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IMPROVED MUSCARINIC ANTAGONISTS AS ANTICHOLINESTERASE ANTIDOTES

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Muscarinic antagonists play an important role in anticholinesterase agent therapy by reducing the response of muscarinic receptors to acetylcholine, acting synergistically with cholinesterase reactivators. Therapy with antagonists such as atropine is difficult to manage because of the toxicity of these compounds. Atropine antagonizes the receptor whether or not acetylcholine levels are elevated.

Our approach to the development of a better antidote is to design a molecule whose concentration and resulting muscarinic antagonist activity is controlled by the degree of cholinesterase inhibition, and thus by the need for the drug. This is accomplished by incorporating into the same molecule features that confer muscarinic antagonism and susceptibility to hydrolysis by cholinesterase. Such compounds should be rapidly degraded by cholinesterase to inactive products in a normal system, but should remain active when cholinesterase has been inhibited. As

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the cholinesterase activity recovers, the compounds should again be hydrolyzed. The proper combination of muscarinic antagonism and susceptibility to cholinesterase hydrolysis should allow these compounds to be used at higher doses with fewer side effects.

During this reporting period we have continued to investigate the structure-activity relationships for esters of S-(-)-tropic acid. A variety of quaternary salts of S-(-)-2-*N,N*-dialkylaminoethyl esters and S-(-)-2-(1-piperidinylethyl) and 2-(1-pyrrolidinylethyl) esters have now been synthesized and tested for muscarinic receptor binding and cholinesterase hydrolysis *in vitro*. Research on the synthesis of novel ester derivatives of S-(-)-tropic acid incorporating *N*-methylpyrrolidine and *N*-methylpiperidine terminal functions linked by suitable side chains through the 2 and 3 positions respectively has also been initiated, but difficulties have been encountered in obtaining the derivatives in crystalline form.

We have now synthesized (±)-4-chlorotropic acid and obtained pure (-)-4-chlorotropic acid by resolution with quinine. Synthesis of quaternary salts of 2-*N,N*-dialkylaminoethyl ester derivatives incorporating onium head groups designed to give optimum musarinic binding affinity are now in progress. The synthesis of three 2-*N,N*-diethylaminoethyl ester derivatives of benzylic acid and their *in vitro* testing has been completed.

In vitro testing carried out by at SRI International has shown that the majority of the compounds synthesized during this contract period bind to the muscarinic receptor in rat brain homogenates with an affinity similar to that of atropine and that several of these compounds (e.g. SR 4952) bind significantly more strongly. Cholinesterase hydrolysis of these compounds proceeded as expected and gave a wide range of values ($t_{1/2}$ = 29-68 min). All results have been completed in duplicate.

In conclusion, during this reporting period several derivatives of S-(-)-tropic acid have been synthesized that demonstrate muscarinic binding affinities similar to, or in some cases significantly better than atropine and which undergo hydrolytic cleavage by serum cholinesterase *in vitro* at a wide range of differing rates. We have in fact, designed compounds that fit our model, for agents that would be potentially useful as antidotes for Organophosphorus poisoning. With the appropriate *in vivo* testing we should be able to determine what hydrolysis rate would be optimal for protection from cholinesterase inhibition. We will then be able to tailor our additional synthetic efforts to produce compounds of the appropriate characteristics to maximize their protective effects.

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the US Army.

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02. 22. 1990.

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The synthesis described in this report was performed by Dr. Michael Tracy, Dr. Andrew B. Kelson, and Mr. Kenneth J. Ryan and the *in vitro* pharmacological assays by Dr. Larry R. Toll and Ms Susan R. Brandt.

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INTRODUCTION

This report summarizes the technical efforts undertaken on U.S. Army Medical Research and Development Command Contract No. DAMD17-C-8147 and covers progress during the period 1 September 1988 through 31 August 1989.

Poisoning by organophosphorous chemical warfare agents and pesticides results in the inhibition of acetylcholinesterase and a concomitant inhibition of nerve function due to the buildup of acetylcholine. Treatment of this type of poisoning involves administering 2-hydroxyiminomethyl-1-methylpyridinium (2-PAM) to reactivate the inhibited enzyme and an antimuscarinic agent (such as atropine) to antagonize the actions of excess acetylcholine.

Antidotal therapy with antimuscarinic agents is difficult to manage because these compounds are quite toxic and can have serious side effects. Thus, although the effective treatment of anticholinesterase poisoning may require 20 to 50 mg of atropine in the first day,[1] soldiers at risk are issued injectors containing only 2 mg because of the antidote's extreme toxicity.[2]. Other muscarinic antagonists, such as benactyzine and quinuclidinyl benzilate (QNB), are better antidotes than atropine, but are not used extensively because of their severe side effects.

The toxicity of atropine is inherent in its mode of action. To counteract the action of the excess acetylcholine that results from anticholinesterase intoxication, atropine competes with acetylcholine for muscarinic receptors in the nervous system and at peripheral organs. Because the binding of atropine, unlike that of acetylcholine, does not cause nerve impulse or mimic the peripheral actions of acetylcholine, atropine reduces the activity in a poisoned system to a level closer to normal. However, in an unpoisoned system atropine also reduces the level of activity induced by acetylcholine, and because it is metabolized very slowly to inactive components, it continues to poison the system even when the levels of enzyme return to normal. Metabolism studies in man have shown that 50% of the administered dose of atropine is excreted unchanged in the urine. For antidotal purposes, the ideal antimuscarinic drug would be one that is active in the poisoned system, yet inactive when the system is functioning normally.

We initially started work on this problem in 1983 (under USAMRDC Contract No. DAMD17-83-C-3109). We proposed that such an ideal antidote can be designed by incorporating into the molecule, features that allow the antimuscarinic activity of the antidote to be modulated by

the degree of cholinesterase activity. This is accomplished by constructing muscarinic antagonists containing an ester linkage that is susceptible to cholinesterase hydrolysis. When such a compound is administered to a system in which cholinesterase is functioning normally, the compound is degraded to inactive products, rendering it nontoxic. If the cholinesterase has been inhibited, the compound retains antimuscarinic activity and thus acts as an antidote. As cholinesterase activity returns, the drug is removed from the system. The antidote should also not exhibit significant inhibition of cholinesterase since the hydrolytic action of the enzyme is essential in reducing the levels of acetylcholine and returning the system to normal.

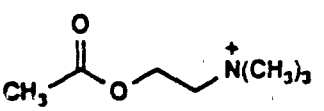
Such a compound has several advantages. First, it could be administered more readily in suspected cases of poisoning without fear of overdose. Second, the side effects would be of a shorter duration, since the drug would only last in the system as long as it was needed. Finally, this type of antidote lends itself to the development of a controlled-release drug that could be administered to personnel at risk, before their exposure to agents, without fear of side effects.

Our research to date has shown that such compounds can be synthesized and that inhibition of cholinesterase prolongs their activity in tissue homogenates. Furthermore, we have found several such compounds whose activity equals or exceeds that of atropine in the Institute for Chemical Defense (ICD) tests.

APPROACH

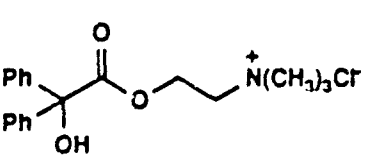
This research is based on the premise that antimuscarinic activity and susceptibility to cholinesterase hydrolysis can be combined in one molecule. The binding sites of cholinesterase [3] and the muscarinic receptor[4,5] have been extensively studied and have several structural requirements in common.

Muscarinic antagonists bind to the muscarinic acetylcholine site but produce no receptor response. As a general rule, substitution of increasingly large hydrocarbon groups on either terminus of acetylcholine (**1**) leads first to muscarinically inactive compounds and then to muscarinic antagonists.[4,5]



1

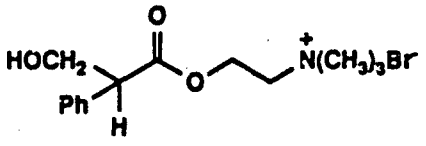
A typical atropine-like anticholinergic agent contains a cationic head and a heavy blocking moiety (cyclic groups), which are connected by a chain of atoms of definite length that generally contains an ester function. The cationic head is an essential group in a large number of anticholinergic compounds and the mechanism of action of such substances has been linked very closely with it. It is assumed that the cationic head with its positive charge is attracted by an anionic site on the muscarinic receptor, which seemingly starts the process of adsorption. Following this attraction, the weaker hydrophobic and dipole-dipole forces go into action to contribute to the stability of the drug-receptor complex. In such an interaction, not only the charge of the cationic head but also its size and shape are vitally important. Thus, successive replacement of the methyl groups of acetylcholine with ethyl groups produces a progressive reduction in muscarinic activity.[6] In contrast, replacing the *N*-methyl groups of *N*,*N*-dimethylamino-ethylbenzilate methochloride (**2**) with ethyl groups produces maximal blocking activity.[7]



2

Further increase in size to butyl or larger alkyl groups reduces or abolishes the activity.[5,7-9] Heterocyclic rings such as tropane in atropine also yield high antimuscarinic activity.

At the acyl end of the molecule, the most active anticholinergics contain two cyclic substituents as blocking groups at the same carbon atom (e.g., 2) or one cyclic substituent and a hydroxyl function as exemplified by the esters of tropic acid (e.g., tropinoylcholine 3).[4]



3

The cyclic structure does not necessarily have to be phenyl, since compounds with cyclohexyl rings also show excellent anticholinergic activity and substances containing both rings are even better.[10] The addition of a second phenyl ring into the α-carbon in the acyl portion of tropinoylcholine, however, actually lowers the anticholinergic activity.[4] Planar heterocyclic groups such as thiophenes have also been introduced at the acyl end of the molecule, and these compounds retain anticholinergic activity. It has been suggested that the cyclic groups form an additional contact with the muscarinic recepter by hydrophobic or van der Waals forces. As a result, this contact is strengthened and the muscarinic receptors are protected from approaching molecules of acetylcholine.

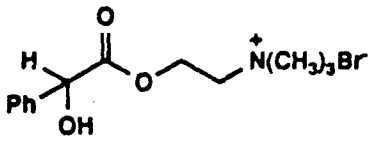
The presence of the cationic head and of cyclic blocking groups is not sufficient for optimal anticholinergic activity; the activity also depends on the mutual distribution of these groups. Several studies[7,9,11] have shown that the linking chain containing a potentially hydrolyzable ester should be of the form CCOCC, with no alkyl substitution on the carbons α or β to the nitrogen for high anticholinergic activity.

The successful antidote will incorporate the above features into a molecule that can be hydrolyzed by cholinesterase. The optimal system would use acetylcholinesterase as the hydrolytic enzyme. However, this enzyme will not accommodate the structural features necessary for muscarinic antagonism. Fortunately, serum cholinesterase is inactivated by anticholinesterase agents at rates similar to the rate of acetylcholinesterase inactivation and hydrolyzes a broader range of substrates.[3,12]

Serum cholinesterase hydrolyzes choline esters containing a variety of hydrophobic acyl groups. Large, aromatic acyl groups have a higher affinity for the enzyme, and in some cases this tighter binding is accompanied by a lower hydrolytic rate. The enzyme is more sensitive to the structure of the choline moiety. Addition of an α- or β-methyl group to choline or increasing the distance from the nitrogen to the ester linkage both cause a dramatic loss of binding affinity of butyrylcholine to the enzyme. Cholinesterase is also very sensitive to the size of the choline "head" in that larger structures have lowered affinity, suggesting that the dimensions of the anionic center in the enzyme are limited.[3]

The binding specificities for cholinesterase hydrolysis and muscarinic antagonism suggest a family of compounds containing aryl, hydroxyl-containing carboxylic acids linked to choline derivatives. Many compounds that fall into this group have been previously synthesized but few have been tested for effectiveness as antidotes for organophosphorous CW agents.

The simplest such compounds and the lead compounds for this study are the R-(+)- and S-(-)- forms of tropinoylcholine (**3**)[13] and the S-(+)- and R-(-)- forms of mandeloylcholine (**4**).[14]



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These compounds are reversible competitive antagonists of acetylcholine at the muscarinic receptors of the guinea pig ileal longitudinal muscle, and one molecule of the antagonist competes with one molecule of the agonist at each site. Their affinity for the muscarinic receptor site is weaker than that for atropine, but they do exhibit the important property of acting as substrates for cholinesterase and being hydrolyzed, albeit slowly, by the enzyme. Both groups of compounds were stereoselective for the muscarinic receptor sites and for cholinesterase, with the (-) configuration exhibiting greater affinity for the receptor site than the (+) configuration and the opposite being the case for the enzyme. These results suggest that the esteratic site of the muscarinic receptor and of cholinesterase may be stereoselective.

In our research we have reasoned that the most effective antidotes would probably have a higher level of antimuscarinic activity and perhaps a slower rate of hydrolysis than mandeloylcholine. It should be remembered that slow hydrolysis for this class of compounds still

probably removes them from the circulation much faster than atropine is removed. From the information available on the binding sites involved, we suggested modifications in the choline head group, in the hydrogen-bonding group of the carboxylic acid moiety, and in the structure of the aromatic ring.

Our *in vitro* results to date (under Contract No. DAMD17-83-C-3109) following the synthesis of a variety of compounds (under Contract Nos. DAMD17-83-C-3109 and DAMD17-85-C-5147), 23 of which have been evaluated *in vivo* by the ICD, have provided insight into how variations in the structure of 3 and 4 affect muscarinic antagonism and cholinesterase hydrolysis.

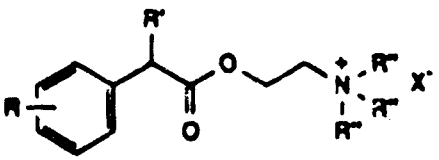
The data in Table 1 shows how the binding affinity for the muscarinic receptor depends on the structure of the amino group for *N,N*-dialkylaminoethyl esters of (+)- and (-)-mandelic and tropic acids. It is clear that the extra methylene group in tropic acid significantly increases the affinity and stereoselectivity of all the esters tested, with the quaternized derivatives of the diethylaminoethyl esters providing consistently lower values of K_i and therefore higher affinities for the receptor. The esters quaternized with alkyl iodides show better affinity for the receptor than do the hydrochlorides in all our *in vitro* tests.

Table 2, which compares the *in vivo* and *in vitro* data for the quaternary salts of the *N,N*-dialkylaminoethyl esters of tropic acid, previously tested by ICD, shows that administration of nine of the compounds resulted in some mice being saved and two were of interest, saving significantly more mice than did atropine. At this point it is difficult to see a firm correlation between the biochemical properties of the compounds and their *in vivo* activity, but several trends seem to be present. Compounds that are hydrolyzed slowly are more likely to be effective, as are compounds that have a higher affinity for the muscarinic receptor. Furthermore, compounds with very high or low toxicities are less likely to be effective.

In addition to the compounds included in the above tables, several other groups of potential muscarinic antagonists have been synthesized and submitted for *in vivo* testing at ICD. The data from these compounds along with that already obtained will help in the refinement of the synthetic goals for the design of more effective antidotes for antimuscarinic agents.

Table 1

Muscarinic Receptor Binding Affinities (K_i) of
N,N-Dialkylaminoethyl Esters of Mandelic and Tropic Acids



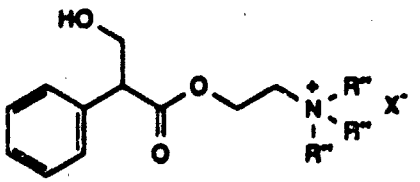
		K_i (nM)			
		Mandelic Acid (R'=OH)		Tropic Acid (R'=CH_2OH)	
R	R" Amine	(+)-isomer	(-)-isomer	(+)-isomer	(-)-isomer
H	NMe_2.HCl	42,000	28,000	280	8.5
H	NMe_3I	1,000	2,000	52.5	5.5
H	NMe_2EtI	1,020	400	15	0.7
H	NEt_2.HCl	50,000	18,000	55	2.4
H	NEt_2MeI	800	290	37	1.5
H	NEt_3I	NA	240	20	0.7
H	pyrrolidine.HCl	NA	NA	55	200
H	morpholine.HCl	NA	NA	NA	66
4-MeO	NMe_2.HCl	NA	NA	650[a]	
1-Naphthyl	NMe_2.HCl	NA		80[a]	
1-Naphthyl	NMe_3I	NA		40[a]	
1-Naphthyl	NEt_2.HCl	NA		213[a]	
H	NMe_3I	NA	NA	110[b]	750[b]
Acetylcholine		3,500			
Atropine		0.32			

[a] (±)Mixture

[b] R' = OH/CH_2OH

Table 2

Comparison of *in vitro* data with *in vivo* Intramuscular Survival Efficacy[a] for *N,N*-Dialkylaminoethyl Tropic Acid Esters in the Mouse



AMINE	ISOMER	Musc. Bind K_i(nM)	Cholin. Hydrol. t ($^1/_2$)min.	IM LD_{50} (mg/kg)	1/16	1/8	1/4
NMe_2.HCl	(+)	280	>120	100	0	0	0
NMe_2.HCl	(-)	8.5	>120	1970	0	1	1
NMe_3I	(+)	52.5	5	736	0	0	0
NMe_3I	(-)	5.5	15	560	0	1	0
NMe_2EtI	(+)	15	>120	180	0	0	0
NMe_2EtI	(-)	0.7	30	940	0	0	0
NEt_2.HCl	(+)	55	NA	NA	NA	NA	NA
NEt_2.HCl	(-)	2.4	60	NA	NA	NA	NA
NEt_2MeI	(+)	37	>120	455	0	0	4
NEt_2MeI	(-)	1.5	>120	243	2	2	2
NEt_3I	(+)	20	>120	1616	0	0	0
NEt_3I	(-)	0.7	>120	284	1	1	3
pyrrolidine.HCl	(+)	55	NA	2420	1	1	0
pyrrolidine.HCl	(-)	200	NA	>400	0	0	1[b]
piperidine.HCl	(+)	NA	NA	2432	1	0	0
morpholine.HCl	(-)	66	NA	>361.5	0	1	0[c]

[a]Compound administered with 2-PAM after GD challenge, at doses equal to the indicated fraction of the LD_{50}. Corrected number of survivors out of 10 is indicated.

[b,c]Dose fractions [b]1/256 1/32 1/4 [c]1/64 1/16 1/4.

RESULTS AND DISCUSSION

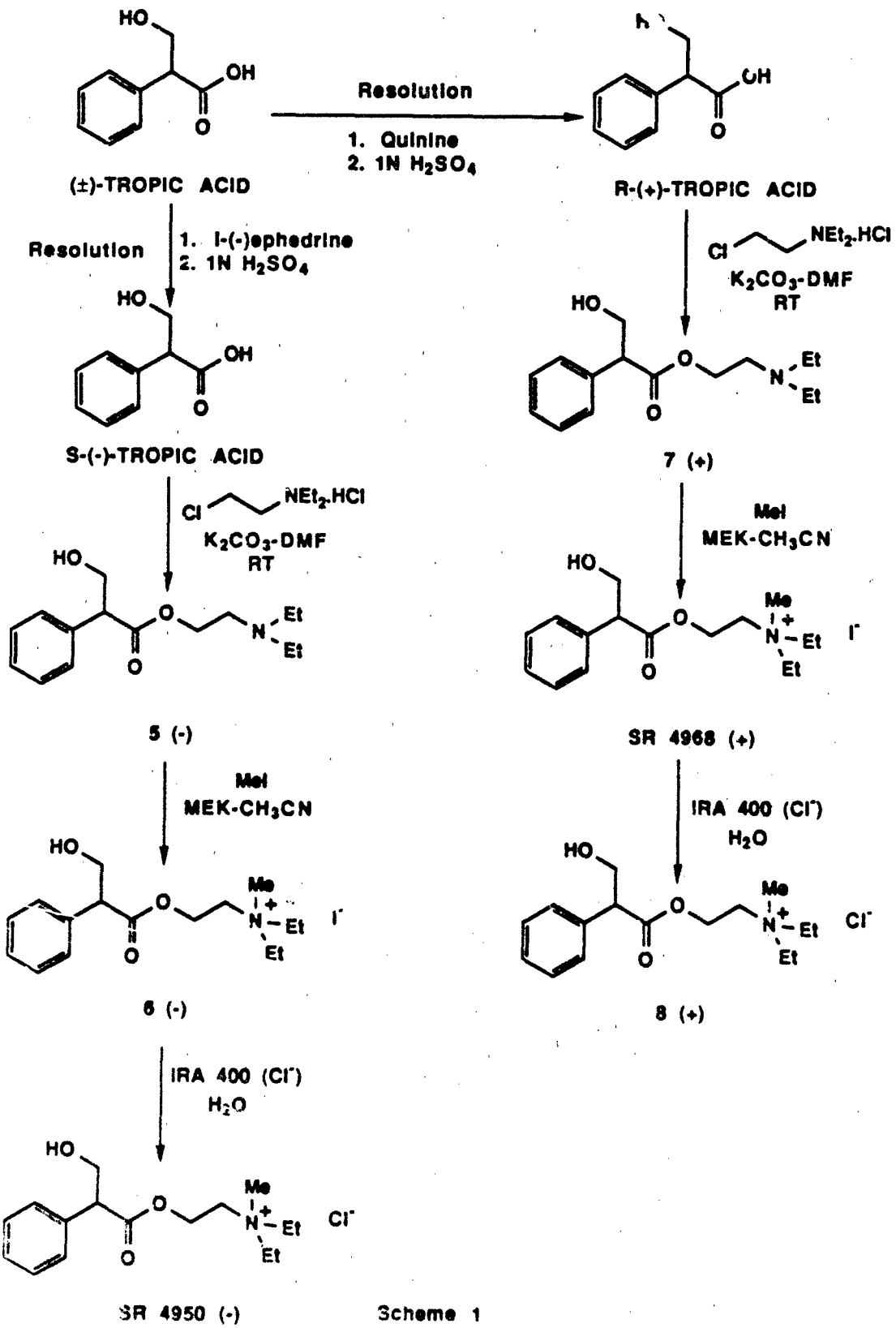
Chemistry

The data from the *in vitro* muscarinic binding studies shown in Table 1 clearly demonstrates the stereoselective specificity of the muscarinic receptor for the S-(-)-isomers of the quaternary salts of the *N,N*-dialkylaminoethyl esters of tropic acid. It is also clear that the presence of the extra methylene group in tropic acid, compared to mandelic acid, significantly increases the affinity and stereoselectivity of all the esters tested, with the quaternized derivatives providing consistently lower values of K_i and therefore higher affinities for the receptor.

It was therefore decided to continue to investigate the tropic acid derivatives, as outlined in the Statement of Work for this contract (Compounds **28-35**), and to concentrate on the synthesis and *in vitro* and *in vivo* testing of esters of S-(-)-tropic acid. Careful choice of the alkyl substituents on the onium end of the molecule should produce muscarinic binding affinity superior to that of atropine, while still yielding a molecule which can be readily hydrolyzed to inactive components by cholinesterase These two factors are of paramount importance in the design of drugs which will be more effective than atropine as antidotes for antimuscarinic agents.

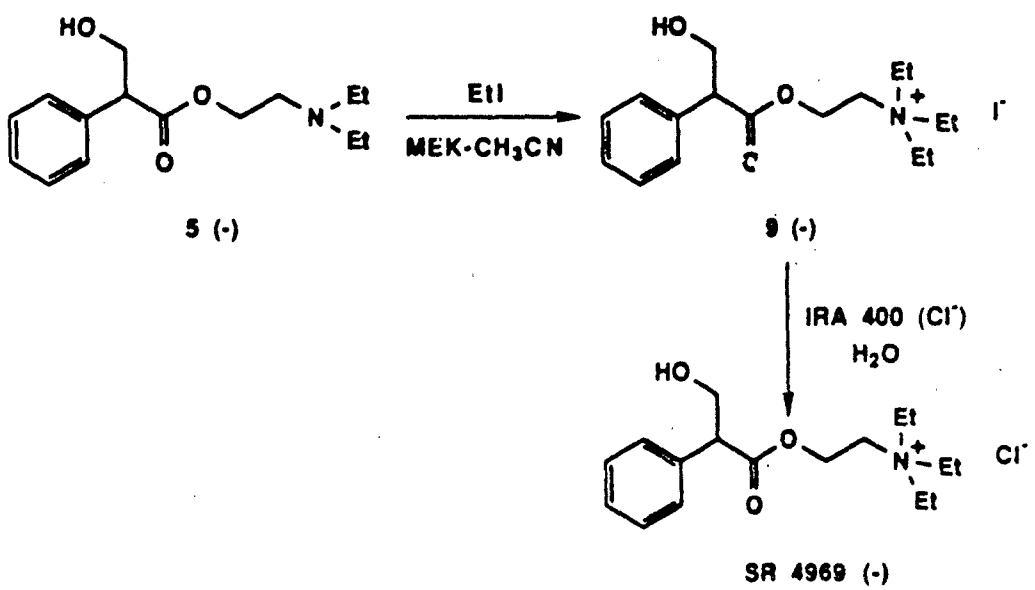
Resolution of (±)-tropic acid was completed on a large scale (3x100g) using methodology previously carried out on a small scale at SRI International (Scheme 1). Initial reaction of (±)-tropic acid with quinine in ethanol gave the R-(+)-tropic acid quinine salt as a white crystalline solid which on recrystallization and treatment with 1N H_2SO_4 yielded R-(+)-tropic acid with an optical purity of 98%, in good yield (40%). Concentration of the combined filtrates from the initial reaction and subsequent recrystallizations, followed by acidification yielded a mixture enriched in S-(-)-tropic acid. Treatment with l-(-)-ephedrine in 60% aq. ethanol, recrystallization of the salt formed, and acidification, gave S-(-)-tropic acid also in good yield (45%) and in high optical purity (~100%).

Reaction of S-(-)-tropic acid with 2-*N,N*-diethylaminoethyl chloride hydrochloride using reaction conditions optimized by us in previous syntheses (K_2CO_3-DMF, RT) gave the 2-*N,N*-diethylaminoethyl ester (**5**) in 77% yield. Reaction with MeI gave the methoiodide (**6**) which was converted into the methochloride (**SR 4950**) by passage down an IRA 400 (Cl^-) resin column. Recrystallization of the lyophilized material gave product which retained the high optical purity of the parent acid (α_D=-21).


(±)-TROPIC ACID
Resolution
1. Quinine
2. 1N H_2SO_4
R-(+)-TROPIC ACID
Resolution
1. l-(-)ephedrine
2. 1N H_2SO_4
S-(-)-TROPIC ACID
NEt_2.HCl
K_2CO_3-DMF
RT
7 (+)
MeI
MEK-CH_3CN
SR 4968 (+)
5 (-)
IRA 400 (Cl^-)
H_2O
6 (-)
8 (+)
SR 4950 (-)

Scheme 1

Quaternization of 5 with ethyl iodide (2-butanone-CH_3CN) gave the ethoiodide (9) which could not be crystallized. However, conversion into the ethochloride (SR 4969), by passage of the compound down an IRA 400 (Cl^-) ion exchange resin, and recrystallization of the lyophilized residue gave product as white crystalline needles (Scheme 2).



Scheme 2

Resynthesis of R-(+)-α-(hydroxymethyl)benzeneacetic acid, 2-*N*,*N*-diethylaminoethyl ester methoiodide (**SR 4968**, Scheme 1), the most active derivative tested by ICD *in vivo* in combination with 2-PAM after GD challenge, and its conversion into the less toxic methochloride (8) was carried out. The synthesis followed closely that described for the S-(-)-isomer (SR 4950) and the product was isolated in 40% overall yield.

Considerable investigation into HPLC methodology necessary for the confirmation of the purity of samples synthesized as part of this contract was carried out on the two methoiodides (6) and (**SR 4968**) but without success. The purchase of HPLC columns, sold by Rainin, and described as being capable of separating optically active isomers suggested that we might be able to use HPLC to confirm whether optically pure starting materials, intermediates or products were

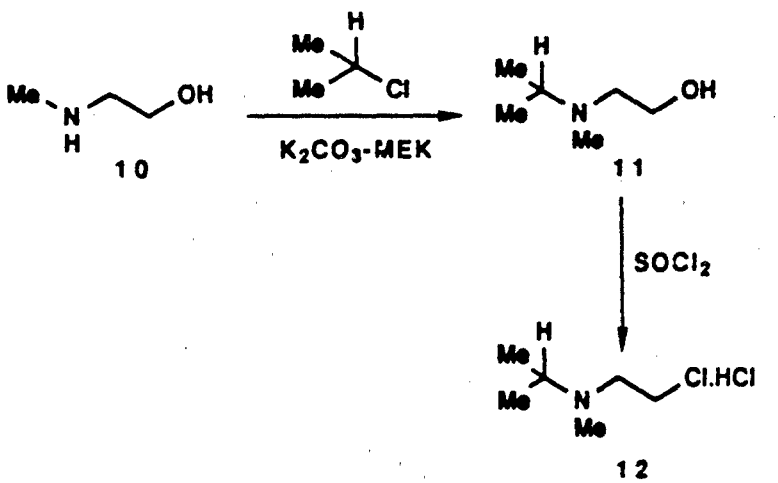
undergoing any racemization during the synthesis of targets. Unfortunately chromatographic separation of pure compounds **6** and **SR 4968** and mixtures of the two compounds was poor using a variety of mobile phases and yielded little information that could not be obtained from measurement of the $[\alpha]_D$ values. When samples of the two compounds were sent to Rainin they were unable to improve upon the disappointing resolution we had obtained. This approach to determining optical purity of the products was therefore discontinued.

During the course of the research on the ion exchange process we have found that there were instances when analytical analysis of the methochlorides produced (e.g. **SR 4969**) clearly showed that the process of converting the iodides into chlorides i.e. by passage down an IRA 400 (Cl^-) ion exchange column, had not gone to completion. In order to expedite the analytical process, since the ion exchange methodology is such an integral part of the synthesis of the majority of the products in this contract, we developed a color test to determine whether a product was pure. The test was a very simple one. A small quantity of the product was dissolved in an acid solution of soluble starch, addition of a few drops of 30% H_2O_2 then immediately indicated the presence of any iodide in the sample by the formation of a dark color due to the presence of I_2. We have now used this test extensively to analyze products and found it to be a good indicator of complete conversion of iodides into chlorides.

Cusic and Robinson have shown[15] that the introduction of *iso*-propyl groups into the onium terminus of the quaternary salts of 2-*N*,*N*-dialkylaminoethyl esters of (±)-tropic acid yielded compounds, that exhibited anti-acetylcholine activity that was superior to that of atropine in their test system.

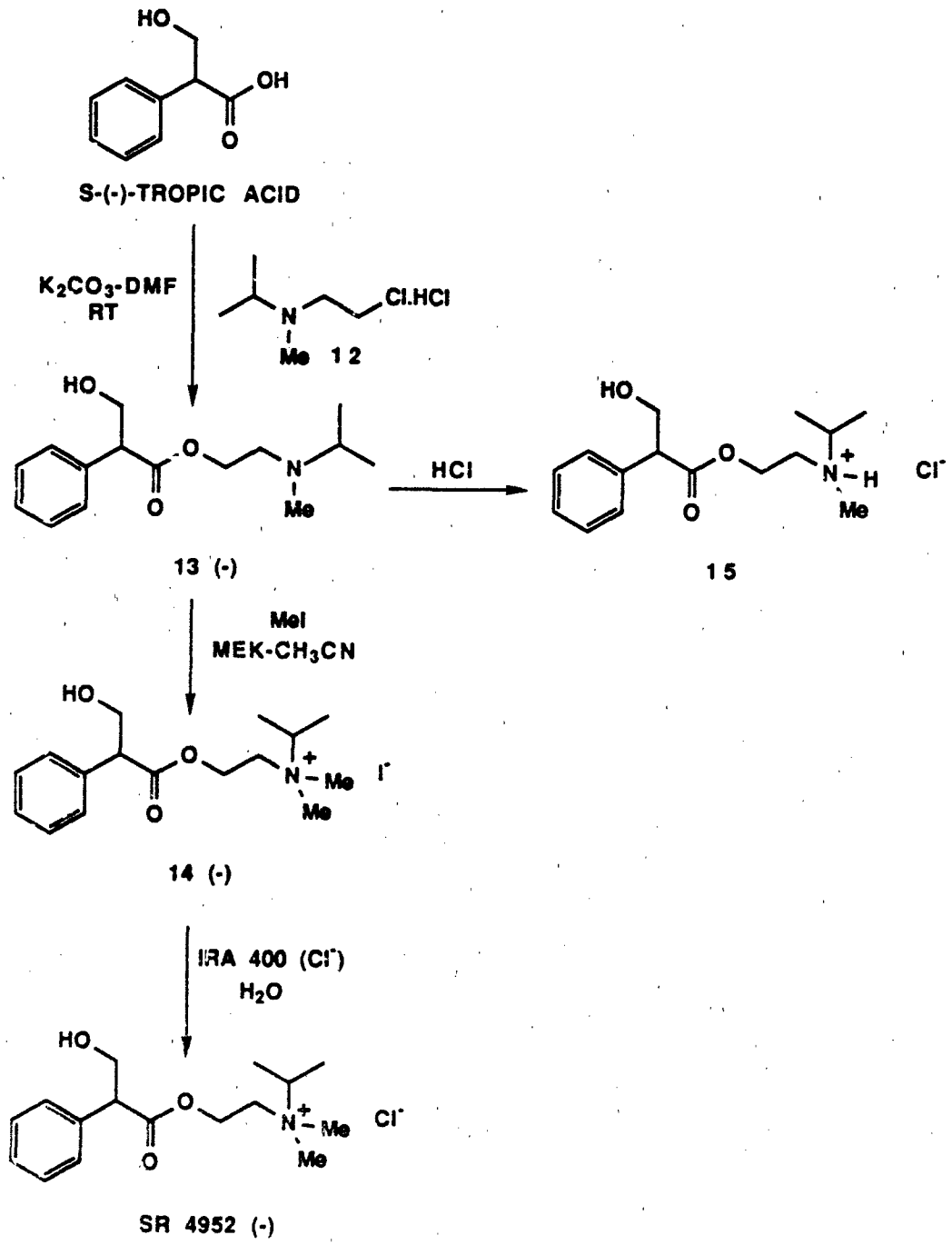
The synthesis of a series of similar compounds (Schemes 3 and 4) incorporating 1 or 2 *iso*-propyl groups starting from S-(-)-tropic acid was therefore initiated, in order to carry out *in vitro* tests to determine the binding affinity of these agents for the muscarinic receptor and their rate of hydrolytic cleavage by cholinesterase. Careful analysis of these data will give us an indication as to whether these agents will possess the necessary *in vivo* activity we are attempting to potentiate.

Synthesis of these two series of compounds was carried out using the methodology we have previously developed at SRI International. The appropriate chloride, 2-*N*-*iso*-propyl-*N*-methylaminoethyl chloride hydrochloride (**12**), was synthesized, as shown below, in high yield.

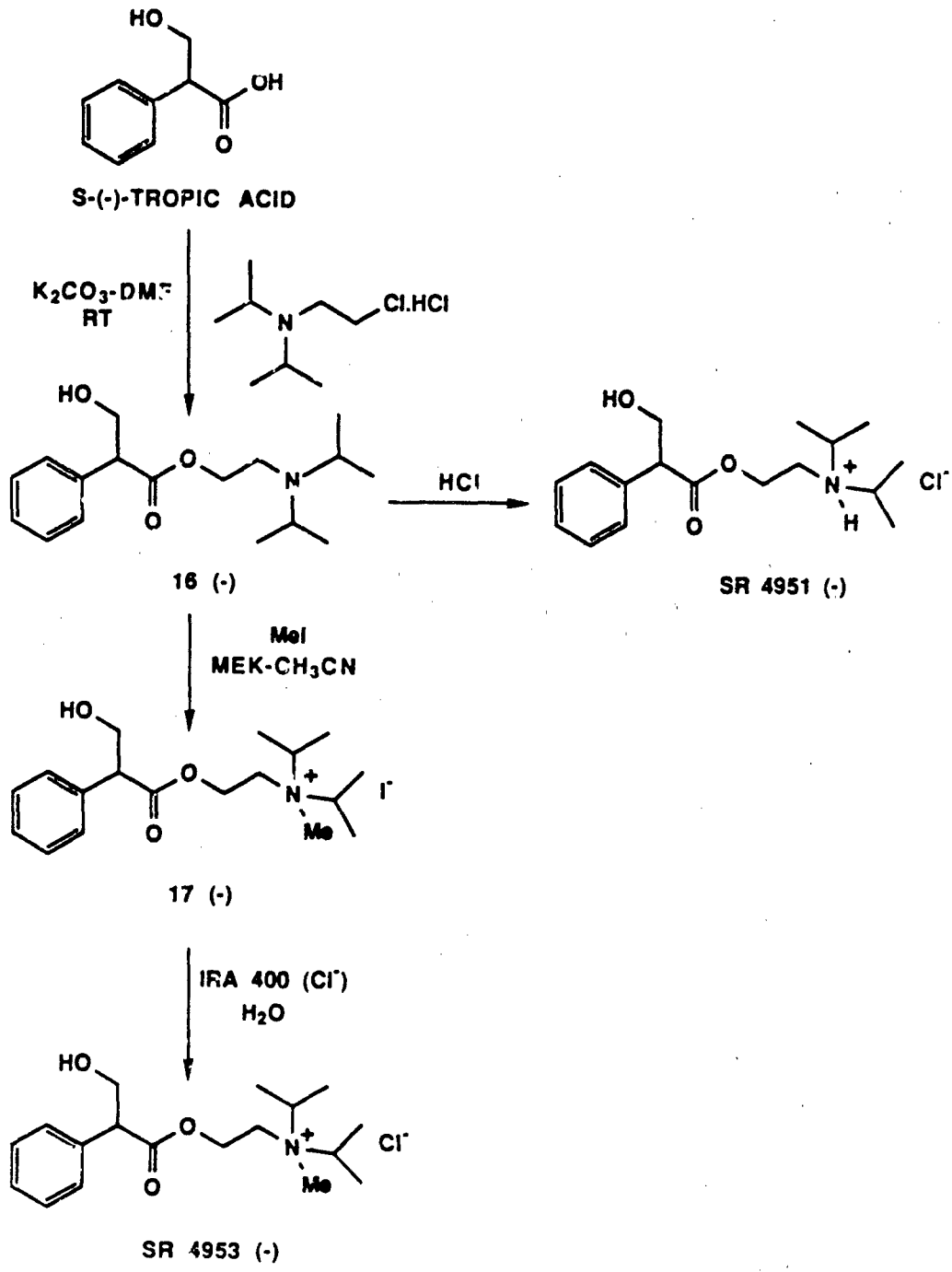


Reaction of **12** with S-(-)-tropic acid, employing usual conditions (Scheme 3), gave the 2-*N-iso*-propyl-*N*-methylaminoethyl ester (**13**) in 77% yield. Acidification with gaseous HCl-Et_2O gave an oil (**15**) which did not crystallize. Examination of the product by ^1H NMR at 400MHz showed the presence of two diastereoisomers. Attempted separation of the two isomers by normal chromatographic techniques proved unsuccessful. Reaction of **13** with methyl iodide gave the methoiodide salt (**14**) as a pure isomer which was converted into the methochloride (**SR 4952**).

The second series of targets incorporating two *iso*-propyl groups (Scheme 4) were synthesized from commercially available 2-*N,N*-di-*iso*-propylaminoethyl chloride hydrochloride. Reaction with S-(-)-tropic acid under usual conditions gave the 2-*N,N*-di-*iso*-propylaminoethyl ester (**16**) in 56% yield. Acidification with gaseous HCl-Et_2O gave the hydrochloride (**SR 4951**) as a white crystalline solid. Reaction of **16** with methyl iodide gave the methoiodide salt (**17**) which was converted into the methochloride (**SR 4953**) by passage down an IRA 400 (Cl^-) ion exchange resin.


HO
OH
O
S-(-)-TROPIC ACID
K2CO3-DMF
RT
Cl.HCl
N
Me
12
HO
O
O
N
Me
13 (-)
HCl
HO
O
O
N+
H
Me
Cl-
15
MeI
MEK-CH3CN
HO
O
O
N+
Me
Me
I-
14 (-)
IRA 400 (Cl-)
H2O
HO
O
O
N+
Me
Me
Cl-
SR 4952 (-)

Scheme 3


HO
OH
O
S-(-)-TROPIC ACID
K_2CO_3-DMF
RT
Cl.HCl
N
HO
O
O
N
16 (-)
HCl
HO
O
O
N
H
Cl⁻
SR 4951 (-)
MeI
MEK-CH_3CN
HO
O
O
N
Me
I⁻
17 (-)
IRA 400 (Cl^-)
H_2O
HO
O
O
N
Me
Cl⁻
SR 4953 (-)

Scheme 4

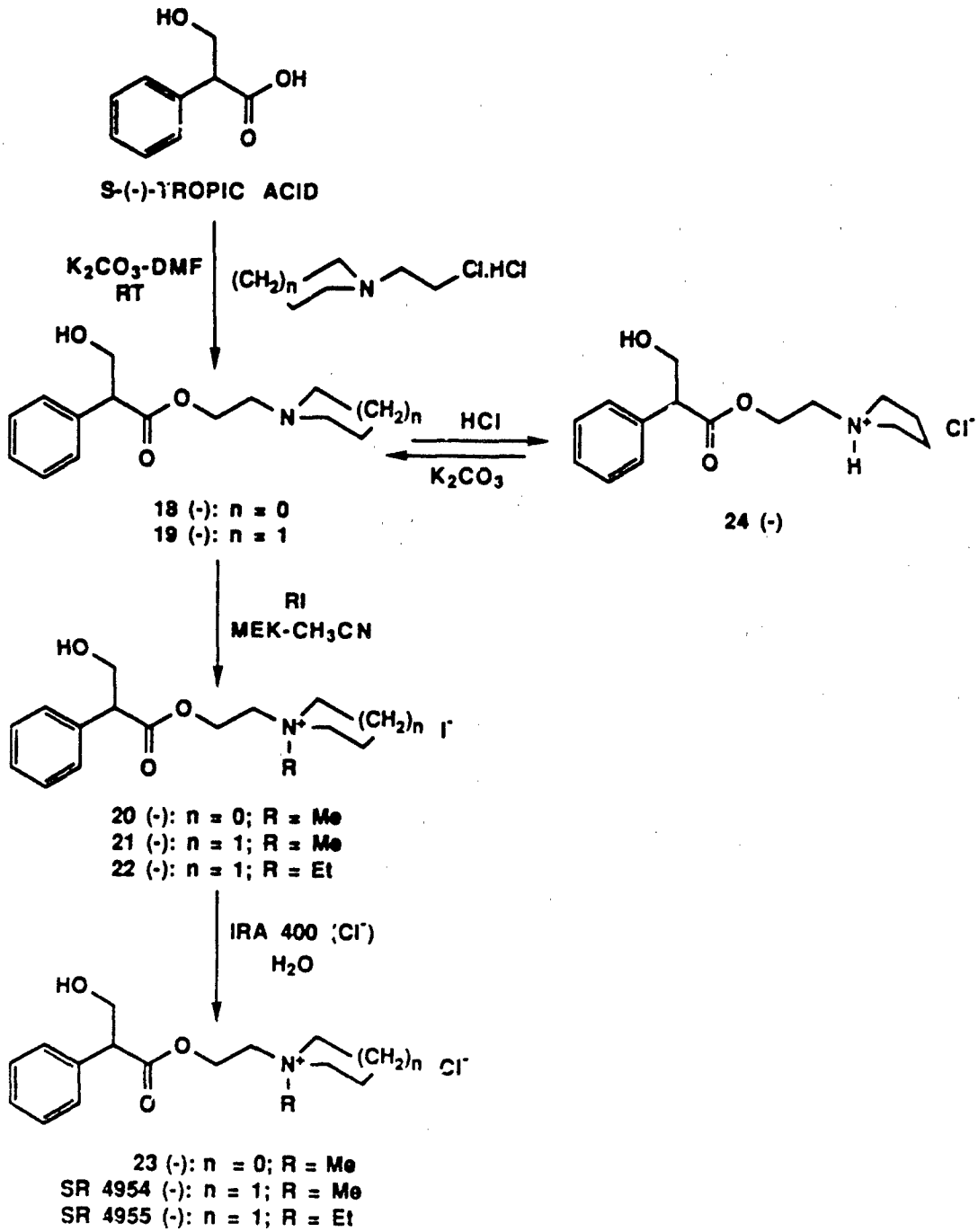
We have also completed, the synthesis of several esters of S-(-)-tropic acid (Scheme 5) incorporating cyclic moieties into the onium end of the molecule. These targets mimic the shape of the more potent analogs investigated by Cusic and Robinson.[15]

Reaction of 1-(2-chloroethyl)pyrrolidine hydrochloride with S-(-)-tropic acid under normal conditions gave the ester (**18**) in low yield (35%), after careful chromatography (Scheme 5, n = 0). Treatment with gaseous HCl in Et_2O had previously been shown to yield a crystalline hydrochloride (**24**). However reaction of **18** with methyl iodide on work-up only gave a yellowish oil (**20**). All attempts to prepare this compound more carefully from extremely pure starting material, or to crystallize the oil, failed, as did attempts to crystallize the methochloride (**23**) formed from passage of the oil down an IRA 400 (Cl^-) ion exchange resin. At this stage, concern over the purity of intermediate (**18**), even though it was shown to be pure by analytical analysis, led us to repurification and formation of the crystalline hydrochloride (**24**). Double recrystallization gave very pure material, which was converted into a diethyl ether solution of (**18**) by treatment with potassium carbonate and careful extraction. All attempts to obtain crystalline material after reaction with methyl iodide and conversion to the methochloride (**20**) failed, even though the target was shown to be analytically pure and anhydrous. Synthesis of targets of this type was therefore been discontinued.

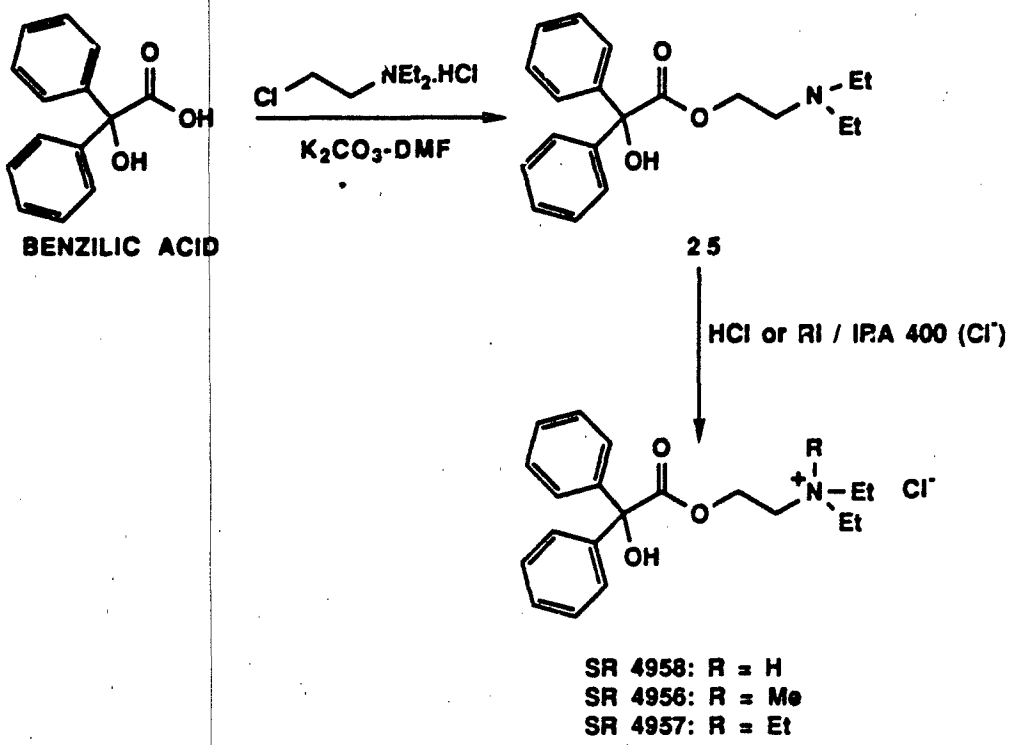
On the other hand the products formed by incorporating a piperidine ring into the targets (Scheme 5, n = 1), crystallized and could be readily recrystallized from *iso*-propanol/2-butanone. The synthesis of two targets, **SR 4954** and **SR 4955**, using standard conditions, is outlined in Scheme 5.

A series of three quaternary salts of 2-*N*,*N*-diethylaminoethyl esters of benzilic acid has also been completed as outlined in Scheme 6. Abramson *et al.*[5] have shown that derivatives of this type bind more strongly than tropic acid derivatives to the postganglionic ("muscarine-sensitive") acetylcholine receptors in the guinea-pig ileum.

During this reporting period we initiated research to synthesize quaternary salts of novel esters of S-(-)-tropic acid incorporating *N*-methylpyrrolidine and *N*-methylpiperidine terminal functions linked by suitable side chains through the 2 and 3 positions respectively, as shown in Schemes 7 and 8. These compounds were designed to attain better muscarinic receptor binding affinity by incorporating an onium head group somewhat similar to that present in atropine while still being able to undergo hydrolysis by cholinesterase.

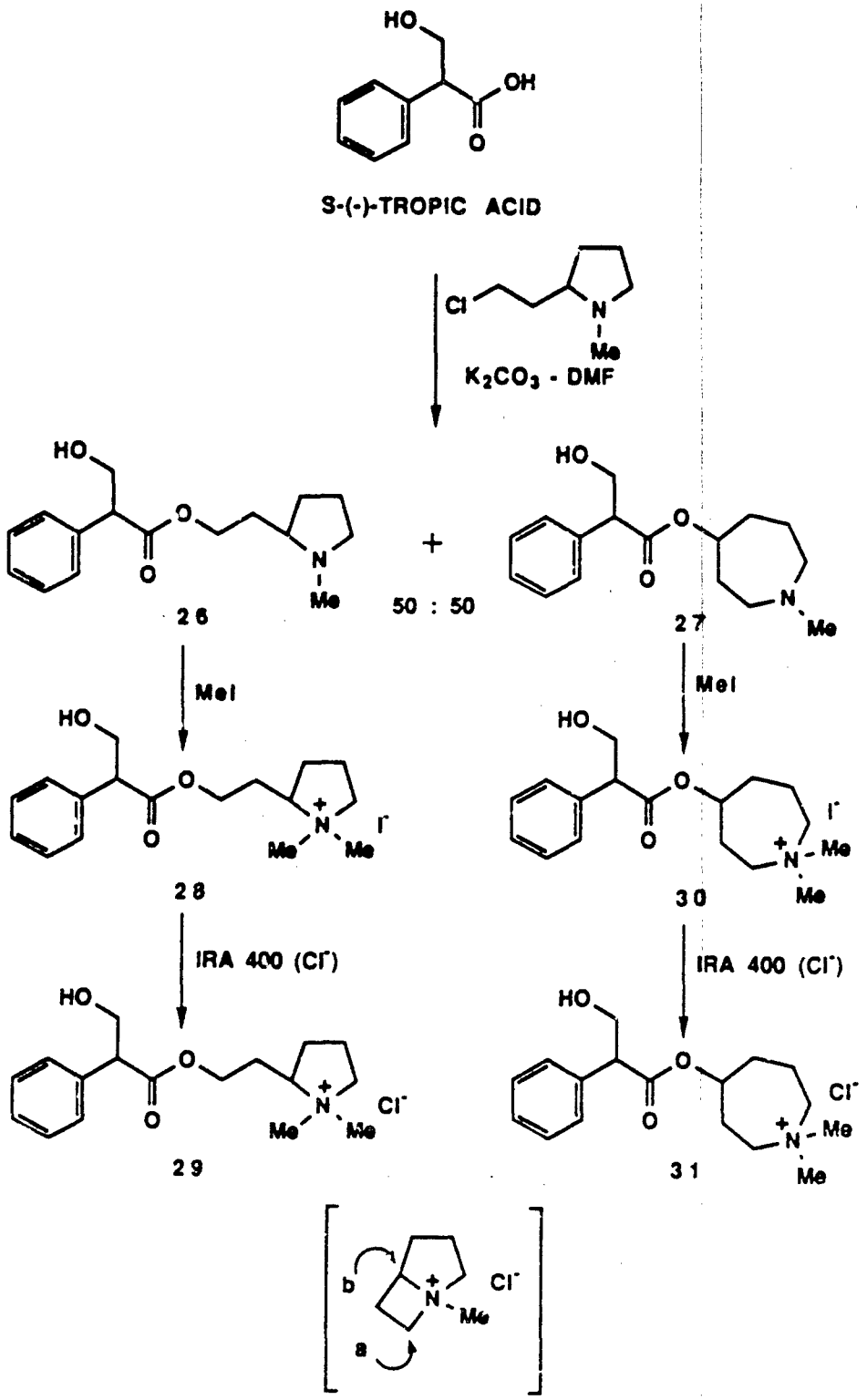

HO
OH
O
S-(-)-TROPIC ACID
K2CO3-DMF
RT
(CH2)n
N
Cl.HCl
HO
O
O
N
(CH2)n
HCl
K2CO3
HO
O
O
N+
H
Cl-
18 (-): n = 0
19 (-): n = 1
24 (-)
RI
MEK-CH3CN
HO
O
O
N+
(CH2)n
I-
R
20 (-): n = 0; R = Me
21 (-): n = 1; R = Me
22 (-): n = 1; R = Et
IRA 400 (Cl-)
H2O
HO
O
O
N+
(CH2)n
Cl-
R
23 (-): n = 0; R = Me
SR 4954 (-): n = 1; R = Me
SR 4955 (-): n = 1; R = Et

Scheme 5

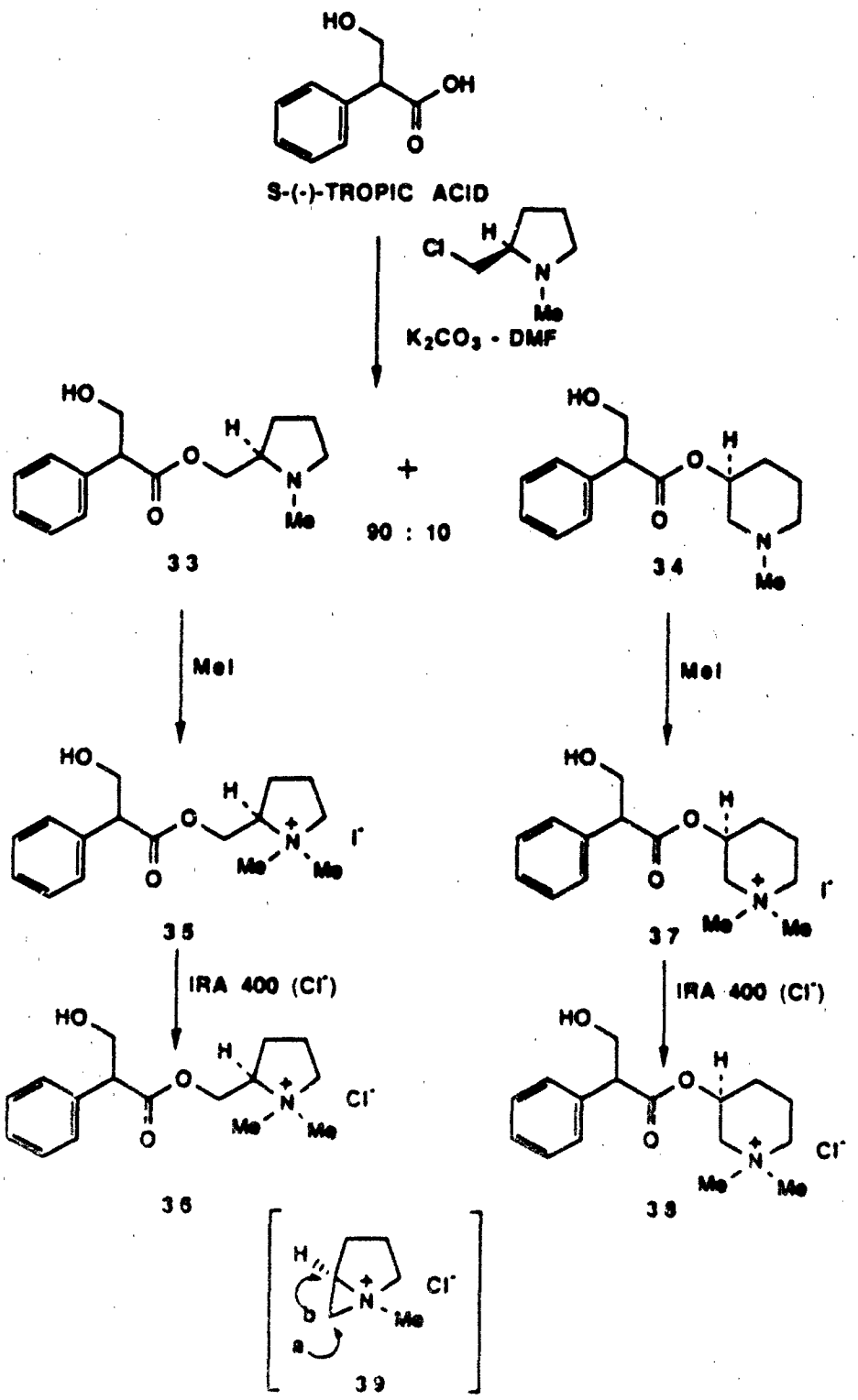


Scheme 6

Initial reaction of S-(-)-tropic acid with racemic 2-(2-chloroethyl)-1-methylpyrrolidine gave a mixture of four diastereomers, instead of the two expected (Scheme 7). High field ^{1}H NMR of the product esters showed the presence of two groups of products in equal ratios, one group containing the pyrrolidine ring (**26**) and the other group containing a seven membered ring (**27**). Separation of the two groups of diastereomers by careful chromatography gave pure products as pale yellow oils and subsequent ^{1}H NMR and mass spectral analysis confirmed the assignment. Reaction had clearly proceeded through a bicyclic intermediate (**32**), formed from the starting material, which had been opened in two directions by the attacking carboxylate nucleophile. Ring opening alpha to the nitrogen from direction **a** led to the pyrrolidine products (**26**), while attack at the bridgehead carbon (direction **b**) led to ring expansion and formation of the hexahydroazepine esters (**27**). In this case the product ratios indicate that both processes are equally facile. Conversion of ester (**26**) into the methoiodide (**28**) proceeded normally, but gave an oil which would not crystallize. Exchange of the iodide for chloride using IRA 400 (Cl^-) ion exchange resin gave the methochloride (**29**) which likewise remained as an oil. All efforts to obtain this compound in crystalline form have been unsuccessful.



Scheme 7



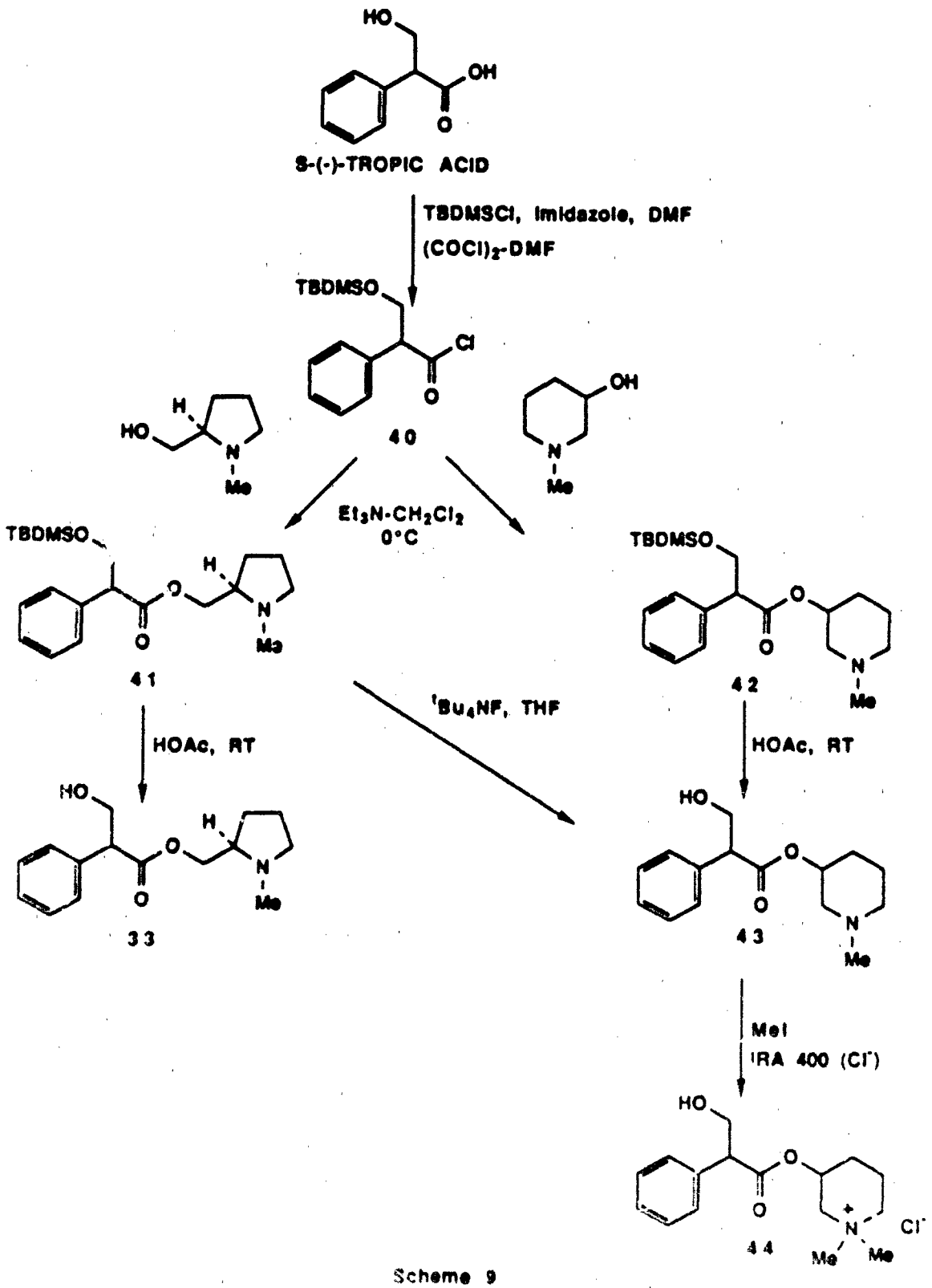
Scheme 8

Reaction of the ester of the hexahydroazepine (27) with methyl iodide gave the methoiodide (31) which was smoothly converted into the white crystalline methochloride (32). Resynthesis and repurification of 32 will be necessary for biological testing to be completed.

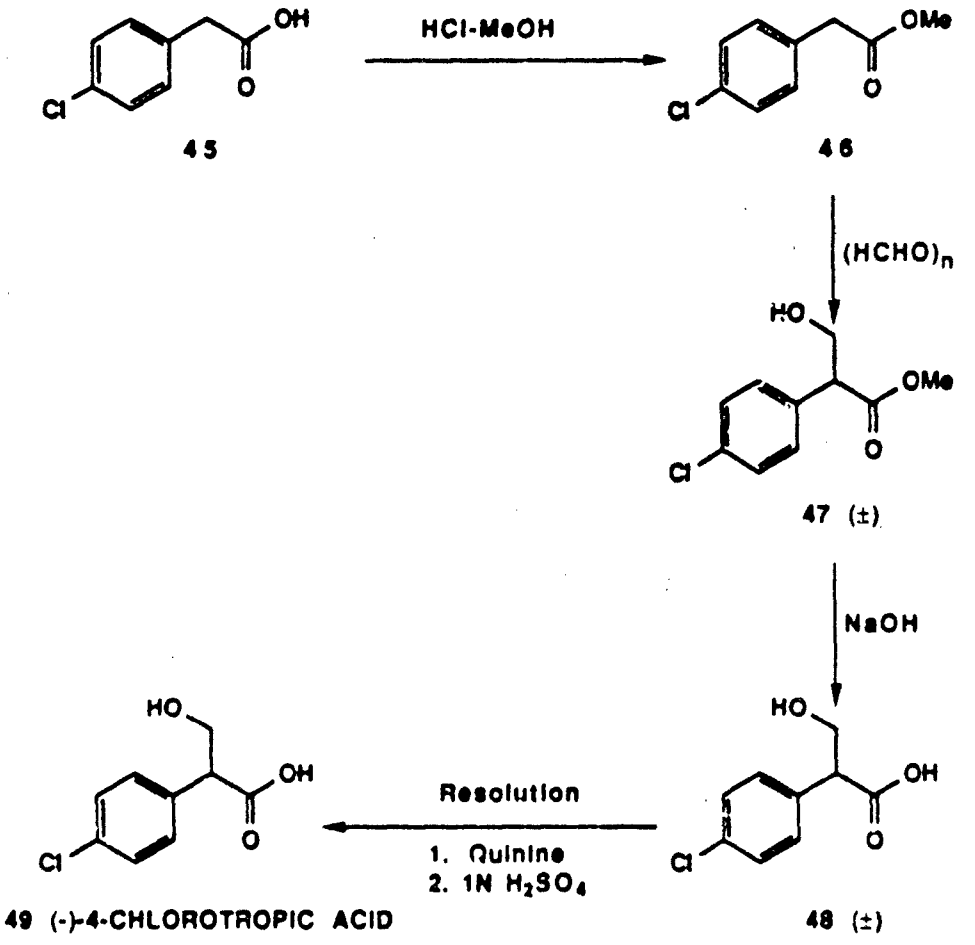
Reaction of S-(-)-tropic acid with pure, optically active S-(-)-2-chloromethyl-1-methylpyrrolidine (Scheme 8) also gave a mixture of two products (33 and 34), in a manner somewhat analogous to the previous case. Again reaction proceeded through a bicyclic intermediate (39), but this time the product ratio indicated that ring opening was favoured from direction a giving the desired product (33) as the major component. Separation of the two esters gave the pyrrolidine (33) in good yield, as a pale yellow oil, and ^{1}H NMR and mass spectral analysis confirmed the assignment. Conversion into the methochloride (36) proceeded as normal but also gave an oil which could not be crystallized. Research on the synthesis of pyrrolidine esters of S-(-)-tropic acid has therefore been discontinued.

A new approach to the synthesis of the S-(-)-tropic acid ester of 3-hydroxy-1-methylpiperidine (43) via an acid chloride intermediate (40) was next investigated (Scheme 9). Reaction of S-(-)-tropic acid with *t*-butyldimethylsilyl chloride gave the bis-(t-butyldimethylsilyl)ester which on treatment with oxalyl chloride gave the protected acid chloride (40). Reaction of 40 with S-(-)-1-methyl-2-pyrrolidinemethanol in dichloromethane, in the presence of triethylamine as base, gave the protected ester (41). Deprotection with tetrabutylammonium fluoride unexpectedly gave a mixture of diastereomers, which included both the product (33) and the ring expanded diastereomeric products (43). Presumably the reaction proceeded via cleavage of the ester, formation of a bicyclic intermediate such as 39 (Scheme 8), and subsequent ring opening by the carboxylate anion to give the two types of products. The structure of 43 was confirmed by independent synthesis. Reaction of the protected acid chloride (40) with 3-hydroxy-1-methylpiperidine gave the protected ester (42) which was deprotected in a mild manner using acetic acid in THF-water to give a mixture of the two diastereomers 43. Treatment of the protected pyrrolidine ester (41) with the same mild deprotection procedure gave the desired product (33) in high yield. Formation of the methochloride (44), from 43, by usual methods gave the target as a white crystalline solid. Resynthesis of 44 on a larger scale is in progress.

Since a considerable amount of the research we have carried out to date has focused on the onium terminal end of the esters we are attempting to potentiate, we turned our attention to examining how changes in the aromatic portion of the molecule would affect both the muscarinic


S-(-)-TROPIC ACID
TBDMSCl, Imidazole, DMF
(COCl)2-DMF
40
Et3N-CH2Cl2
0°C
41
42
HOAc, RT
tBu4NF, THF
33
43
MeI
IRA 400 (Cl-)
44

Scheme 9



Scheme 10

receptor binding affinity and the rate of cholinesterase hydrolysis. The initial targets are modified by the introduction of a variety of substituents into the 4-position of the benzene ring portion of the molecule.

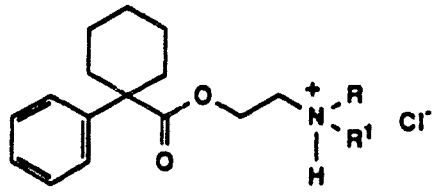
Synthesis of (±)-4-chlorotropic acid (**48**), using methodology previously developed at SRI International, is outlined in Scheme 10. 4-Chlorobenzeneacetic acid (**45**) was converted into the methyl ester (**46**) by treatment with gaseous HCl in methanol. Reaction with paraformaldehyde in DMSO employing NaOMe as base introduced the hydroxymethyl moiety and cleavage of the ester with NaOH gave (±)-4-chlorotropic acid (**48**) in good overall yield. Resolution of the racemic mixture was carried out in a manner similar to that described for (±)-tropic acid. Formation of the

quinine salt , separation of the less soluble diastereomer, recrystallization and acidification with sulphuric acid gave pure (-)-4-chlorotropic acid (**49**). Resynthesis on a large scale for conversion into 2-*N,N*-dialkylaminoethyl esters and subsequent testing *in vitro* is in progress.

Research by Dan Parish (Private Communication 02-1989; Table 3) has shown excellent activity for a series of 2-*N,N*-dialkylaminoethyl-1-phenylcyclohexane-1-carboxylates, acting as pretreatment drugs protecting cholinesterase against phosphonylation and therefore poisoning by organophosphorus agents. The similarity in structure between these compounds and many of the esters we have synthesized suggested that we should attempt to introduce a hydroxyl function into the cyclohexane ring portion of the molecule in order to potentiate muscarinic receptor binding and introduce the potential for cleavage by cholinesterase. The endpoint for this modification could be the emergence of a series of drugs which would act both as pretreatment and as anticholinesterase agents.

Table 3

Intramuscular Pretreatment Efficacy[a] of
2-*N,N*-Dialkylaminoethyl-1-phenylcyclohexane-1-carboxylates in the Mouse.

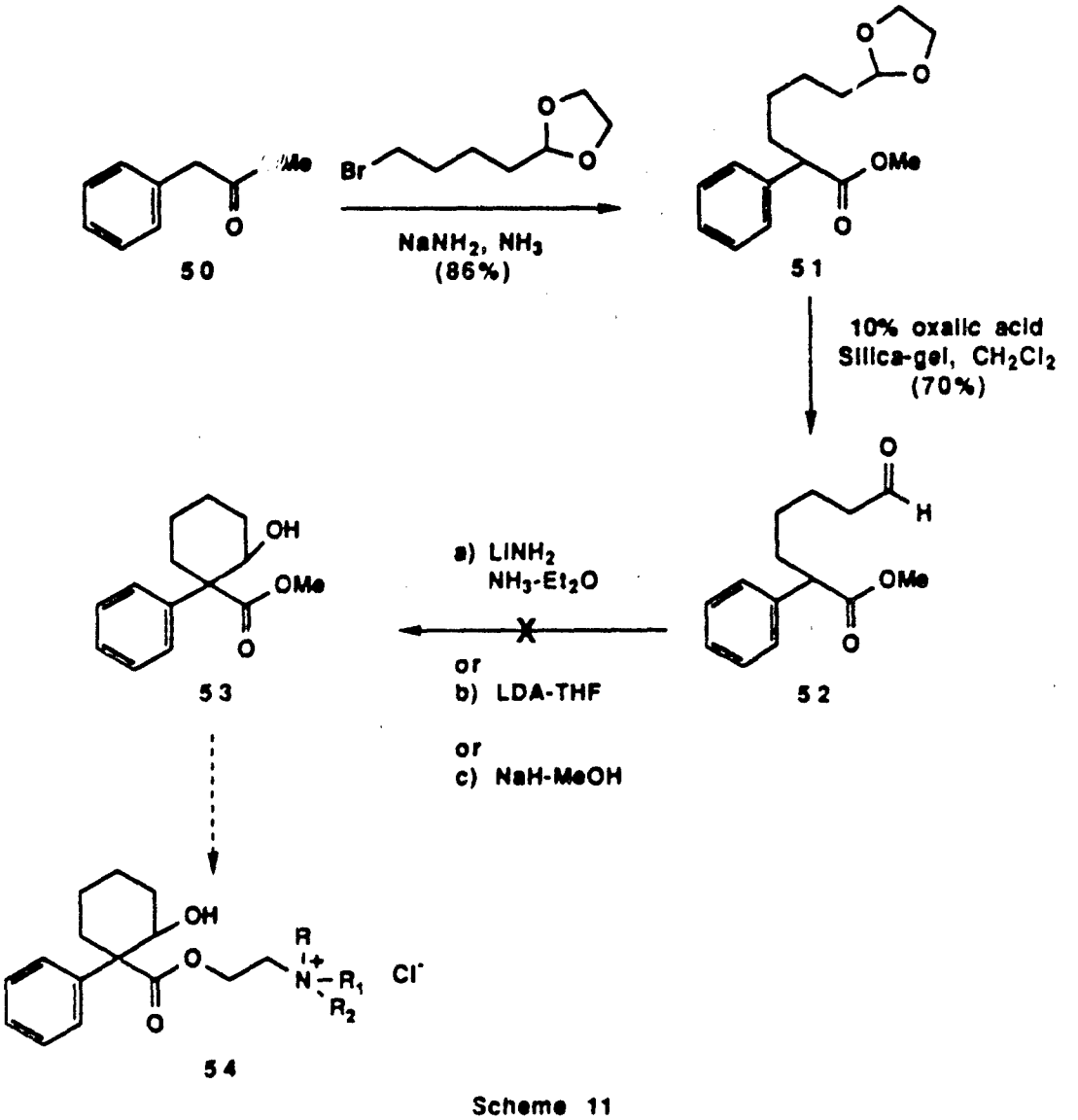


SRI Code #	AMINE	IM LD_{50} (mmol/kg)	15 min. 1/64	1/16	1/4	60 min. 1/64	1/16	1/4
PRE-078	$N(CH_3)_2$	>0.91	2	0	6	0	0	0
PRE-079	pyrrolidine	>1.04	0	0	6	0	0	4

[a]Pretreatment compound administered 15 or 60 minutes prior to GD challenge, at doses equal to the indicated fraction of their LD_{50}. Number of survivors out of 10 is indicated.

Dan Parish. Private Communication 02-89

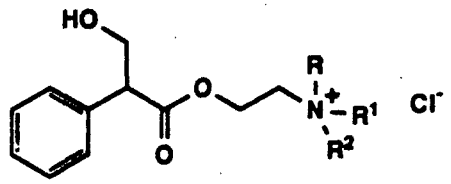
The synthesis of 2-hydroxy-1-phenylcyclohexylcarboxylic acid, methyl ester (**50**; Scheme 11) has therefore been initiated, for conversion into suitable 2-*N,N*-dialkylaminoethyl esters (**54**). Reaction of the acetal of 5-bromovaleraldehyde with benzeneacetic acid, methyl ester using sodamide in liquid ammonia as base gave the intermediate (**51**) in 86% yield, which was readily



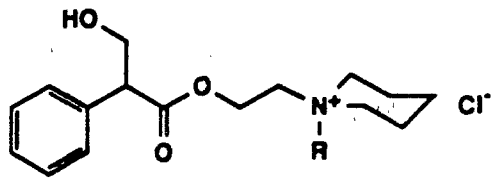
Scheme 11

deprotected to the appropriate aldehyde (52). Attempted cyclization with a variety of bases has failed to yield any desired product. Other methods for cyclization are presently being investigated.

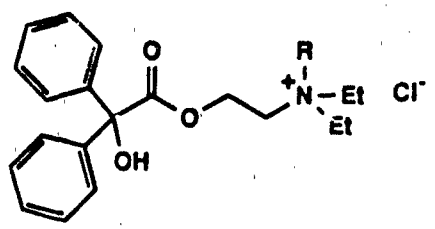
All crystalline products described in this report have been, or will be tested *in vitro* at SRI International for muscarinic receptor binding affinity and rate of hydrolysis by cholinesterase. Ten compounds, shown in Figure 1, have been resynthesized in quantities of 2-3.0g and submitted



SR 4950: R = Me; $R^1 = R^2$ = Et
SR 4951: R = H; $R^1 = R^2 = {}^iPr$
SR 4952: R = R^1 = Me; $R^2 = {}^iPr$
SR 4953: R = $R^1 = {}^iPr$; R^2 = Me
SR 4969: R = $R^1 = R^2$ = Et



SR 4954 (-): R = Me
SR 4955 (-): R = Et



SR 4956: R = Me
SR 4957: R = Et
SR 4958: R = H

Figure 1

to USAMRICD for *in vivo* testing as atropine substitutes in the Anticholinergic efficacy screen. The data sheets for these compounds are attached as an Appendix.

Biology

In vitro Pharmacology

In vitro testing to determine muscarinic receptor binding affinity and rates of cholinesterase hydrolysis for twelve quaternary salts of 2-(-)-*N,N*-dialkylaminoethyl esters of benzilic acid (Table 4) and of S-(-)-tropic acid (Table 5) has now been completed in duplicate.

Each compound was tested for binding affinity at the muscarinic receptor, and for rate of hydrolysis, in the presence of serum cholinesterase at physiological levels. Our aim was to develop compounds with high affinity for the muscarinic acetylcholine receptor, and with a range of hydrolysis rates in the presence of serum cholinesterase. With these compounds, and appropriate *in vivo* testing, we will be able to test our hypothesis, that a hydrolyzable muscarinic antagonist would be a superior antidote to anticholinesterase poisoning.

Binding was conducted on rat brain membranes, as we have described in previous reports. Briefly, membranes were incubated in the presence of [^{3}H] QNB and the appropriate test compound. Incubations lasted two hours at 37°C and then samples were filtered over glass fiber filters. IC_{50} values were determined graphically, and K_i values calculated from the Chang-Prusoff equation:

$$K_i = \frac{IC_{50}}{1 + L/K_d}$$

In this equation, L is the radioligand concentration, and K_d is the dissociation constant of the radioligand. We have previously determined that the K_d for [^{3}H] QNB is approximately 0.2 nM.

Hydrolysis rates were determined using a modified radioreceptor assay for each compound. For these experiments, the test compound was incubated at 37°C in brain membranes that had been supplemented with 6 U/ml of serum cholinesterase. The reaction was stopped at various times with 40 μM eserine, at which time [^{3}H] QNB was added to the reaction mixture. The incubation was continued for an additional 2 h, at which time the samples were filtered as previously. This method depends on the ability of the compound to inhibit [^{3}H] QNB binding i.e. that in the presence of the cholinesterase, the test compound will hydrolyze at a particular rate, and

thus its ability to inhibit [^{3}H] QNB binding will diminish. By determining the extent of inhibition after various lengths of incubation with cholinesterase, we can estimate the rate at which the test compounds will be hydrolyzed *in situ*.

The results, shown in Tables 4 and 5, clearly demonstrate some definite trends. As expected, the affinity of atropine was in the sub-nanomolar range, and that of acetylcholine in the micromolar range. In addition, atropine was not hydrolyzed under the conditions of the experiments, but acetylcholine was rapidly hydrolyzed, so that within 10 minutes it no longer significantly inhibited [^{3}H] QNB binding.

The esters of benzilic acid exhibited binding affinity to the muscarinic receptor somewhat similar to that of atropine, but were cleaved readily by cholinesterase. Benactyzine hydrochloride (**SR 4958**), which has been used as an antidote for organophosphorus poisoning in combination with atropine, bound less strongly in our studies but exhibited a half-life of 60 minutes. This stability falls in the range we suggested would be appropriate for an effective agent.

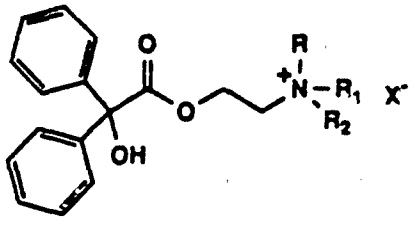
The *in vitro* results for the 2-*N*,*N*-dialkylaminoethyl esters of S-(-)-tropic acid are extremely promising, and show that several of the compounds synthesized exhibited enhanced muscarinic receptor binding affinity, when compared to atropine, and that all the chlorides were cleaved by cholinesterase with half-lives in the range of 29-68 minutes. These results demonstrate that we have now synthesized molecules which exhibit in the *in vitro* screens, the properties we were attempting to introduce into a drug. The results from the *in vivo* experimentation on these compounds will demonstrate whether any of these agents will be more effective and less toxic than atropine as antidotes for organophosphorus poisoning.

In vivo Testing by USAMRICD

Ten compounds have been submitted to USAMRICD for *in vivo* testing as atropine substitutes in the Anticholinergic efficacy screen, during this report period. No results have as yet been forthcoming.

Table 4

In vitro Data for Quaternary salts of *N,N*-dialkylaminoethyl Benzilic acid Esters.

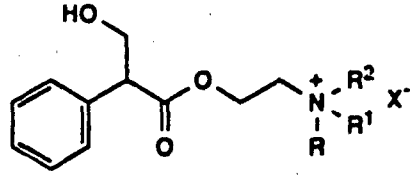


SR No.	AMINE	Musc. Bind. K_i(nM)	Cholin. Hydrol. t(1/2)min.
SR 4956	NEt_2MeCl	0.48	5
SR 4957	NEt_3Cl	0.55	25
SR 4958[a]	$NEt_2.HCl$	0.76	60

[a] Benactyzine HCl

Table 5

In vitro Data for Quaternary salts of 2-*N,N*-Dialkylaminoethyl Tropic acid Esters.



SR No.	AMINE	ISOMER	Musc Bind K_i(nM)	Cholin. Hydrol. t(1/2)min.
SR 4950	NEt_2MeCl	(-)	0.28	NA
NA	NEt_2MeI	(-)	1.50	>120
SR 4968	NEt_2MeI	(+)	9.10	30
SR 4951	$N^iPr_2.HCl$	(-)	0.60	35
SR 4952	$NMe_2{}^iPrCl$	(-)	0.07	35
SR 4953	N^iPr_2MeCl	(-)	0.16	29
SR 4954	PiperidineMeCl	(-)	0.58	68
SR 4955	PiperidineEtCl	(-)	0.49	32
SR 4969	NEt_3Cl	(-)	0.33	NA
Atropine		(-)	0.32	

CONCLUSIONS

During this reporting period several derivatives of S-(-)-tropic acid have been synthesized that demonstrate muscarinic binding affinities similar to, or in some cases significantly better than atropine and which undergo hydrolytic cleavage by serum cholinesterase *in vitro* at a wide range of differing rates. We have in fact designed compounds that fit our model for agents that would be potentially useful as antidotes for Organophosphorus poisoning. With the appropriate *in vivo* testing we should be able to determine what hydrolysis rate would be optimal for the protection from cholinesterase inhibition. We will then be able to tailor our additional synthetic efforts to produce compounds of the appropriate characteristics to maximize their protective effects.

EXPERIMENTAL DETAILS

R-(+)-Tropic Acid Quinine Salt. To a solution of 200 g (0.616 mol) of quinine in 1 L (abs) EtOH was added 102 g (0.614 mol) of (±)-tropic acid in 1 L EtOH. A white solid formed to a solid mass within 1 h. The mixture was allowed to stand at RT for 18 h, filtered, and washed with 50 mL abs EtOH. The solid was recrystallized 3 times from 3.5 L of refluxing EtOH to give 120 g (40%) of R-(+)-tropic acid quinine salt, mp 190.5-192 °C.

S-(-)-Tropic Acid Ephedrine Salt. The filtrate from the above reaction was evaporated to dryness and partitioned between 1 L H_2SO_4 and 1 L diethyl ether. After stirring for 0.5 h, the ether layer was separated and the aqueous layer washed with ether (2 x 1L). The combined ether fractions were washed with satd NaCl solution, dried over $MgSO_4$, filtered and evaporated to give 38 g. This was taken up in 50 mL of 60% EtOH and added to a hot solution of 38 g (0.229 mol) of ephedrine in 50 mL of 60 % EtOH. The product which crystallized upon standing overnight was collected by filtration and recrystallized twice from refluxing 60% EtOH (100 mL) to give 39 g (52%) of S-(-)-tropic acid ephedrine salt, mp 127-129 °C.

R-(+)-Tropic Acid. In a large flask, 29.5 g (60.1 mmol) of R-(+)-tropic acid quinine salt was stirred with a mixture of 500 mL of 1 N H_2SO_4 and 500 mL of diethyl ether for 0.5 h. The ether was separated and the aqueous layer extracted with more ether (2 x 300 mL). The combined ether layer was washed with 500 mL of satd NaCl solution, dried over $MgSO_4$, filtered and evaporated to give 7 g (70%) of R-(+)-tropic acid, mp 127-129 °C. $[\alpha]_D = 69.6^\circ$ (2% in 95% EtOH.).

S-(-)-Tropic Acid. In a large flask, 39 g (0.118 mol) of S-(-)-tropic acid ephedrine salt was stirred with a mixture of 750 mL of 1 N H_2SO_4 and 500 mL of diethyl ether for 0.5 h. The ether was separated and the aqueous layer extracted with ethyl acetate (3 x 250 mL). The combined organic fractions were washed with 500 mL of satd NaCl solution, dried over $MgSO_4$, filtered and evaporated to give 18.5 g (94%) of S-(-)-tropic acid, mp 128-129 °C. $[\alpha]_D = -72.6^\circ$ (2% in 95% EtOH).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester (5). To 4.50 g (27.1 mmol) of S-(-)-tropic acid in 150 mL dry DMF under argon was added 5.0 g (36 mmol) of powdered K_2CO_3. The cloudy mixture was stirred at RT for 0.5 h, followed by the addition of 4.8 g (28 mmol) of 2-diethylaminoethyl chloride hydrochloride. The mixture was

stirred at RT for 40 h, then poured into 500 mL of ice water and extracted with diethyl ether (3 x 250 mL). The ether layer was washed with 250 mL satd NaCl solution, dried over Na_2SO_4, filtered and evaporated to give 5.5 g (77%) of **5** as an oil, Rf=0.25 (95% CH_2Cl_2/5% (MeOH/NH_4OH[95:5]). ^{1}H-NMR ($CDCl_3$) δ 7.31 (s, 5H, aromatic), 4.51-3.72 (m, 5H, $CHCH_2OH$, OCH_2), 2.75 (t, 2H, CH_2N), 2.56 (q, 4H, $N[CH_2Me]_2$), 1.02 (t, 6H, $N[CH_2CH_3]_2$). $[\alpha]_D$=-25 ° (1.38% in 95% EtOH.).

R-(+)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester (7). Prepared from R-(+)-tropic acid (83 mg, 0.50 mmol) by the same method as **5** to give 100 mg (75%) of **7** as an oil, Rf=0.25 (95% CH_2Cl_2/5% (MeOH/NH_4OH[95:5]). ^{1}H-NMR ($CDCl_3$) same as in **5**.

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester Methoiodide (6). To 3.0 g (11 mmol) of **5** in 20 mL of 2-butanone and 5 mL CH_3CN was slowly added 3 mL of CH_3I (48 mmol). The reaction, kept under argon and protected from light, was stirred at RT for 48 h, then chilled at -4 °C for 24 h to give a white solid. This was filtered to give 2.4 g (54%) of **6**, mp 85-87 °C. $[\alpha]_D$=-17.5 ° (1.2% in 95% EtOH.) ^{1}H-NMR ($CDCl_3$) δ 7.31 (s, 5H, aromatic), 5.05 (m, 1H, OH), 4.47 (br t, 2H, CO_2CH_2), 3.5-4.1 (m, 3H, $CHCH_2OH$), 3.27 (q & t, 6H, $CH_2N[CH_2CH_3]_2$), 2.91 (s, 3H, NCH_3), 1.15 (t, 6H, $N[CH_2CH_3]_2$).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester Methochloride (SR 4950). A solution of 2.4 g (5.89 mmol) of **6** in 10 mL of H_2O was passed down an IRA 400 (Cl-) resin column and the product was eluted with 150 mL of H_2O. The solvent was removed by lyophilization to give 1.90 g of a foamy solid which was recrystallized from 2-butanone/iPrOH (40/5 mL) at -5 °C to give 1.46 g (78%) of **SR 4950**, mp 110-112 °C. $[\alpha]_D$=-21 ° (1.32% in 95% EtOH.) ^{1}H-NMR ($CDCl_3$) δ 7.30 (s, 5H, aromatic), 5.4 (m, 1H, OH), 4.46 (br t, 2H, CO_2CH_2), 3.1-4.1 (m, 5H, $CHCH_2OH$, CH_2N), 3.33 (q, 4H, $N[CH_2CH_3]_2$), 2.95 (s, 3H, NCH_3), 1.14 (t, 6H, $N[CH_2CH_3]_2$). Anal calcd for $C_{16}H_{26}ClNO_3$: C, 60.85; H, 8.30; N, 4.43; Cl, 11.22. Found: C, 60.82; H, 8.51; N, 4.40; Cl, 11.21.

R-(+)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester Methoiodide (SR 4968). Prepared from **7** (4.5 g, 16.9 mmol) by the same method as **6** to give 5.6 g (81.4 %) of **SR 4968** as a pale yellow oil, mp 85-87 °C. $[\alpha]_D$=16.5 ° (2.5% in 95%

EtOH.) ^{1}H-NMR (CD_3CN) δ 7.33 (s, 5H, aromatic), 4.44 (m, 2H, CH_2N), 4.2-3.6 (m, 6H, $CHCH_2OH$, CO_2CH_2), 3.26 (q, 4H, NCH_2Me), 2.88 (s, 3H, NCH_3), 1.19 (t, 6H, NCH_2CH_3).

R-(+)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester Methochloride (8). Prepared from **SR 4968** (5.50 g, 13.5 mmol) by the same method as **SR 4950** to give 4.0 g (93.8%) of **8**, mp 109.5-112 °C. $[\alpha]_D$=21.4 ° (2.57% in 95% EtOH.) 400 MHz ^{1}H-NMR (CD_3CN) δ 7.34 (m, 5H, aromatic), 4.56-4.48 (br ddd, 1H, CO_2CH_2), 4.48-4.40 (br ddd, 1H, CO_2CH_2), 3.62 (m, 2H, CH_2N), 4.04 (ddd, 1H, $CHCH_2OH$), 3.91 (ddd, 1H, $CHCH_2OH$), 3.73 (quint, 1H, $CHCH_2OH$), 2.3-2.4 (br, 1H, OH), 3.36 (q, 4H, NCH_2Me), 2.97 (s, 3H, NCH_3), 1.23 (t, 6H, J=7.3 Hz, NCH_2CH_3). Anal calcd for $C_{16}H_{26}ClNO_3$: C, 60.84; H, 8.30; N, 4.43; Cl, 11.23. Found: C, 60.64; H, 8.26; N, 4.40; Cl, 10.98.

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester Ethoiodide (9). Prepared from **5** (3.2 g, 12 mmol) and ethyl iodide in the same manner as **6** to give 4.8 g (93%) of **9** as a syrup. ^{1}H-NMR ($CDCl_3$-CD_3OD) δ 7.30 (s, 5H, aromatic), 4.53 (t, 2H, CO_2CH_2), 4.5-3.5 (m, 3H, $CHCH_2OH$), 3.31 (q, 2H, CH_2CH_3), 2.57 (q, 4H, CH_2CH_3), 1.25 (t, 3H, CH3), 1.02 (t, 6H, CH_3).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester Ethochloride (SR 4969). Prepared from **9** (2.4 g, 5.64 mmol) in the same manner as **SR 4950** to give 1.65 g (88%) of **SR 4969**, mp 112-115 °C. $[\alpha]_D$=-19.2 ° (2.17% in 95% EtOH.) ^{1}H-NMR (DMSO-d_6) δ 7.30 (s, 5H, aromatic), 5.29 (t, 1H, OH), 4.43 (br t, 2H, CO_2CH_2), 3.2-4.1 (m, 5H, $CHCH_2OH$, CH_2N), 3.26 (q, 6H, $N[CH_2Me]_3$), 1.12 (t, 9H, CH_3). Anal calcd for $C_{17}H_{28}ClNO_3$: C, 61.90; H, 8.56; N, 4.25; Cl, 10.75. Found: C, 61.79; H, 8.79; N, 4.39 Cl, 10.74.

2-(*N*-Isopropyl-*N*-methylamino)ethano (11). In a flask was combined 20 g (0.266 mol) of 2-(methylamino)ethanol, 40 g (0.34 mol) of 2-bromopropane and 40 g of K_2CO_3 in 100 mL of 2-butanone. The mixture was heated at reflux for 2 days, then cooled and filtered. The filtrate was evaporated and the residue triturated with 500 mL of diethyl ether and filtered. The filtrate was evaporated to give 26 g (84%) of **11** as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ 3.55 (t, 2H, $HOCH_2$), 2.85 (5, 1H, $CHMe_2$), 2.53 (t, 2H, CH_2N), 2.20 (s, 3H, NCH_3), 1.01 (d, 6H, $CH[CH_3]_2$).

2-(*N*-Isopropyl-*N*-methylamino)ethyl Chloride Hydrochloride (12). To 25 g (0.21 mol) of **11** in 400 mL of dichloromethane under argon in an ice bath was added 26 mL of $SOCl_2$ in a dropwise manner. The solution was stirred at RT overnight, then reduced to ~100 mL and poured into 500 mL of diethyl ether. The resulting mixture was chilled at -5 °C overnight and the red-brown solid was filtered under argon and washed with ether to give 16 g (44%) of **12**. ^{1}H-NMR (DMSO-d_6) δ 3.58 (t, 2H, $ClCH_2$), 3.2-2.8 (m, 3H, CH_2NCH), 2.18 (d, 3H, NCH_3), 0.78 (d, 3H, $CH[CH_3]_2$), 0.73 (d, 3H, $CH[CH_3]_2$).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N*-Methyl-*N*-isopropylamino)-ethyl Ester (13). S-(-)-Tropic acid (5.0 g, 30.2 mmol) was treated with **12** (5.8 g, 33.6 mmol) in the same manner as in **5** to give 7.2 g of an oil which was chromatographed on silica gel (98% CH_2Cl_2/2% [MeOH/NH_4OH (95/5)]) to give 6.1 g (77%) of **13**, crystallized from cyclohexane/pentane, mp 35-37 °C. $[\alpha]_D$ = -25.2 ° (2.31 % in 95% EtOH). ^{1}H-NMR ($CDCl_3$) δ 7.31 (s, 5H, aromatic), 4.6-3.7 (, m, 5H, CH_2OH, CO_2CH_2, NCH), 2.87 (t, 2H, $CHCH_2OH$), 2.65 (t, 2H, CH_2N), 1.00 (d, 6H, $CH[CH_3]_2$).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N*-Methyl-*N*-isopropylamino)-ethyl Ester Methoiodide (14). Prepared from **13** (4.0 g, 15.1 mmol) by the same method as **6**. Recrystallization from MEK/iPrOH gave 4.5 g (73%) of **14**. $[\alpha]_D$ = -15.8 ° (2.66 % in 95% EtOH). ^{1}H-NMR (DMSO-d_6) δ 7.31 (s, 5H, aromatic), 5.07 (t, 1H, OH), 4.49 (br t, 2H, CO_2CH_2), 3.94 (q, 1H, NCH), 3.80 (m, 3H, $CHCH_2OH$), 3.59 (t, 2H, CH_2N), 2.93 (s, 3H, NCH_3), 1.23 (d, 6H, $CH[CH_3]_2$).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N*-Methyl-*N*-isopropylamino)-ethyl Ester Methochloride (SR 4952). Prepared from **14** (4.2 g, 10.3 mmol) by the same method as **SR 4950** to give 1.6 g (49%) of **SR 4952**, mp 118-120 °C. $[\alpha]_D$ = -21.1 ° (2.50 % in 95% EtOH). ^{1}H-NMR (DMSO-d_6) δ 7.32 (s, 5H, aromatic), 5.18 (t, 1H, OH), 4.50 (br t, 2H, CO_2CH_2), 4.1-3.5 (m, 4H, $CHCH_2OH$, NCH),3.62 (br t, 2H, CH_2N), 2.94 (s, 3H, NCH_3), 1.24 (d, 6H, $CH[CH_3]_2$). Anal calcd for $C_{16}H_{26}ClNO_3 \cdot 1/2H_2O$: C, 59.71; H, 8.35; N, 4.35; Cl, 11.01. Found: C, 59.73; H, 8.27; N, 4.28; Cl, 10.70.

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N*-Methyl-*N*-isopropylamino)-ethyl Ester Hydrochloride (15). To 3.0 g (11.3 mmol) of **13** in 100 mL of ether was added ethereal HCl until no more solid precipitated. The mixture was evaporated to an oil, which was taken up in iPrOH and MEK added until the solution began to cloud. The mixture was placed in

the freezer to give a precipitate which melted as the temp was warmed to 0 °C. Repeated attempts to recrystallize the material have been unsuccessful. Evaporation of the solvent gave 3.2 g (94%) of **15** as a pair of diastereomeric salts. 400 MHz ^{1}H-NMR ($CDCl_3$) δ 7.32 (d, 5H, aromatic), 4.45 (m, 3H, CO_2CH_2, OH), 3.96 (dd, 1H, $CHCH_2OH$), 3.84 (ddd, 1H, $CHCH_2OH$), 3.63 (ddd, 1H, $CHCH_2OH$), 3.42 (m, 2H, CH_2N), 3.21 (m, 1H, NCH), 2.58 (d, NCH_3), 2.57 (d, NCH_3), 1.23 (d, $CHCH_3$), 1.21 (d, $CHCH_3$), 1.16 (d, $CHCH_3$), 1.15 (d, $CHCH_3$).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N*,*N*-Diisopropylamino)ethyl Ester (16). Prepared from S-(-)-Tropic acid (6.70 g, 40.3 mmol) and 2-diisopropylaminoethyl chloride hydrochloride (8.9 g, 44.5 mmol) by the same method as **5** to give 10 g of an oil. This was chromatographed on silica gel (98% CH_2Cl_2/2% [MeOH/NH_4OH [95/5]]) to give 8 g (67.6%) of **16** as a syrup. $[\alpha]_D$ = -30 ° (2.68 % in 95% EtOH). ^{1}H-NMR ($CDCl_3$) δ 7.62 (s, 5H, aromatic), 4.43 (t, 2H, CO_2CH_2), 4.6-4.0 (m, 3H, $CHCH_2OH$), 3.31 (sept, 1H, $CHMe_2$), 2.96 (t, CH_2N), 1.31 (d, 6H, $CH[CH_3]_2$).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N*,*N*-Diisopropylamino)-ethyl Ester Methoiodide (17). Prepared from **16** (4.0 g, 13.6 mmol) by the same method as **6**. Recrystallization from MEK/iPrOH gave 4.5 g (76%) of **17**. $[\alpha]_D$ = -16.7 ° (2.50 % in 95% EtOH). ^{1}H-NMR (DMSO-d_6) δ 7.32 (s, 5H, aromatic), 5.18 (t, 1H, OH), 4.44 (t, 2H, CO_2CH_2), 4.1-3.5 (m, 4H, $CHCH_2OH$, NCH),3.55 (q, 2H, CH_2N), 2.80 (s, 3H, NCH_3), 1.28 (d, 6H, $CH[CH_3]_2$).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N*,*N*-Diisopropylamino)-ethyl Ester Methochloride (SR 4953). Prepared from **17** (4.50 g, 10.3 mmol) by the same method as **SR 4950** to give 3.4 g (95%) of **SR 4953**, mp 111-113.5 °C. $[\alpha]_D$ = -20.6 ° (2.50 % in 95% EtOH). ^{1}H-NMR (DMSO-d_6) δ 7.32 (s, 5H, aromatic), 5.18 (t, 1H, OH), 4.45 (t, 2H, CO_2CH_2), 4.2-3.7 (m, 4H, $CHCH_2OH$, NCH),3.56 (q, 2H, CH_2N), 2.81 (s, 3H, NCH_3), 1.25 (d, 6H, $CH[CH_3]_2$). Anal calcd for $C_{18}H_{30}ClNO_3$: C, 62.87; H, 8.79; N, 4.07; Cl, 10.31. Found: C, 63.10; H, 9.00; N, 3.94; Cl, 10.12.

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N*,*N*-Diisopropylamino)-ethyl Ester Hydrochloride (SR 4951). To 3.0 g (10.2 mmol) of **16** in 100 mL of diethyl ether under argon at 0 °C was added ethereal HCl until no more solid was formed. Filtration of the solid gave 1.9 g (50%) of **SR 4951**, mp 91-94 °C. $[\alpha]_D$ = -15.9 ° (2.38% in 95% EtOH). ^{1}H-NMR (DMSO-d_6) δ 7.30 (s, 5H, aromatic), 5.10 (t, 1H, OH), 4.41 (t, 2H, CO_2CH_2), 4.1-3.4 (m,

4H $CHCH_2OH$, NCH),3.36 (q, 2H, CH_2N), 1.27 (dd, 6H, $CH[CH_3]_2$). Anal calcd for $C_{17}H_{28}ClNO_3$: C, 61.90; H, 8.56; N, 4.25; Cl, 10.76. Found: C, 61.68; H, 8.62; N, 4.18; Cl, 10.52.

S-(-)-α-Hydroxymethyl)benzeneacetic Acid, 2-(Pyrrolidinyl)ethyl Ester (18). Prepared from S-(-)-tropic acid (4.00 g, 24.1 mmol) and *N*-(2-chloroethyl)pyrrolidine hydrochloride (4.09 g, 24.1 mmol) by the same method as **5** to give 4.31 g of a brown oil. This was chromatographed on a silica gel column eluting with CH_2Cl_2, followed by 3% MeOH/NH_4OH[95/5] in CH_2Cl_2, then 5% MeOH/NH_4OH[95/5] in CH_2Cl_2 to give 2.84 g (45%) of **18** as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 7.20 (s, 5H, aromatic), 4.40 (q, 2H, $CHCH_2OH$), 4.1-3.6 (m, 4H, CO_2CH_2, $CHCH_2OH$), 2.70 (t, 2H, CH_2N), 2.4-2.6 (m, 4H, NCH_2), 1.8-1.6 (m, 4H, CH_2CH_2).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(Piperidinyl)ethyl Ester (19). S-(-)-Tropic acid (7.00 g, 42.1 mmol) was treated with 8.5 g (46.1 mmol) of *N*-(2-chloroethyl)piperidine hydrochloride in the same manner as in **5** to give 10.6 (91%) of **19** as a low melting solid. $[\alpha]_D$ = -21.1 ° (2.64% in 95% EtOH). ^{1}H-NMR ($CDCl_3$) δ 7.31 (s, 5H, aromatic), 3.5-4.5 (br m, 5H, $CHCH_2OH$, CO_2CH_2), 2.9 (q, 2H, CH_2N), 2.2-2.7 (m, 4H, NCH_3) and 1.3-1.8 (m, 6H, ring CH_2s).

S-(-)-α-Hydroxymethyl)benzeneacetic Acid, 2-(Pyrrolidinyl)ethyl Ester Methoiodide (20). Prepared from **18** (3.48 g, 13.22 mmol) by the same method as **6** to give 5.41 g (100%) of **20** as a brown oil. The material resisted recrystallization and was not purified or characterized further.

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(Piperidinyl)ethyl Ester Methoiodide (21). Prepared from **19** (4.6 g, 16.0 mmol) by the same method as in **6** to give 6.66 g (96%) of **21**, mp 119-122 °C. $[\alpha]_D$ = -15.7 ° (2.67% in 95% EtOH). ^{1}H-NMR (DMSO-d_6) δ 7.31 (s, 5H, aromatic), 5.04 (t, 1H, OH), 4.49 (br t, 2H, CO_2CH_2), 4.1-3.5 (m, 3H, $CHCH_2OH$),3.30 (br t, 2H, CH_2N), 3.00 (s, 3H, NCH_3), 1.8-1.3 (m, 10H, ring CH_2s).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(Piperidyl)ethyl Ester Methochloride (SR 4954). Prepared from **21** (4.5 g, 10.7 mmol) by the same method as **SR 4950** to give 3.2 g (91%) of **SR 4954**, mp 126-127.5 °C. $[\alpha]_D$ = -22.6 ° (2.53% in 95% EtOH). ^{1}H-NMR (DMSO-d_6) δ 7.31 (s, 5H, aromatic), 5.24 (t, 1H, OH), 4.50 (br t, 2H,

CO_2CH_2), 4.1-3.55 (m, 3H, $CHCH_2OH$),3.75 (br t, 2H, CH_2N), 3.02 (s, 3H, NCH_3), 3.3-3.95 (m, 10H, ring CH_2s). Anal calcd for $C_{17}H_{26}ClNO_3$: C, 62.28; H, 7.99; N, 4.27; Cl, 10.81. Found: C, 62.54; H, 8.09; N, 4.08; Cl, 10.88.

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(Piperidyinl)ethyl Ester Ethoiodide (22). Prepared from **19** (5.0 g, 18.0 mmol) and EtI by the same method as **6** to give 7.3 g (94%) of **22**, mp 123-125 °C. $[\alpha]_D$ = -14.7 ° (2.53% in 95% EtOH). ^{1}H-NMR ($CDCl_3$-CD_3OD) δ 7.32 (s, 5H, aromatic), 4.55 (t, 2H, CO_2CH_2), 4.11 (q, 2H, NCH_2Me), 4.0-3.5 (m, 3H, $CHCH_2OH$), 3.40 (br t, 2H, CH_2N), 1.76 (br s, 10H, ring CH_2s), 1.25 (t, 3H, CH_3).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(Piperidinyl)ethyl Ester Ethochloride (SR 4955). Prepared from **22** (5.0 g, 11.5 mmol) by the same method as **SR 4950** to give 3.8 g (76%) of **SR 4955**, mp 109-111 °C. $[\alpha]_D$ = -17.4 ° (1.91% in 95% EtOH). ^{1}H-NMR (DMSO-d_6) δ 7.31 (s, 5H, aromatic), 5.19 (t, 1H, OH), 4.44 (br t, 2H, CO_2CH_2), 4.1-3.2 (m, 7H, $CHCH_2OH$, CH_2NCH_2Me), 1.3-1.95 (br s, 10H, ring CH_2s), 1.11 (t, 3H, CH_3). Anal calcd for $C_{18}H_{28}ClNO_3$: C, 63.24; H, 8.26; N, 4.10; Cl, 10.37. Found: C, 63.36; H, 8.35; N, 4.02; Cl, 10.36.

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(Pyrrolidinyl)ethyl Ester Hydrochloride (24). Prepared from **18** (2.75 g, 10.45 mmol) and ethereal HCl by the same method as **SR 4951**. Recrystallization from EtOH/Et_2O gave 2.81 g (90%) of **24**. Anal calcd for $C_{15}H_{22}ClNO_3$: C, 60.10; H, 7.40; N, 4.67; Cl, 11.87. Found: C, 60.13; H, 7.47; N, 4.71; Cl, 11.60.

2,2-Diphenyl-2-hydroxyacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester (25). Treatment of benzilic acid (16.0 g, 17.0 mmol) and 2-diethylaminoethyl chloride hydrochloride (12.5 g, 72.6 mmol) by the same method as **5** gave 20 g (87%) of **25**. ^{1}H-NMR ($CDCl_3$) δ 7.41 (m, 10H, aromatic), 4.31 (t, 2H, CO_2CH_2), 2.66 (t, 2H, CH_2N), 2.46(q, 4H, CH_2Me), 0.93 (t, 6H, CH_3).

2,2-Diphenyl-2-hydroxyacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester Hydrochloride (SR 4958). Prepared from **25** (5.0 g, 15.3 mmol) by the same method as **SR 4951** to give 5.2 g (93.4%) of **SR 4953**, mp 176.5-178 °C. ^{1}H-NMR (DMSO-d_6) δ 7.31 (s, 10H, aromatic), 6.85 (s, 1H, OH), 4.32 (br t, 2H, CO_2CH_2), 3.33 (br t, 2H, CH_2N), 2.29

(q, 4H, CH_2Me), 1.07 (t, 6H, CH_3). Anal calcd for $C_{20}H_{26}ClNO_3$: C, 66.01; H, 7.20; N, 3.85; Cl, 9.74. Found: C, 65.74; H, 7.31; N, 3.87; Cl, 9.91.

2,2-Diphenyl-2-hydroxyacetic Acid, 2-(*N,N*-Diethylamino)ethyl Ester Methoiodide. Prepared from **25** (5.0 g, 15.3 mmol) by the same method as **6** to give 6.0 g (84%) of product, mp 139-141 °C. ^{1}H-NMR (DMSO-d_6) δ 7.34 (s, 10H, aromatic), 6.75 (s, 1H, OH), 4.57 (br t, 2H, CO_2CH_2), 3.58 (br t, 2H, CH_2N), 3.20 (q, 4H, CH_2Me), 2.82 (s, 3H, CH_3), 1.05 (t, 6H, CH_3).

2,2-Diphenyl-2-hydroxyacetic Acid, 2-(*N,N*-Diethylamino)ethyl Ester Ethoiodide. Prepared from **25** (5.0 g, 15.3 mmol) and EtI (6 mL, 74 mmol) by the same method as **6** to give 6.1 g (83%) of product, mp 163-165 °C. ^{1}H-NMR (DMSO-d_6) δ 7.34 (s, 10H, aromatic), 6.75 (s, 1H, OH), 4.54 (br t, 2H, CO_2CH_2), 3.53 (br t, 2H, CH_2N), 3.17 (q, 4H, CH_2Me), 1.01 (t, 6H, CH_3).

2,2-Diphenyl-2-hydroxyacetic Acid, 2-(*N,N*-Diethylamino)ethyl Ester Methochloride (SR 4956). Prepared from the methoiodide (5.0 g, 10.6 mmol) by the same method as **SR 4950** to give 3.45 g (86%) of **SR 4956**, mp 202-204 °C. ^{1}H-NMR (DMSO-d_6) δ 7.34 (s, 10H, aromatic), 6.84 (s, 1H, OH), 4.55 (br t, 2H, CO_2CH_2), 3.60 (br t, 2H, CH_2N), 3.22 (q, 4H, CH_2Me), 1.06 (t, 6H, CH_3). Anal calcd for $C_{21}H_{28}ClNO_3$: C, 66.74; H, 7.47; N, 3.71; Cl, 9.32. Found: C, 66.80; H, 7.58; N, 3.62; Cl, 9.33.

2,2-Diphenyl-2-hydroxyacetic Acid, 2-(*N,N*-Diethylamino)ethyl Ester Ethochloride (SR 4957). Prepared from the ethoiodide (5.0 g, 10.3 mmol) by the same method as **SR 4950** to give 3.7 (91.7%) of **SR 4957**, mp 232-233 °C dec. ^{1}H-NMR (DMSO-d_6) δ 7.34 (s, 10H, aromatic), 6.82 (s, 1H, OH), 4.53 (br t, 2H, CO_2CH_2), 3.55 (br t, 2H, CH_2N), 3.18 (q, 4H, CH_2Me), 1.02 (t, 6H, CH_3). Anal calcd for $C_{22}H_{30}ClNO_3$: C, 67.42; H, 7.71; N, 3.57; Cl, 9.05. Found: C, 67.48; H, 7.78; N, 3.51; Cl, 9.16.

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, (*N*-Methylpyrrolidin-2-yl)-ethyl Ester (26) and S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, *N*-methylhexahydro-azepin-4-yl Ester (27). S-(-)-Tropic acid (5.00 g, 30.1 mmol) was treated with 2-(2-chloroethyl)-1-methylpyrrolidine hydrochloride in the same manner as **5** for 7 days. Chromatography (2x) on silica gel (95% CH_2Cl_2/5%[MeOH/NH_4OH(95/5)]) gave 0.95 g of **26** and 2.4 g of **27**. **26**: MS m/e 277. ^{1}H-NMR ($CDCl_3$) δ 7.28 (s, 5H, aromatic), 4.3-3.6 (m,

5H, $CHCH_2OH$, OCH_2), 3.0 (m, 1H, CHN), 2.21 (s, 3H, NCH_3), 2.4-1.3 (br, 6H, ring CH_2). **27**: MS m/e 277. ^{1}H-NMR ($CDCl_3$) δ 7.27 (s, 5H, aromatic), 5.05 (m, 1H, OCH), 4.3-3.6 (m, 4H, $CHCH_2OH$), 2.5 (m, 4H, CH_2N), 2.1-1.5 (m, 6H, ring CH_2), 2.3 (s, 3H, NCH_3).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, (*N*-Methylpyrrolidin-2-yl)ethyl Ester Methoiodide (28). Prepared from **26** (0.95 g, 3.42 mmol) by the same method as **6**. Reaction gave an oil which has failed to crystallize and has not been purified or characterized further.

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, *N*-Methylhexahydro-1H-azepin-4-yl Ester Methoiodide (30). Prepared from **27** (2.2 g, 7.93 mmol) by the same method as **6** to give 2.9 g (87%) of **30**. ^{1}H-NMR (DMSO-d_6) δ 7.33 (s, 5H, aromatic), 5.15 (m, 1H, OCH), 4.2-3.4 (m, 7H, $CHCH_2OH$, CH_2NCH_2), 3.32 (s, 3H, NCH_3), 3.19 (s, 3H, NCH_3), 1.8-2.5(br m, 6H, ring CH_2).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, *N*-Methylhexahydro-1H-azepin-4-yl Ester Methochloride (31). Prepared from **30** (2.4 g, 5.7 mmol) by the same method as **SR 4950** to give 1.7 g (90%) of **31**, mp 158-160 °C. ^{1}H-NMR ($CDCl_3$-CD_3OD) δ 7.33 (s, 5H, aromatic), 5.0 (m, 2H, CHO, OH), 4.1-3.4 (m, 3H, $CHCH_2OH$), 3.3 (m, 4H, CH_2N), 3.29 (s, 3H, NCH_3), 3.04 (s, 3H, NCH_3), 1.5-2.4 (br d, 6H, ring CH_2). Anal calcd for $C_{17}H_{26}ClNO_3$: C, 62.25; H, 7.99; N, 4.27; Cl, 10.81. Found: C, 60.01; H, 7.45; N, 4.07; Cl, 11.20 and C, 60.44; H, 7.93 N, 4.44; Cl, 11.56

S-(-)-1-Methyl-2-(chloromethyl)pyrrolidine Hydrochloride. To 24 g (0.208 mol) of S-(-)-1-Methyl-2-(hydroxymethyl)pyrrolidine in 100 mL of $CHCl_3$ (EtOH free) at 0 °C was added 19 mL (0.26 mol) of thionyl chloride in 60 mL of $CHCl_3$ over 20 min. The resulting brown solution was stirred at RT for 45 min, then heated at reflux for 30 min. The now purple solution was cooled and evaporated to dryness and the residue taken up in abs EtOH and filtered. Diethyl ether was added until the solution became cloudy, then chilled and filtered to give 22 g (62%) of S-(-)-1-methyl-2-(chloromethyl)pyrrolidine hydrochloride, mp 148-153 °C ^{1}H-NMR ($CDCl_3$) δ 4.5-3.5 (m, 4H, $ClCH_2$, CH_2N), 3.04 (m, 1H, CHN), 3.03 (d, 3H, NCH_3), 2.4-1.9 (m, 6H, ring CH_2s).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, S-(-)-1-Methyl-2-pyrrolidinylmethyl Ester (33) and S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, S-(-)-1-

Methyl-3-piperidinyl Ester (34). Prepared from S-(-)-tropic acid (0.333 g, 2.00 mmol) and 0.350 g (2.06 mmol) of S-(-)-1-methyl-2-(chloroethyl)pyrrolidine hydrochloride by the same method as **5** to give 0.5 g (95%) of a 9:1 mixture of **33** and **34** as an oil. ^{1}H-NMR ($CDCl_3$) δ 7.30 (s, 5H, aromatic), 4.6-3.7 (m, 7H, $CHCH_2OH$, CO_2CH_2 [pyrrolidine], CO_2CH [piperidine]), 3.3-1.5 (m, ring CH_2s)2.19 (s, **34**-NCH_3), 2.28 (s, **33**-NCH_3).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, S-(-)-1-Methyl-2-pyrrolidinylmethyl Ester Methoiodide (35) and S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, S-(-)-1-Methyl-3-piperidinyl Ester Methoiodide (37). Prepared from the mixture of **33** and **34** (0.5 g, 1.9 mmol) by the same method as **6** to give 0.8 g (103%) of an oil consisting of a mixture of **35** and **37**. ^{1}H-NMR (CD_3OD) δ 7.33 (s, 5H, aromatic), 4.3-4.5 (m, 3H, $CHCH_2OH$), 5.2 (m, 1H, CO_2CH [piperidine]), 4.53 d, 2H, CO_2CH_2 [pyrrolidine]), 3.17 (s, NCH_3 [pyrrolidine]), 3.00 (s, NCH_3 [pyrrolidine]), 3.22 (s, NCH_3 [piperidine]), 2.92 (s, NCH_3 [piperidine]), 2.7-1.8 (m, ring CH_2s).

S-(-)-α-(t-Butyldimethylsilyloxymethyl)phenylacetyl Chloride (40). In a flask under argon, 0.5 g (3.00 mmol) of S-(-)-tropic acid was combined with 0.96 g (6.37 mmol) of *t*-butyldimethylsilane and 0.865 g (12.7 mmol) of imidazole in 3 mL of DMF and stirred at RT for 18 h. The mixture was poured into 20 mL of H_2O and extracted with ether. The ether was washed with saturated NaCl solution, dried over $MgSO_4$, filtered and evaporated to give 1.15 g of an oil. This was taken up in 5 mL of CH_2Cl_2 and 1 drop of DMF, followed by the addition of 286 μL (3.35 mmol) of oxalyl chloride at 0 °C, stirred at 0 °C for 1.5 h, then at RT for 0.5 h. The solution was evaporated to yield 1.2 g (137 %) of **40** as a syrup which was not purified further. ^{1}H-NMR ($CDCl_3$) δ 7.38 (s, 5H, aromatic), 4.3-3.7 (m, 3H, $CHCH_2$), 0.84 (s, 9H, t-butyl), 0.02 (s, 3H, CH_3), 0.01 (s, 3H, CH_3).

S-(-)-α-(t-Butyldimethylsilyloxymethyl)benzeneacetic Acid, S-(-)1-Methyl-2-pyrrolidinylmethyl Ester (41). To 0.335 g (2.91 mmol) of S-(-)-1-methyl-2-pyrrolidinemethanol and 295 μL (2.92 mmol) of triethylamine in 5 mL of CH_2Cl_2 at 0 °C was added 0.872 g (2.91 mmol) of **40** in 2 mL of CH_2Cl_2. The solution was stirred at 0 °C for 1 h, then washed with satd $NaHCO_3$ solution. The organic fraction was dried over $MgSO_4$ filtered and evaporated to dryness. The residue was purified by flash chromatography to give 0.211 g (19%) of **41**. ^{1}H-NMR ($CDCl_3$) δ 7.42 (s, 5H, aromatic), 4.5-3.7 (m, 3H, $CHCH_2$, OCH_2), 2.43 (s, 3H, NCH_3), 2.7-1.5 (m, 6H, ring CH_2), 0.98 (s, 9H, *t*-butyl), 0.15 (s, 3H, CH_3), 0.13 (s, 3H, CH_3).

R-(+)-α-(Hydroxymethyl)benzeneacetic Acid, S-(-)-1-Methyl-2-pyrrolidinylmethyl Ester (33) and R-(+)-α-(Hydroxymethyl)benzeneacetic Acid, 1-Methyl-3-piperidinyl Ester (43). A solution of 0.250 g (0.66 mmol) of **50** in 5 mL of THF was treated with 0.6 g (1.98 mmol) of tetrabutylammonium fluoride, stirred for 1 h, then evaporated to dryness. The residue was partitioned between H_2O (20 mL) and ether (20 mL), and the ether layer washed with satd NaCl solution, dried over $MgSO_4$, filtered and evaporated to give 0.150 g (86%) of an oil consisting of a mixture of **33** and **43**.

R-(+)-α-(Hydroxymethyl)benzeneacetic Acid, S-(-)-1-Methyl-2-pyrrolidinylmethyl Ester (33). In a small flask, **41** in 3 mL of AcOH/H_2O/THF (3/1/1/) was stirred at RT for 5 days. The solution was evaporated to dryness in vacuo to give 0.110 g (90%) of **33** as a syrup.

4-Chlorobenzeneacetic acid, Methyl Ester (46). To 34 g (0.200 mol) of p-chlorobenzeneacetic acid (**45**) in 120 mL of MeOH at 0 °C was added 80 mL of MeOH saturated with HCl gas. The solution was stirred for 20 h, then evaporated to an oil. This was taken up in 150 mL of CH_2Cl_2, washed with satd $NaHCO_3$ and satd NaCl solution, dried over $MgSO_4$, filtered and evaporated to give 37 g (100%) of **46**. ^{1}H-NMR ($CDCl_3$) δ 7.27 (q 4H, aromatic), 4.3-3.7 (m, 2H, CH_2), 3.71 (s, 3H, OCH_3).

Methyl *p*-Chloro-α-hydroxymethylbenzene Acetate (47). Into a flask, flame dried under argon, was placed a slurry of 37 g (0.20 mol) of **46** and 750 g of paraformaldehyde in 120 mL of dry DMF, followed by the addition of 0.650 g (12 mmol) of sodium methoxide in one portion. This was stirred for 1.5 h, then poured into 300 mL of H_2O and extracted with ether (3 x 250 mL). The ether fraction was washed with satd NaCl solution, dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography eluting with 1%MeOH in $CHCl_3$ to give 21 g (49%) of **47**. ^{1}H-NMR ($CDCl_3$) δ 7.27 (q 4H, aromatic), 4.3-3.7 (m, 3H, $CHCH_2OH$), 3.71 (s, 3H, OCH_3).

(±)-Chlorotropic Acid (48). To 22 g of **47** in 10 mL of THF was added 18 mL (108 mmol) of 6 N NaOH and the mixture stirred for 18 h. The THF was removed by evaporation and the residue taken up in H_2O, followed by the addition of 6N HCl until no more solid precipitated. The solid was collected by filtration and washed with water, then dried in vacuo to give 20 g (98%) of

48. ^{1}H-NMR (DMSO-d_6) δ 7.19 (s 4H, aromatic), 4.1-3.5 (m, 3H, C<u>H</u>C<u>H</u>$_2$), 6.90 (br, 2H, CO_2<u>H</u>, O<u>H</u>).

(-)-4-Chlorotropic Acid (49). Prepared from **48** (10 g, 50 mmol) and quinine hydrate (17.5 g, 51 mmol) by the same method as **1** to give 3.5 g (13%) of **48•quinine salt**, mp 190-192 °C. This was stirred in 20 mL of 1N H_2SO_4 for 0.5 h, followed by the addition of 100 mL of EtOAc and 25 mL of satd NaCl solution. The layers were separated and the aqueous layer extracted with EtOAc. The combined organic fraction was washed with satd NaCl solution, dried over $MgSO_4$, filtered and evaporated to give 1.3 g (13%) of **49**. $[\alpha]_D$ = -58 (2.5% in 95%EtOH).

5-Bromovaleraldehyde Ethylene Acetal. 5-Bromovaleraldehyde (23 g, 139 mmol) was combined with 12.5 g (402 mmol) of ethylene glycol and 3 crystals of *p*-toluenesulfonic acid in 400 mL of toluene and heated at reflux in a Dean-Stark trap for 10 h. The solvent was reduced to ~20 mL, diluted with 200 mL of CH_2Cl_2, washed with 200 mL of satd $NaHCO_3$ and 200 mL of NaCl solution, dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography to give 5.2 g (18%) of 5-bromovaleraldehyde ethylene acetal. Additional fractions were obtained, of lower purity (6.2 g, 98% purity; 5.0 g, 89% purity). ^{1}H-NMR ($CDCl_3$) δ 4.86 (t, 1H, C<u>H</u>), 4.0-3.8 (m, 4H, OC<u>H</u>$_2$), 3.41 (t, 2H, C<u>H</u>$_2$Br), 1.4 -2.1 (m, 6H, C<u>H</u>$_2$).

Methyl 7-Ethylenedioxy-2-phenylheptanoate (51). A trace of Na was added to ~15 mL of liquid ammonia, followed by a crystal of ferric nitrate. This was stirred until the blue color changed to a clear solution with a dark solid. To this mixture was added 0.132 g (5.62 mmol) of Na and stirring continued until the blue color became a black precipitate. To this was slowly added 0.90 g (6.0 mmol) of methyl phenylacetate, followed by stirring at -33 °C for 0.5 h. To this brown mixture was added 1.0 g (4,78 mmol) of 5-bromovaleraldehyde ethylene acetal in 5 mL of ether with stirring continued at -33 °C for 2 h. Ammonium chloride (0.30 g, 5.6 mmol) was added and the ammonia allowed to evaporate off. The residue was taken up in ether, washed with satd NaCl solution, dried over $MgSO_4$, filtered and evaporated to give an oil. This was purified by flash chromatography eluting with CH_2Cl_2 to give 1.2 g (86%) of **51**. R_f 0.3 (CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) δ 7.28 (s, 5H, aromatic), 4.81 (t, 1H, OC<u>H</u>O), 4.0-3.7 (m, 4H, OC<u>H</u>$_2$), 3.64 (s, 3H, OC<u>H</u>$_3$), 3.54 (t, 1H, C<u>H</u>), 1.1-2.4 (m, 8H, C<u>H</u>$_2$).

Methyl 7-Oxo-2-phenylheptanoate (52). To a mixture of 8 g silica gel and 0.8 mL of 10% oxalic acid in 5 mL of CH_2Cl_2 was added 0.8 g (2.87 mmol) of **51**. The mixture was stirred at

RT for 5 days, followed by the addition of 0.075 g (0.9 mmol) of powdered $NaHCO_3$ and stirring for an additional 0.5 h. To this mixture was added ~2 g of $MgSO_4$, and the entire mixture added to a flash chromatography column and eluted with CH_2Cl_2/cyclohexane/MEK (50/49.5/0.5) to give 0.430 g (66%) of **52** and 0.200 g of recovered starting material. ^{1}H-NMR ($CDCl_3$) δ 9.72 (t, 1H, aldehyde H), 7.28 (s, 5H, aromatic), 3.64 (s, 3H, OCH_3), 3.54 (t, 1H, $CHCO_2Me$), 2.41 (d of t, 2H, CH_2CHO), 1.8-0.9 (m, 6H, CH_2).

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APPENDIX

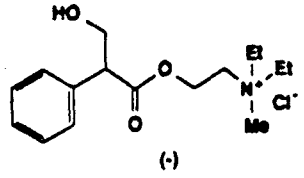
DATA SHEET FOR COMPOUNDS

WR NR.	SUBMITTER	SUBMITTER KEY NR.
	MICHAEL TRACY SRI International	1317

DATE SHIPPED	DAY	MO	YR	DATE RECEIVED	DAY	MO	YR	DATE ACKNOWLEDGED	DAY	MO	YR
	18	4	89								

NAME OF COMPOUND: S-(-)-α-(Hydroxymethyl)benzeneacetic acid 2-(N,N-diethylamino)ethyl ester methochloride

STRUCTURE



(-)

MOL FORMULA	MOL WT
$C_{16}H_{26}ClNO_3$	315.80

APPEARANCE: White crystalline solid

QUANTITY	CODE NR.
2.5g	SR 4950

NOTEBOOK REF.	PREPARED BY
KJR 8792H-19.2	K. Ryan

TEST SYSTEM

SHELF LOCATION :

B.P.	M.P.	REFRACT. INDEX
	110-112°C	

$[\alpha]_D^{25}$ -21.0 1.32% in 95% EtOH

WARNING

ANALYSES

ELEMENT	CALCULATED	FOUND	WR FOUND
C	60.84	60.82	
H	8.30	8.51	
N	4.43	4.40	
Cl	11.23	11.21	

LITERATURE

STABILITY (Check Where Applicable)

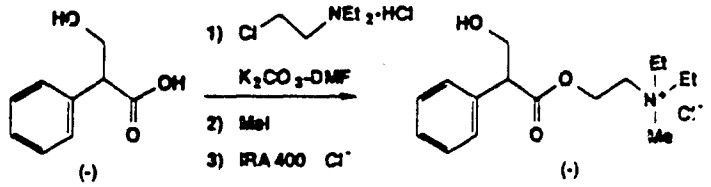
	STABLE		UNSTABLE		OTHER	STABLE		UNSTABLE	
ACID	☐	86	☐						
BASE	☐	87	☐			☐	90	☐	
HEAT	☐	88	☐			☐	91	☐	
LIGHT	☐ 1	89	☐ 2			☐ 1	92	☐ 2	

HYGROSCOPIC: YES ☐ 1 92 NO ☐ 2 93

SOLUBILITY (Check Where Applicable)

		v. sol	mod. sol	sl. sol			v. sol	mod. sol	sl. sol
WATER	84	☒	☐	☐	CHLOROFORM	70	☐	☐	☐
ACID	85	☐	☐	☐	ETHER	71	☐	☐	☐
BASE	86	☐	☐	☐	PET. ETHER	72	☐	☐	☐
METHANOL	87	☒	☐	☐	BENZENE	73	☐	☐	☐
ETHANOL	88	☒	☐	☐	DMSO-d6	74	☐	☒	☐
ACETONE	89	☐	☐	☐		75	☐	☐	☐
		1	2	3			1	2	3

EQUATIONS INDICATING SYNTHETIC ROUTE



Quantitative water solubility: 1200 mg/ml

REMARKS

^{1}H NMR : √ 90 MHz-DMSO-d6

IR : √

78 COMMERCIALLY DISCREET 1 ☐	Cont. Nr. DMAD17-88-C-8147 SYNTHESIZED UNDER GOVT SUPPORT 2 ☒	GIFT 3 ☐	PURCHASED 4 ☐

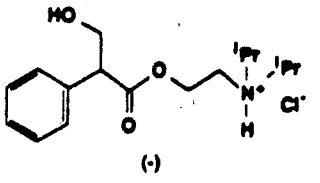
DATA SHEET FOR COMPOUNDS

WR NR.	SUBMITTER	SUBMITTER KEY NR
	MICHAEL TRACY SRI International	1317

	DAY	MO	YR		DAY	MO	YR		DAY	MO	YR
DATE SHIPPED	18	4	89	DATE RECEIVED				DATE ACKNOWLEDGED			

NAME OF COMPOUND S-(-)-α-(Hydroxymethyl)benzeneacetic acid 2-[N,N-di(1-methylethyl)amino]ethyl ester hydrochloride

STRUCTURE



(-)

MOL FORMULA	MOL WT
$C_{17}H_{28}ClNO_3$	329.90

APPEARANCE: White crystalline solid

QUANTITY: 2.5 — CODE NR: SR 4951

NOTEBOOK REF: KJR 8792H-47.2 — PREPARED BY: K. Ryan

TEST SYSTEM

SHELF LOCATION:

B.P.	M.P.	REFRACT. INDEX
	91-94°C	

$[\alpha]_D$= -15.9 2.38% in 95% EtOH

WARNING

ANALYSES

ELEMENT	CALCULATED	FOUND	WR FOUND
C	61.90	61.68	
H	8.56	8.62	
N	4.25	4.18	
Cl	10.75	10.52	

LITERATURE

STABILITY (Check Where Applicable)

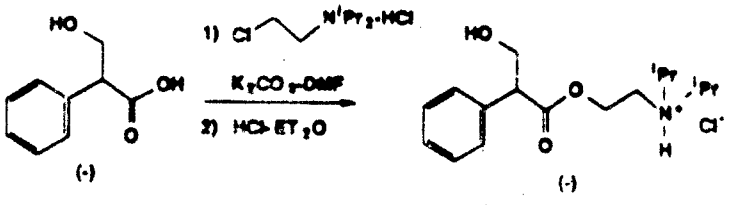
	STABLE	UNSTABLE		STABLE	UNSTABLE
ACID	☐ 86	☐	OTHER	☐	☐
BASE	☐ 87	☐	_____	☐ 93	☐
HEAT	☐ 88	☐	_____	☐ 94	☐
LIGHT	☐ 89	☐	_____	☐ 95	☐

HYGROSCOPIC YES ☐ 82 NO ☐ 83

SOLUBILITY (Check Where Applicable)

		V sol	mod sol	sl sol			V sol	mod sol	sl sol
WATER	64	☒	☐	☐	CHLOROFORM	70	☐	☐	☐
ACID	65	☐	☐	☐	ETHER	71	☐	☐	☐
BASE	66	☐	☐	☐	PET ETHER	72	☐	☐	☐
METHANOL	67	☒	☐	☐	BENZENE	73	☐	☐	☐
ETHANOL	68	☒	☐	☐	DMSO-d6	74	☐	☒	☐
ACETONE	69	☐	☐	☐	_____	75	☐	☐	☐
		1	2	3			1	2	3

EQUATIONS INDICATING SYNTHETIC ROUTE



Quantitative water solubility: 570 mg/ml

REMARKS

^{1}H NMR: √ 90 MHz-DMSO-d6

IR: √

76 COMMERCIALLY DESCRIBED	Cont. Nr. DMAD17-88-C-8147 SYNTHESIZED UNDER GOVT SUPPORT 77	78 GIFT	79 PURCHASED
☐ 1	☒ 2	☐ 3	☐ 4

WRAMC FORM 108 APR 1984 SUPERSEDES WRAMC FORM 108, 13 AUG 68, WHICH IS OBSOLETE

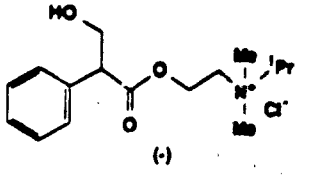
DATA SHEET FOR COMPOUNDS

WRITER	SUBMITTER	SUBMITTER KEY NR
	MICHAEL TRACY SRI International	1317

DATE SHIPPED	DAY	MO	YR	DATE RECEIVED	DAY	MO	YR	DATE ACKNOWLEDGED	DAY	MO	YR
	18	4	89								

NAME OF COMPOUND S-(-)-α-(Hydroxymethyl)benzeneacetic acid 2-[N-(1-methylethyl)-N-methylamino]ethyl ester methochloride

STRUCTURE



(-)

MOL FORMULA	MOL WT
$C_{16}H_{26}ClNO_3 \cdot 1/3\ H_2O$	321.90

APPEARANCE: White Crystalline solid

QUANTITY: 2.5g

CODE NR: SR 4952

NOTE BOOK REF: KJR 8792H-76.2

PREPARED BY: K. Ryan

TEST SYSTEM:

SHELF LOCATION:

BP	MP	REFRACT INDEX
	118-120°C	

$(\alpha)_D^{20}$ -21.1 in 95% EtOH

REMARKS:

LITERATURE:

ANALYSES

ELEMENT	CALCULATED	FOUND	NR FOUND
C	59.71	59.73	
H	8.32	8.27	
N	4.35	4.25	
Cl	11.01	10.70	

STABILITY (Check Where Applicable)

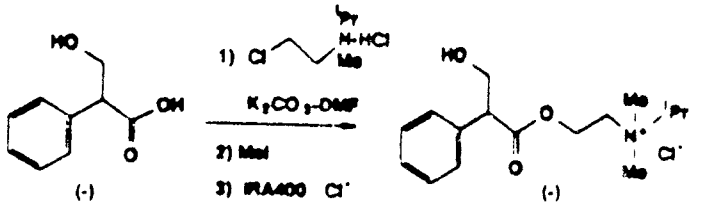
	STABLE	UNSTABLE		OTHER	STABLE	UNSTABLE
ACID	☐	☐			☐	☐
BASE	☐	☐			☐	☐
HEAT	☐	☐			☐	☐
LIGHT	☐	☐			☐	☐

HYGROSCOPIC: YES ☒ NO ☐

SOLUBILITY (Check Where Applicable)

	1	2	3		1	2	3
WATER	☒	☐	☐	CHLOROFORM	☐	☐	☐
ACID	☐	☐	☐	ETHER	☐	☐	☐
BASE	☐	☐	☐	PET. ETHER	☐	☐	☐
METHANOL	☒	☐	☐	BENZENE	☐	☐	☐
ETHANOL	☒	☐	☐	DMSO-d6	☐	☒	☐
ACETONE	☐	☐	☐		☐	☐	☐

EQUATIONS INDICATING SYNTHETIC ROUTE



Quantitative water solubility ~690 mg/ml

REMARKS

^{1}H NMR: √ 90 MHz-DMSO-d6

IR: √

COMMERCIALLY DESCRIBED	Contr. No. (NIMH) 17-88-C-8147 SYNTHESIZED UNDER GOVT SUPPORT	GIFT	PURCHASED
☐	☒	☐	☐

WRAMC FORM [illegible] SUPERSEDES WRAMC FORM [illegible] 13 AUG 88 WHICH IS OBSOLETE

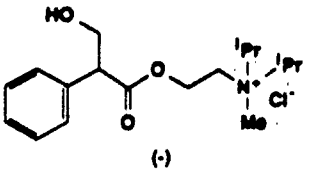
DATA SHEET FOR COMPOUNDS

WR NR.	SUBMITTER	SUBMITTER KEY NR.
	MICHAEL TRACY SRI International	1317

DATE SHIPPED	DAY	MO	YR	DATE RECEIVED	DAY	MO	YR	DATE ACKNOWLEDGED	DAY	MO	YR
	18	4	89								

NAME OF COMPOUND S-(-)-α-(Hydroxymethyl)benzeneacetic acid 2-[N,N-di(1-methylethyl)amino]ethyl ester methochloride

STRUCTURE



(-)

MOL FORMULA	MOL WT
$C_{18}H_{30}ClNO_3$	343.90

APPEARANCE	
White crystalline Solid	

QUANTITY	CODE NR.
2.5g	SR 4953

NOTEBOOK REF.	PREPARED BY
KJR 8792H-85.2	K. Ryan

TEST SYSTEM	

SHELF LOCATION :	

B.P.	M.P.	REFRACT. INDEX
	113-115°C	

$[\alpha]_D$= -20.6 2.50% in 95% EtOH

WORKING

ANALYSES

ELEMENT	CALCULATED	FOUND	WR FOUND
C	62.87	63.10	
H	8.79	9.00	
N	4.07	3.94	
Cl	10.31	10.12	

LITERATURE

STABILITY (Check Where Applicable)

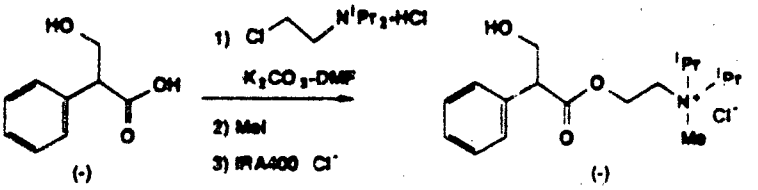
	STABLE		UNSTABLE		OTHER	STABLE		UNSTABLE	
ACID	☐	86	☐			☐	90	☐	
BASE	☐	87	☐			☐	91	☐	
HEAT	☐	88	☐			☐	92	☐	
LIGHT	☐	89	☐			☐	93	☐	
		1		2			1		2

HYGROSCOPIC YES ☐ 92 (1) NO ☐ 93 (2)

SOLUBILITY (Check Where Applicable)

	V. sol	mod sol	sl sol		V sol	mod sol	sl sol
WATER	64 ☒	☐	☐	CHLOROFORM	70 ☐	☐	☐
ACID	65 ☐	☐	☐	ETHER	71 ☐	☐	☐
BASE	66 ☐	☐	☐	PET. ETHER	72 ☐	☐	☐
METHANOL	67 ☒	☐	☐	BENZENE	73 ☐	☐	☐
ETHANOL	68 ☒	☐	☐	DMSO-d6	74 ☐	☒	☐
ACETONE	69 ☐	☐	☐		75 ☐	☐	☐
		1	2	3		1	2

EQUATIONS INDICATING SYNTHETIC ROUTE



Quantitative water solubility ~670 mg/ml

REMARKS

NMR √ 90 MHz-DMSO-d6

IR √

PURCHASED	GIFT	SYNTHESIZED UNDER GOVT SUPPORT	Cont. Nr. DMAD17-88-C-8147	ROUTINELY DISBURSED
4	3	2		1
☐	☐	☒		☐

SUPERSEDES WRAMC FORM 108, 13 AUG 85, WHICH IS OBSOLETE

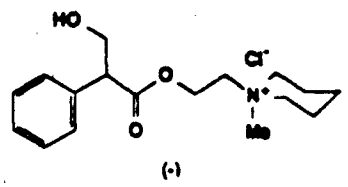
DATA SHEET FOR COMPOUNDS

WR NR.	SUBMITTER	SUBMITTER KEY NR.
	MICHAEL TRACY SRI International	1317

DATE SHIPPED	DAY	MO	YR	DATE RECEIVED	DAY	MO	YR	DATE ACKNOWLEDGED	DAY	MO	YR
	18	4	89								

NAME OF COMPOUND: S-(-)-α-(Hydroxymethyl)benzeneacetic acid 2-(1-piperidinyl)ethyl ester methochloride

STRUCTURE



(-)

MOL FORMULA	MOL WT
$C_{17}H_{26}ClNO_3$	327.90

APPEARANCE: White crystalline solid

QUANTITY	CODE NR.
2.5g	SR 4954

NOTEBOOK REF.	PREPARED BY
KJR 8792H-86.2	K. Ryan

TEST SYSTEM:

SHELF LOCATION :

B.P.	M.P.	REFRACT. INDEX
	126-127.5°C	

$[\alpha]_D^{25}$ -22.6 2.53% in 95% EtOH

WARNING:

LITERATURE:

ANALYSES

ELEMENT	CALCULATED	FOUND	WR FOUND
C	62.28	62.54	
H	7.99	8.09	
N	4.27	4.06	
Cl	10.81	10.86	

STABILITY (Check Where Applicable)

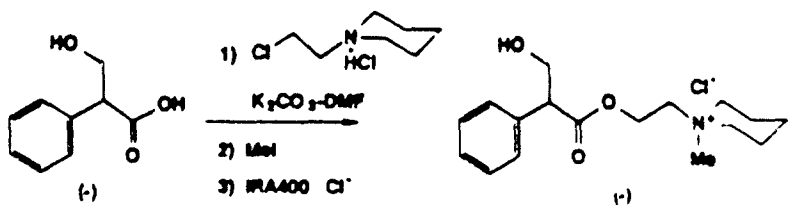
	STABLE	UNSTABLE		OTHER	STABLE	UNSTABLE
ACID	☐ 86	☐				
BASE	☐ 87	☐			☐ 90	☐
HEAT	☐ 88	☐			☐ 91	☐
LIGHT	☐ 89 1	☐ 2			☐ 1	☐ 2

HYGROSCOPIC: YES ☐ 92 (1) NO ☐ 93 (2)

SOLUBILITY (Check Where Applicable)

	V. sol 1	mod sol 2	sl sol 3		V. sol 1	mod sol 2	sl sol 3
WATER	64 ☒	☐	☐	CHLOROFORM	70 ☐	☐	☐
ACID	65 ☐	☐	☐	ETHER	71 ☐	☐	☐
BASE	66 ☐	☐	☐	PET. ETHER	72 ☐	☐	☐
METHANOL	67 ☒	☐	☐	BENZENE	73 ☐	☐	☐
ETHANOL	68 ☒	☐	☐	DMSO-d6	74 ☐	☒	☐
ACETONE	69 ☐	☐	☐		75 ☐	☐	☐
		1 2 3				1 2 3	

EQUATIONS INDICATING SYNTHETIC ROUTE



Quantitative water solubility ~580 mg/ml

REMARKS

^{1}H NMR : √ 90 DMSO-d6

IR : √

0 ☐	Cont. Nr. DMAD17-88-C-8147 SYNTHESIZED UNDER GOVT SUPPORT 2 ☒	GIFT 3 ☐	PURCHASED 4 ☐

SUPERSEDES WRAMC FORM 108, 13 AUG 68, WHICH IS OBSOLETE

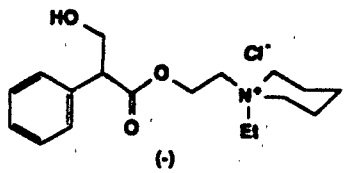
DATA SHEET FOR COMPOUNDS

WR NR.	SUBMITTER	SUBMITTER KEY NR
	MICHAEL TRACY SRI International	1317

DATE SHIPPED	DAY	MO	YR	DATE RECEIVED	DAY	MO	YR	DATE ACKNOWLEDGED	DAY	MO	YR
	18	4	89								

NAME OF COMPOUND: S-(-)-α-(hydroxymethyl)benzeneacetic acid 2-(1-piperidinyl)ethyl ester ethochloride

STRUCTURE



(-)

MOL FORMULA	MOL WT
$C_{19}H_{29}ClNO_3$	341.90

APPEARANCE: White crystalline solid

QUANTITY	CODE NR.
2.5g	SR 4955

NOTEBOOK REF.	PREPARED BY
KJR 8792H-87.2	K. Ryan

TEST SYSTEM

SHELF LOCATION :

B.P.	M.P.	REFRACT. INDEX
	109-111°C	

$[\alpha]_D$= -17.4 1.91% in 95% EtOH

WARNING

LITERATURE

ANALYSES

ELEMENT	CALCULATED	FOUND	WR FOUND
C	63.24	63.36	
H	8.26	8.35	
N	4.10	4.02	
Cl	10.37	10.36	

STABILITY (Check Where Applicable)

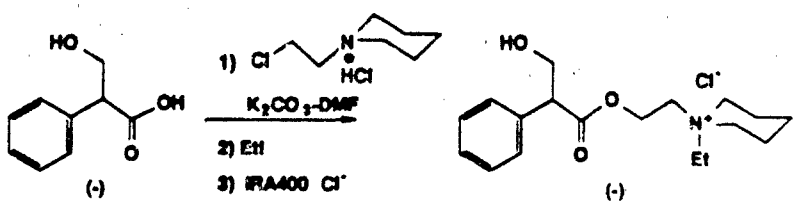
	STABLE	UNSTABLE		OTHER	STABLE	UNSTABLE
ACID	56 ☐	☐				
BASE	57 ☐	☐			60 ☐	☐
HEAT	58 ☐	☐			61 ☐	☐
LIGHT	59 ☐ 1	☐ 2			62 ☐ 1	☐ 2

HYGROSCOPIC: YES ☒ 1 63 NO ☐ 2 64

SOLUBILITY (Check Where Applicable)

	v. sol	mod. sol	sl. sol		v. sol	mod. sol	sl. sol
WATER 64	☒	☐	☐	CHLOROFORM 70	☐	☐	☐
ACID 65	☐	☐	☐	ETHER 71	☐	☐	☐
BASE 66	☐	☐	☐	PET. ETHER 72	☐	☐	☐
METHANOL 67	☒	☐	☐	BENZENE 73	☐	☐	☐
ETHANOL 68	☒	☐	☐	DMSO-d6 74	☐	☒	☐
ACETONE 69	☐	☐	☐	_____ 75	☐	☐	☐
	1	2	3		1	2	3

EQUATIONS INDICATING SYNTHETIC ROUTE



Quantitative water solubility ~350 mg/ml

REMARKS

^{1}H NMR : √ 90 MHz-DMSO-d6

IR : √

76 COMMERCIALLY DISCREET 1 ☐	Cont. Nr. DMAD17-88-C-8147 SYNTHESIZED UNDER GOVT SUPPORT 2 ☒	GIFT 3 ☐	PURCHASED 4 ☐

WRAMC FORM 1 APR 1984 108

SUPERSEDES WRAMC FORM 108, 13 AUG 83, WHICH IS OBSOLETE.

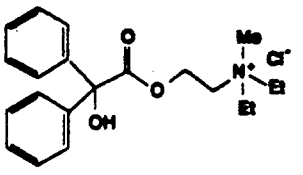
DATA SHEET FOR COMPOUNDS

WR NR.	SUBMITTER	SUBMITTER KEY NR
	MICHAEL TRACY SRI International	1317

DATE SHIPPED	DAY	MO	YR	DATE RECEIVED	DAY	MO	YR	DATE ACKNOWLEDGED	DAY	MO	YR
	18	4	89								

NAME OF COMPOUND: α-Hydroxy-α-phenylbenzeneacetic acid 2-(N,N-diethylamino)ethyl ester methochloride

STRUCTURE



MOL FORMULA	MOL WT
$C_{21}H_{26}ClNO_3$	377.90

APPEARANCE: White crystalline solid

QUANTITY	CODE NR.
2.5g	SR 4956

NOTEBOOK REF.	PREPARED BY
KJR 8792H-92.5	K. Ryan

TEST SYSTEM

SHELF LOCATION :

B.P.	M.P.	REFRACT. INDEX
	204-205°C	

$[\alpha]_D^{\infty}$

WARNING

ANALYSES

ELEMENT	CALCULATED	FOUND	WR FOUND
C	66.74	66.86	
H	7.47	7.58	
N	3.71	3.62	
Cl	9.38	9.33	

LITERATURE

STABILITY (Check Where Applicable)

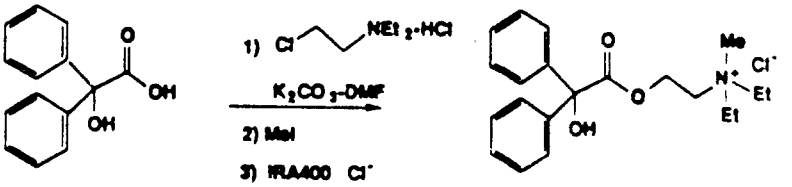
	STABLE	UNSTABLE		STABLE	UNSTABLE
ACID	56 ☐	☐	OTHER		
BASE	☐ 57	☐	_____	☐ 60	☐
HEAT	☐ 58	☐	_____	☐ 61	☐
LIGHT	☐ 59 1	☐ 2	_____	☐ 62 1	☐ 2

HYGROSCOPIC: YES ☐ 62 (1) NO ☐ 63 (2)

SOLUBILITY (Check Where Applicable)

	v. sol	mod. sol	sl. sol		v sol	mod sol	sl sol
WATER 64	☒	☐	☐	CHLOROFORM 70	☐	☐	☐
ACID 65	☐	☐	☐	ETHER 71	☐	☐	☐
BASE 66	☐	☐	☐	PET. ETHER 72	☐	☐	☐
METHANOL 67	☒	☐	☐	BENZENE 73	☐	☐	☐
ETHANOL 68	☒	☐	☐	DMSO-d6 _____ 74	☐	☒	☐
ACETONE 69	☐	☐	☐	_____ 75	☐	☐	☐
	1	2	3		1	2	3

EQUATIONS INDICATING SYNTHETIC ROUTE



Quantitative water solubility ~250 mg/ml

REMARKS

^{1}H NMR : √ 90 MHz -DMSO-d6

IR : √

COMMERCIALLY DESCRIBED (76, 1)	Cont. Nr. DMAD17-88-C-8147 SYNTHESIZED UNDER GOVT SUPPORT (2)	GIFT (3)	PURCHASED (4)
☐	☒	☐	☐

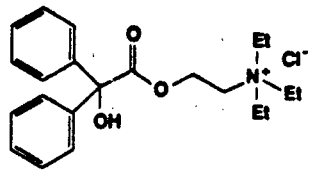
DATA SHEET FOR COMPOUNDS

WR NR.	SUBMITTER	SUBMITTER KEY NR
	MICHAEL TRACY SRI International	1317

DATE SHIPPED	DAY	MO	YR	DATE RECEIVED	DAY	MO	YR	DATE ACKNOWLEDGED	DAY	MO	YR
	18	4	89								

NAME OF COMPOUND: α-Hydroxy-α-phenylbenzeneacidic acid 2(N,N-diethylamino)ethyl ester ethochloride

STRUCTURE



MOL FORMULA	MOL WT
$C_{22}H_{30}ClNO_3$	495.70

APPEARANCE: White crystalline solid

QUANTITY	CODE NR.
2.5g	SR 4957

NOTEBOOK REF.	PREPARED BY
KJR 8792H-93.2	K. Ryan

TEST SYSTEM

SHELF LOCATION :

B.P.	M.P.	REFRACT. INDEX
	232-233°C	

$[\alpha]_D^{\infty}$

WARNING

ANALYSES

ELEMENT	CALCULATED	FOUND	WR FOUND
C	67.42	67.48	
H	7.71	7.78	
N	3.57	3.51	
Cl	9.05	9.16	

LITERATURE

STABILITY (Check Where Applicable)

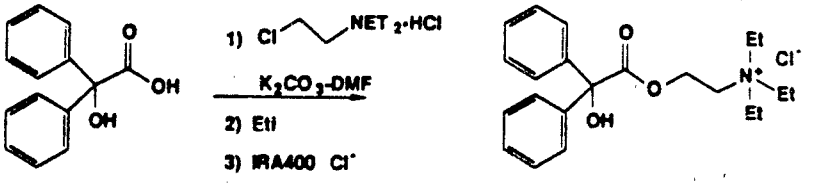
	STABLE		UNSTABLE		OTHER	STABLE		UNSTABLE	
ACID	☐	56	☐						
BASE	☐	57	☐			☐	60	☐	
HEAT	☐	58	☐			☐	61	☐	
LIGHT	☐ 1	59	☐ 2			☐ 1	62	☐ 2	

HYGROSCOPIC: YES ☐ 1 62 NO ☐ 2 63

SOLUBILITY (Check Where Applicable)

	v. sol	mod. sol	in sol		v. sol	mod. sol	in sol
WATER 64	☒	☐	☐	CHLOROFORM 70	☐	☐	☐
ACID 65	☐	☐	☐	ETHER 71	☐	☐	☐
BASE 66	☐	☐	☐	PET. ETHER 72	☐	☐	☐
METHANOL 67	☒	☐	☐	BENZENE 73	☐	☐	☐
ETHANOL 68	☒	☐	☐	DMSO-d6 74	☐	☒	☐
ACETONE 69	☐	☐	☐	75	☐	☐	☐
	1	2	3		1	2	3

EQUATIONS INDICATING SYNTHETIC ROUTE



Quantitative water solubility ~220 mg/ml

REMARKS

^{1}H NMR : √ 90 MHz-DMSO-d6

IR : √

76 COMMERCIALLY DESCREET 1 ☐	Cont. Nr. DMAD17-88-C-8147 SYNTHESIZED UNDER GOVT SUPPORT 2 ☒	3 GIFT ☐	4 PURCHASED ☐

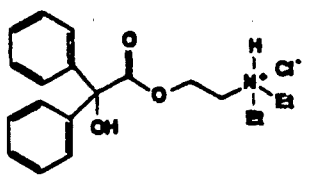
DATA SHEET FOR COMPOUNDS

WR NR.	SUBMITTER	SUBMITTER KEY NR.
	MICHAEL TRACY SRI International	1317

DATE SHIPPED	DAY	MO	YR	DATE RECEIVED	DAY	MO	YR	DATE ACKNOWLEDGED	DAY	MO	YR
	18	4	89								

NAME OF COMPOUND: α-Hydroxy-α-phenylbenzeneacetic acid 2-(diethyl amino)ethyl ester hydrochloride

STRUCTURE



MOL FORMULA	MOL WT
$C_{20}H_{25}ClNO_3$	363.90

APPEARANCE: White crystalline solid

QUANTITY	CODE NR.
2.5g	SR 4958

NOTEBOOK REF.	PREPARED BY
KJR 8792H-94.2	K. Ryan

TEST SYSTEM

SHELF LOCATION :

B.P.	M.P.	REFRACT. INDEX
	176.5-178°C	

$[\alpha]_D^{25}$

WEIGHED

ANALYSES

ELEMENT	CALCULATED	FOUND	WR FOUND
C	66.01	65.74	
H	7.20	7.31	
N	3.85	3.87	
Cl	9.74	9.91	

LITERATURE

STABILITY (Check Where Applicable)

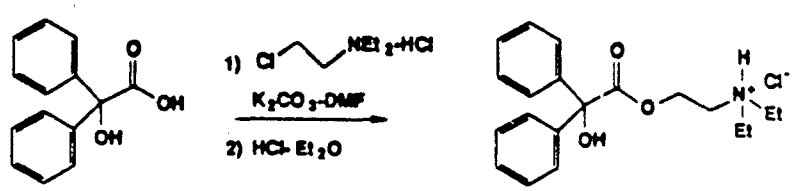
	STABLE	UNSTABLE		STABLE	UNSTABLE
ACID	86 ☐	☐	OTHER		
BASE	87 ☐	☐	_____	90 ☐	☐
HEAT	88 ☐	☐	_____	91 ☐	☐
LIGHT	89 ☐ 1	☐ 2	_____	92 ☐ 1	☐ 2

HYGROSCOPIC: YES ☐ 92 (1) NO ☐ 93 (2)

SOLUBILITY (Check Where Applicable)

	v. sol	mod. sol	sl. sol		v. sol	mod. sol	sl. sol
WATER 64	☐	☒	☐	CHLOROFORM 70	☐	☐	☐
ACID 65	☐	☐	☐	ETHER 71	☐	☐	☐
BASE 66	☐	☐	☐	PET. ETHER 72	☐	☐	☐
METHANOL 67	☒	☐	☐	BENZENE 73	☐	☐	☐
ETHANOL 68	☒	☐	☐	DMSO-d6	☐	☒	☐
ACETONE 69	☐	☐	☐	_____	☐	☐	☐
	1	2	3		1	2	3

EQUATIONS INDICATING SYNTHETIC ROUTE



Quantitative water solubility ~110 mg/ml

REMARKS

^{1}H NMR : √ 90 MHz-DMSO-d6

IR : √

78 COMMERCIALLY DISCREET	1 ☐	Cont. Nr. DMAD17-88-C-8147 SYNTHESIZED UNDER P. GOV'T SUPPORT	2 ☒	3 GIFT ☐	4 PURCHASED ☐

WRAMC FORM 106
1 APR 1984

SUPERSEDES WRAMC FORM 106, 13 AUG 83, WHICH IS OBSOLETE

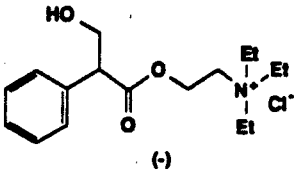
DATA SHEET FOR COMPOUNDS

WR NR.	SUBMITTER	SUBMITTER KEY NR.
	MICHAEL TRACY SRI International	1317

DATE SHIPPED	DAY	MO	YR	DATE RECEIVED	DAY	MO	YR	DATE ACKNOWLEDGED	DAY	MO	YR
	5	5	89								

NAME OF COMPOUND: S-(-)-α-(Hydroxymethyl)benzeneacetic acid 2-(N,N-diethylamino)ethyl ester ethochloride

STRUCTURE



(-)

MOL FORMULA	MOL WT
$C_{17}H_{28}ClNO_3$	329.85

APPEARANCE: White crystalline solid

QUANTITY	CODE NR.
2.5g	SR 4969

NOTEBOOK REF.	PREPARED BY
KJR 8958H-24.3	K. Ryan

TEST SYSTEM

SHELF LOCATION :

B.P.	M.P.	REFRACT. INDEX
	112-115°C	

$[\alpha]_D$= -19.2 2.17% in EtOH

WARNING

ANALYSES

ELEMENT	CALCULATED	FOUND	WR FOUND
C	61.90	61.79	
H	8.56	8.79	
N	4.25	4.39	
Cl	10.75	10.74	

LITERATURE

STABILITY (Check Where Applicable)

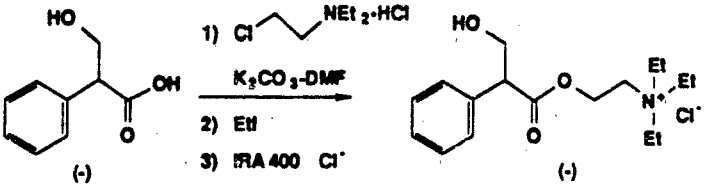
	STABLE	UNSTABLE		STABLE	UNSTABLE
ACID	☐ 56	☐	OTHER		
BASE	☐ 57	☐	_____	☐ 60	☐
HEAT	☐ 58	☐	_____	☐ 61	☐
LIGHT	☐ 59 (1)	☐ (2)	_____	☐ 62 (1)	☐ (2)

HYGROSCOPIC: YES ☒ 62 (1) NO ☐ 63 (2)

SOLUBILITY (Check Where Applicable)

	v. sol	mod. sol	in sol		v. sol	mod. sol	in sol
WATER 64	☒	☐	☐	CHLOROFORM 70	☐	☐	☐
ACID 65	☐	☐	☐	ETHER 71	☐	☐	☐
BASE 66	☐	☐	☐	PET. ETHER 72	☐	☐	☐
METHANOL 67	☒	☐	☐	BENZENE 73	☐	☐	☐
ETHANOL 68	☒	☐	☐	DMSO-d6	☐	☒	☐
ACETONE 69	☐	☐	☐	_____	☐	☐	☐
	(1)	(2)	(3)		(1)	(2)	(3)

EQUATIONS INDICATING SYNTHETIC ROUTE



Quantitative water solubility >1100 mg/ml

REMARKS

^{1}H NMR : √ 90 MHz-DMSO-d6

IR : √

73	Cont. Nr. DMAD17-88-C-8147	GIFT	PURCHASED
COMMERCIALLY DISCREET ☐ (1)	SYNTHESIZED UNDER GOVT SUPPORT ☒ (2)	☐ (3)	☐ (4)