous solution was carefully neutralized with sodium bicarbonate to pH 7 and extracted with chloroform. Drying and evaporation gave 0.82 g of the ketooxime.

% yield 16.85

(-) 3-Oximino-2-tropinone Methiodide (67)

The above ketone (40, 0.80 g, 0.0049 mole), was dissolved in 50 ml of dry chlorofrom and treated with a large excess of methyl iodide. The solution was stoppered and allowed to sit overnight. Filtration gave 0.986 g of the methiodide as a pale yellow powder. Spectrl data, NMR and IR, matched that of the (+) isomer.

% yield	65
$[\alpha]^{25}D$	-17.28 (H_2O, c = 2 mg/ml)
Analysis	% Calc.: C = 34.84, H = 4.84, N = 9.03, I = 40.96
	% Found: C = 35.18, H = 4.88, N = 8.85

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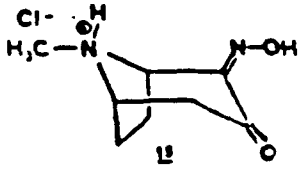
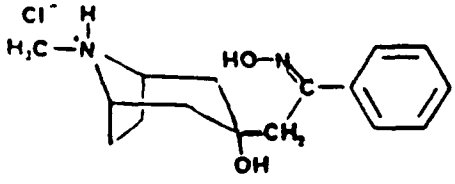
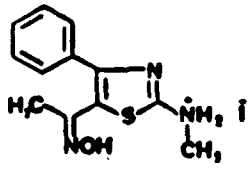
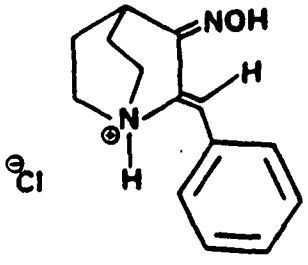
9. PUBLICATIONS FROM THE THIRD YEAR

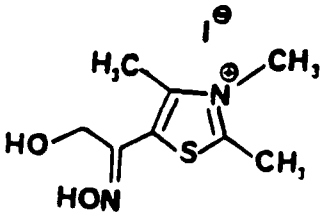
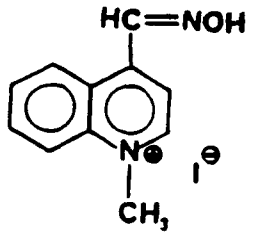
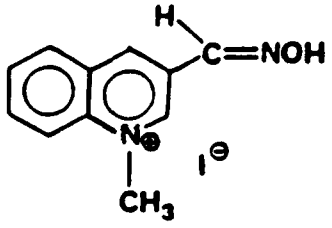
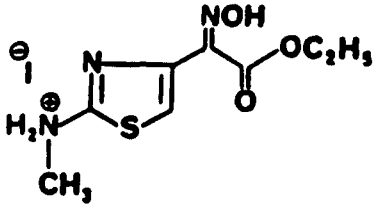
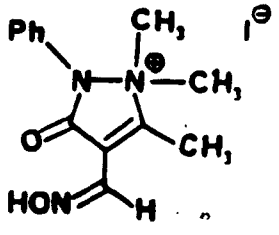
1. Hypervalent Iodine Oxidation of 1-Trimethylsilyloxy, 1-(2'-Trimethylsilyloxyphenyl)ethene. Synthesis of 3-Coumaranone and 2,2'-Dihydroxyacetophenone. R.M. Moriarty, O. Prakash and M.P. Duncan, *Syn. Comm.*,**16**, 10 (1986).
2. Hypervalent Iodine Oxidation of Silyl Enol Ethers Under Lewis Acid Conditions in Methanol. General Route α-Methoxy Ketones. R.M. Moriarty, O. Prakash, M.P. Duncan and R.K. Vaid, *J. Org. Chem.*, **52**, 150 (1987).
3. Hypervalent Iodine Oxidation of Silyl Enol Ethers. A Direct Route to a-Hydroxy Ketones. R.M. Moriarty, O. Prakash and M.P. Duncan *J. Chem. Soc. Perkin Tran. I*, 1781 (1987).
4. Carbon-Carbon Bond Formation Using Hypervalent Iodine Under Lewis Acid Conditions: Scope of the Method for the Synthesis of Butane-1,4-diones. R.M. Moriarty, O. Prakash and M.P. Duncan *J. Chem. Soc. Perkin Tran I*, 559 (1987).
5. Hypervalent Iodine Oxidation of 5-Substituted and 5-Methyl-4-substituted Pyrazol-3(2H)-ones. A Facile Synthesis of 2-Alkylonic an 2,3-Allenic Esters. R.M. Moriarty, R.K. Vaid, V.T. Vravikumar, T.E. Hopkins and P. Farid, *J. Org. Chem.*, **711**, 1634 (1987).
6. Hypervalent Iodine Oxidation: α-Functionalization of β-Dicarbonyl Compounds using Iodosobenzene. R.M. Moriarty, R.K. Vaid, V.T. Vravikumar, B.K. Vaid and T.E. Hopkins*Tetrahedron*, Submitted (1987).

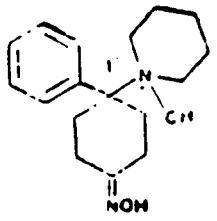
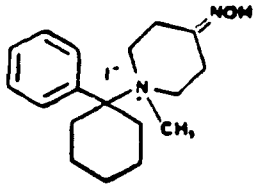
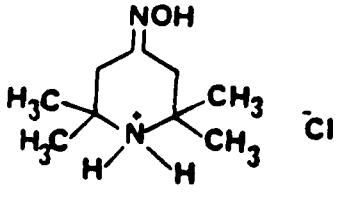
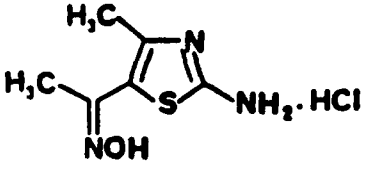
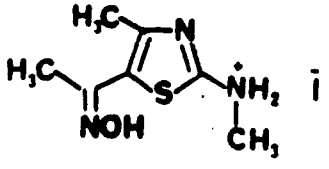
10. PAPERS PRESENTED AT *ACS* MEETINGS

1. One Pot Synthesis of 2-Amino-4,5-substituted Thiazoles and 2-Amino-4,5-substituted Seleanazoles Using [Hydroxy(tosyloxy)iodo]benzene, Ketones and Thiourea/Selanaaaaurea in Acetonitrile. R.M. Moriarty, B.K. Vaid, R.K. Vaid and M.P. Duncan.
2. Hypervalent Iodine Oxidation of 5-Substituted and 5-Methyl-4-substituted Pyrazol-3(2H)-ones. A Facile Synthesis of 2-Alkynoic an 2,3-Allenic Esters. R.M. Moriarty, R.K. Vaid and P. Farid.

11. COMPOUNDS SUBMITTED TO WRAIR

CODE NO	COMPOUND STRUCTURE	COMPOUND NAME	QUANTITY
PRV-234		Tropan-3-one oxime hydrochloride	1.90 g
PRV-188		2-Oximino tropan-3-one hydrochloride	2.0 g
PRV-244		3-α-Acetophenyl tropine oxime hydrochloride	2.0 g
BKV-158		2-Methylamino-4-phenyl-5-acetyl-thiazole oxime hydroiodide	1.95 g
PRV-255		2-Benzylidene-3-quinuclidinone oxime hydrochloride	1.95 g

CODE NO	COMPOUND STRUCTURE	COMPOUND NAME	QUANTITY
RKV-88		2,4-Dimethyl-5-(α-hydroxymethyl oximino)thiazole methiodide	1.7 g
RKV-102		Quinoline-4-aldoxime methiodide	2.0 g
RKV-101		Quinoline-3-aldoxime methiodide	2.0 g
RKV-122		Ethyl 2-amino-α-(hydroxyimino)-4-thiazoleacetate methiodide	2.0 g
RKV-141		Antipyrine-4-aldoxime methiodide	2.0 g

CODE NO	COMPOUND STRUCTURE	COMPOUND NAME	QUANTITY
RKV-138		4-(1-Piperidinyl)-4-phenyl cyclohexanone oxime methiodide	1.95 g
PRV-157		1-(1-Phenylcyclohexyl) 4-piperidone oxime methiodide	2.0 g
BKV-22		2,2,6,6-Tetramethyl-4-piperidone hydrochloride	2.0 g
BKV-1-23		2-Amino-4-methyl-5-acetyl oximinothiazole hydrochloride	1.95 g
BKV-1-24		2-Methylamino-4-methyl-5-acetyl thiazole oxime hydroiodide	1.95 g