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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 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.

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During this contract period we have synthesized quaternary salts of 2-*N*,*N*-dialkylaminoethyl esters of (±)-α-hydroxymethyl-1-naphthaleneacetic acid, (±)-α-hydroxymethyl-2-furanacetic acid, α-(1-hydroxycyclohexyl)benzeneacetic acid and α-(1-hydroxycyclopentyl)benzeneacetic acid. Six compounds, previously synthesized and tested in the first two years of the contract, were also resynthesized. The compounds have been tested *in vivo* by USAMRICD, in a variety of screens, but the results were disappointing.

FOREWORD

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The synthesis described in this report was performed by Dr. Michael Tracy, Mr. Jac L. Crase, Ms. Mary T. Fong, Dr. Andrew B. Kelson, Mr. Kenneth J. Ryan, and Dr. Bernard Sheldon.

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INTRODUCTION

This report summarizes the technical efforts undertaken on U.S. Army Medical Research and Development Command Contract No. DAMD17-85-C-5147 and covers progress during the period 15 June 1985 through 14 December 1987.

Poisoning by organophosphorous chemical warfare agents and pesticides results in the inhibition of acetylcholinesterase and a concomitant inhibition of nerve function caused by the buildup of acetylcholine. Treatment of this type of poisoning involves administering 2-hydroxy-iminomethyl-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 on 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 humans 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 that is active in the poisoned system yet inactive when the system is functioning normally.

We 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 goal 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, and rendered 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 significantly inhibit cholinesterase because the hydrolytic action of the enzyme is essential for reducing the levels of acetylcholine and returning the system to normal.

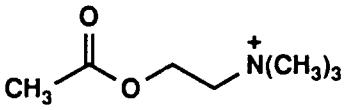
Such a compound has several advantages. First, it could be administered more readily in suspected cases of poisoning without fear of overdose. Second, the side effects would be of a shorter duration because the drug would stay in the system only as long as it was needed. Finally, this type of antidote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

APPROACH

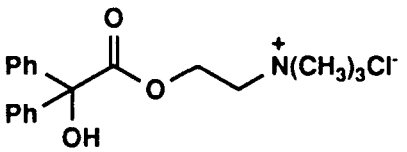
This research is based on the premise that antimuscarinic activity and susceptibility to cholinesterase hydrolysis can be combined in one molecule. The binding sites of cholinesterase [3] and the muscarinic receptor [4-6] have been extensively studied and have several structural requirements in common.

Muscarinic antagonists bind to the muscarinic acetylcholine site but produce no receptor response. As a general rule, substitution of increasingly larger hydrocarbon groups on either terminus of acetylcholine (**1**) leads first to muscarinically inactive compounds and then to muscarinic antagonists.[4-6]



1

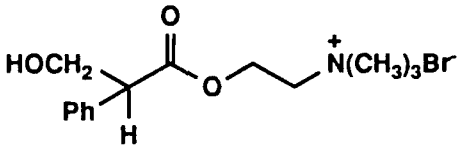
A typical atropinelike anticholinergic agent contains a cationic head and a heavy blocking moiety (cyclic groups), which are connected by a chain of atoms of definite lengths that generally contains an ester function. The cationic head is an essential group in a large number of anticholinergic compounds and the mechanism of action of such substances has been linked very closely with it. The cationic head with its positive charge is assumed to be attracted by an anionic site on the muscarinic receptor, which seemingly starts the process of adsorption. After 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.[7] In contrast, replacing the *N*-methyl groups of 2-*N*,*N*-dimethylaminoethylbenzilate 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.[5-10] 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 need not necessarily be phenyl, because compounds with cyclohexyl rings also show excellent anticholinergic activity, and substances containing both rings are even better.[11] Adding a second phenyl ring to 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. The cyclic groups have been suggested to form an additional contact with the muscarinic receptor 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.

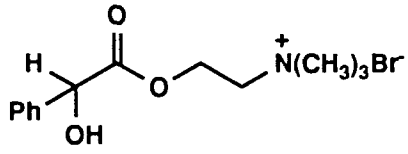
The presence of the cationic head and of cyclic blocking groups is not enough for optimal anticholinergic activity, which also depends on the mutual distribution of these groups. Several studies [8,10,12] have shown that the linking chain containing a potentially hydrolyzable ester should be of the form 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 that of acetylcholinesterase inactivation and hydrolyzes a broader range of substrates.[3,13]

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. Adding an α- or β-methyl group to choline or increasing the distance from the nitrogen to the ester linkage causes 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**)[14] and the S-(+)- and R-(-)- forms of mandeloylcholine (**4**).[15]



4

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; the opposite was 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 reasoned that the most effective antidotes would probably have a higher level of antimuscarinic activity and perhaps a slower rate of hydrolysis than mandeloylcholine. 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), after the synthesis of a variety of compounds (15 of which have been evaluated *in vivo* by the USAMRICD), have provided insight into how variations in the structure of **3** and **4** affect muscarinic antagonism and cholinesterase hydrolysis.

The data in Table 1 show how the binding affinity for the muscarinic receptor depends on the structure of the amino group for 2-*N*,*N*-dialkylaminoethyl esters of (+)- and (-)-mandelic, tropic, and other acids. All the compounds appear to competitively inhibit [^{3}H] quinuclidinyl benzylate (^{3}H QNB) binding to rat brain membranes. The extra methylene group in tropic acid significantly increases the affinity and stereoselectivity of all the esters tested, with the quaternized derivatives of the 2-*N*,*N*-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 the *in vitro* assays.

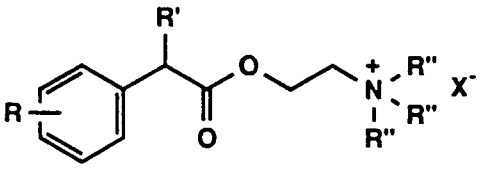
The compounds with modifications to the tropic acid moiety generally show reductions in affinity for the muscarinic receptor relative to the tropic acid esters but were tested only as racemic mixtures. The methoiodide of the 2-*N*,*N*-dimethylaminoethyl ester of (±)-α-hydroxymethyl-1-naphthaleneacetic acid was an exception and bound to the muscarinic receptor as effectively as the corresponding tropic acid derivative.

The compounds with the extra hydroxyl group are quite interesting. The results with mandelic and tropic acid derivatives suggest that a hydroxymethyl group makes a more effective hydrogen bond to the enzyme than does a hydroxyl group. When both groups are present in the same molecule, the affinity reduction could be the result of steric crowding or the higher polarity of the molecule. Because the steric preference for the isomers is reversed compared with that of tropic acid, the steric effect may be the dominant one.

Table 2, which compares the in *vitro* and *in vivo* data for the quaternary salts of the 2-*N*,*N*-dialkylaminoethyl esters of mandelic acid, recently tested by USAMRICD, shows that administration of only four of these compounds resulted in any mice being saved, and none of the

Table 1

In vitro Muscarinic Receptor Binding Affinities (K_i) of
2-*N*,*N*-Dialkylaminoethyl Esters of Mandelic, Tropic, and other Acids



		K_i(nM)			
		Mandelic Acid (R'=OH)		Tropic Acid (R'=CH_2OH)	
R	Amine	(+)-isomer	(-)-isomer	(+)-isomer	(-)-isomer
H	NMe_2.HCl	42,000	28,000	280	8.5
H	NMe_2EtI	1,020	400	15	0.7
H	NMe_3I	1,000	2,000	52.5	5.5
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		1,200[b]	
1-Naphthyl	NEt_2.HCl	NA		200[b]	
1-Naphthyl	NMe_2.HCl	NA		80[a]	
1-Naphthyl	NMe_3I	NA		40[a]	
1-Naphthyl	NEt_2.HCl	NA		213[a]	
3-Pyridinyl	NMe_2.HCl	NA		17,000[b]	
H	NMe_3I	NA	NA	110[c]	750[c]
Acetylcholine				3,500	
Atropine				0.32	

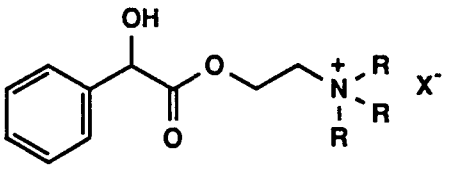
[a] (±)Mixture

[b] R' = H

[c] R' = $(OH)CH_2OH$

Table 2

Comparison of *In vitro* data with *In vivo* Intramuscular Anticholinergic Survival Efficacy data[a] for 2-*N*,*N*-Dialkylaminoethyl Mandelic Acid Esters in the Mouse

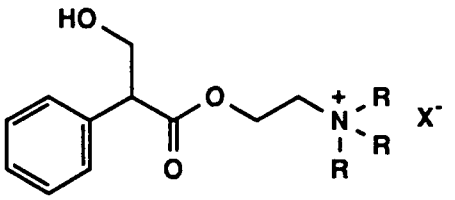


WR No.	Bottle No.	Amine	Isomer	Musc. Bind. K_i(nM)	Cholin. Hydrol. t($^1/_2$)min.	IM LD_{50} (mmol/kg)	1/16	1/8	1/4
251881	BK71552	NMe_2.HCl	(+)	42,000	NA	7.66	1	0	0
251866	BK71221	NMe_2.HCl	(-)	28,000	NA	5.89	0	0	2
251865	BK71230	NMe_3I	(+)	1,000	4	4.24	0	0	0
251882	BK71561	NMe_3I	(-)	2,000	4	0.31	0	0	0
251884	BK71543	NEt_2MeI	(+)	800	27	0.68	0	0	1
251883	BK71472	NEt_2MeI	(-)	290	5	0.15	0	0	0
251886	BK71534	NEt_3I	(+)	NA	NA	1.08	0	1	1
251885	BK71481	NEt_3I	(-)	240	>120	0.34	0	0	0

[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.

Table 3

Comparison of *In vitro* data with *In vivo* Intramuscular Anticholinergic Survival Efficacy data[a] for 2-*N,N*-Dialkylaminoethyl Tropic Acid Esters in the Mouse



WR. No.	Bottle No.	Amine	Isomer	Musc. Bind. K_i(nM)	Cholin. Hydrol. t ($^1/_2$)min.	IM LD_{50} (mmol/kg)	1/16	1/8	1/4
251864	BK71249	NMe_2.HCl	(+)	280.0	>120	7.18	0	1	1
251862	BK71258	NMe_3I	(+)	52.5	5	1.94	0	0	0
251861	BK71285	NMe_3I	(-)	5.5	15	1.48	0	1	0
251887	BK71507	NEt_2MeI	(+)	37.0	>120	1.12	0	0	4
251888	BK71525	NEt_2MeI	(-)	1.5	>120	0.60	2	2	2
251889	BK71490	NEt_3I	(+)	20.0	>120	3.83	0	0	0
251890	BK71516	NEt_3I	(-)	0.7	>120	0.67	1	1	3

[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.

compounds showed any degree of significant activity.

Table 3 compares the in *vitro* and *in vivo* data for the quaternary salts of the 2-*N*,*N*-dialkylaminoethyl esters of tropic acid, also recently tested by USAMRICD. Five of the seven compounds saved, at least one mouse and two were of further interest, saving significantly more mice than did atropine.

At this point, a firm correlation between the biochemical properties of the compounds and their *in vivo* activity is difficult to see, 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, as shown by their LD_{50} values, are less likely to be effective.

RESULTS AND DISCUSSION

CHEMISTRY

Resynthesis

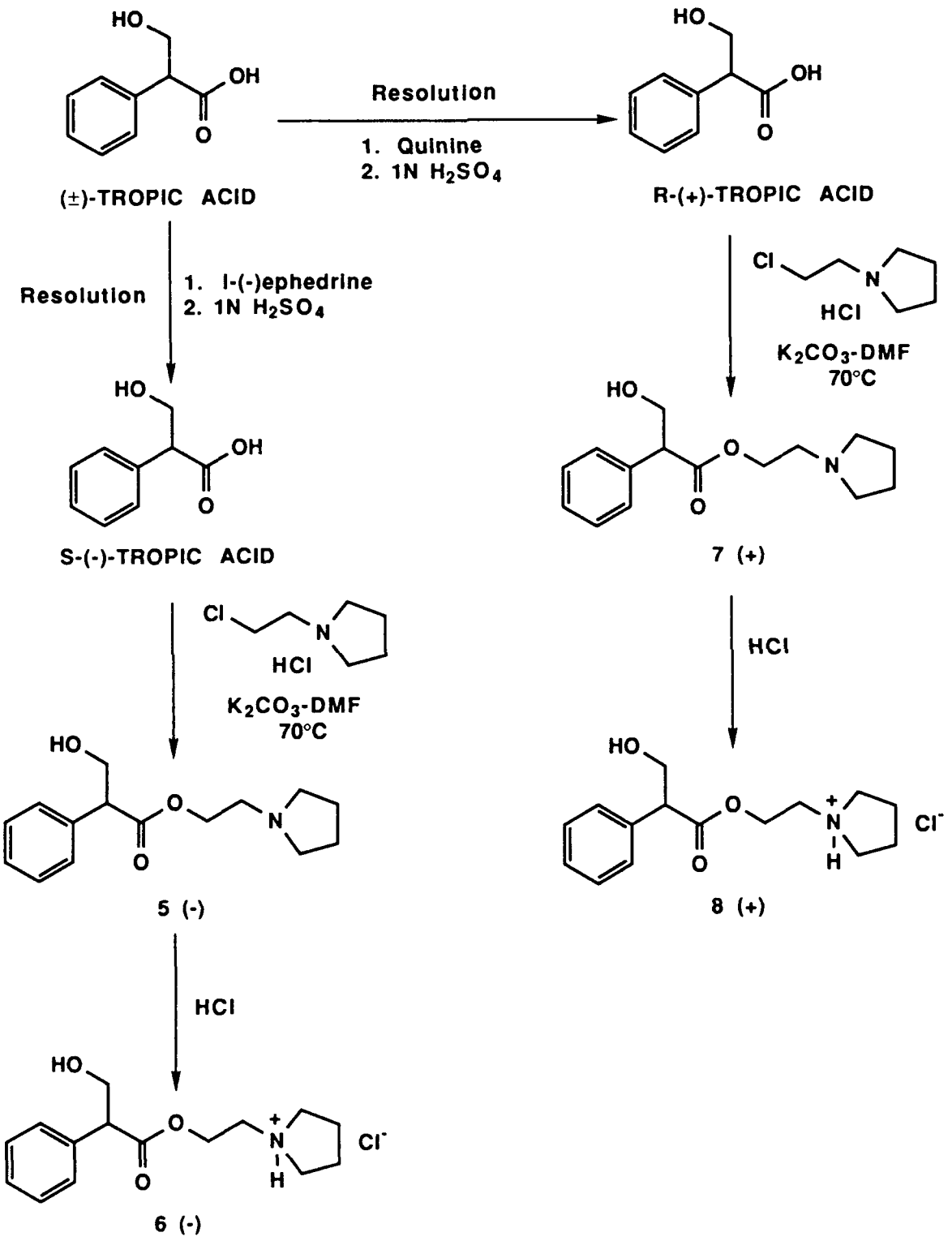
The resyntheses of six compounds (**6**, **8**, **10**, **12**, **15**, and **17**), requested by USAMRDC to conduct further *in vivo* testing by USAMRICD in the anticholinergic efficacy screen were performed as outlined in Schemes 1-4. All compounds were synthesized in 2 to 3 g quantities, except for **12**, which was resynthesized on a larger scale (7-8 g).

Resolution of (±)-tropic acid was completed on a large scale (200 g) 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 that, on recrystallization and treatment with 1N H_2SO_4, yielded R-(+)-tropic acid with an optical purity of 98% in 28% overall yield. 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 also gave S-(-)-tropic acid in good yield (49%) and in high optical purity (~100%).

Reaction of S-(-)-tropic acid with 1-(2-chloroethyl)pyrrolidine hydrochloride, using conditions we had optimized in the previous synthesis (K_2CO_3-DMF, 70°C), gave the 2-(pyrrolidin-1-yl)ethyl ester (**5**) as a pale yellow oil in 46% yield (Scheme 1). Treatment with ethereal HCl and recrystallization from ethanol-ether gave the hydrochloride (**6**) as white needles. Similarly, reaction of R-(+)-tropic acid with 1-(2-chloroethyl)pyrrolidine hydrochloride and subsequent treatment with ethereal HCl gave the (+) hydrochloride (**8**) in 35% overall yield.

The routes for the resynthesis of S-(-)-α-(hydroxymethyl)benzeneacetic acid, 2-(morpholin-4-yl)ethyl ester hydrochloride (**10**), and R-(+)-α-(hydroxymethyl)benzeneacetic acid, 2-*N*,*N*-diethylaminoethyl ester methoiodide (**12**) (the most active derivative tested by USAMRICD *in vivo* in the anticholinergic efficacy screen), are outlined in Scheme 2.

The synthesis of **10** followed closely that described for **5**, and the product was isolated in 40% overall yield. The hydrochloride was extremely hygroscopic, quickly became sticky on


HO
OH
O
(±)-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
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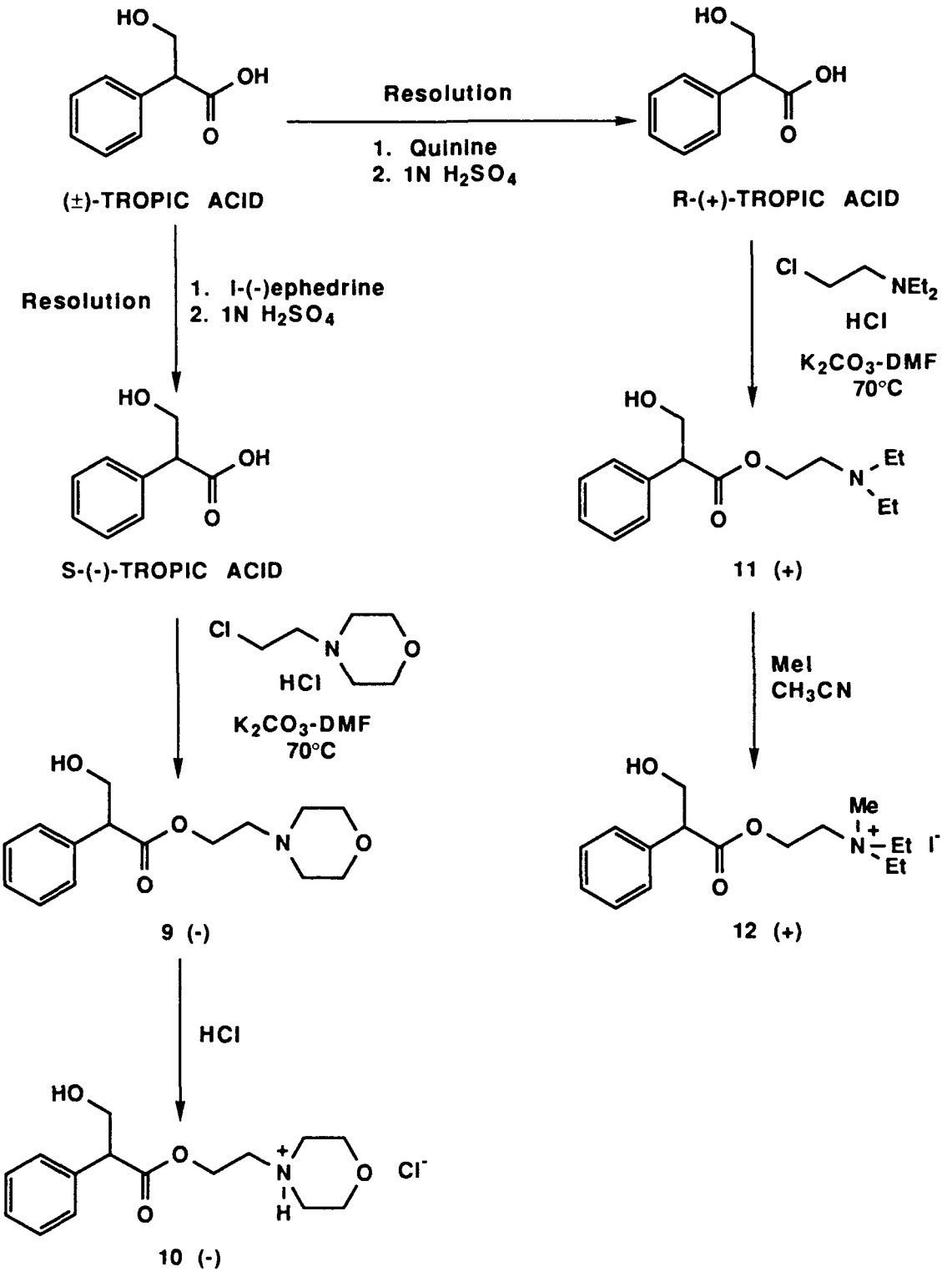
7 (+)
HCl
8 (+)
Cl⁻
5 (-)
6 (-)

Scheme 1


HO
OH
O
(±)-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
Cl
NEt_2
HCl
K_2CO_3-DMF
70°C
11 (+)
Cl
N
O
HCl
K_2CO_3-DMF
70°C
9 (-)
MeI
CH_3CN
Me
Et
Et
I^-
12 (+)
HCl
Cl^-
10 (-)

Scheme 2

exposure to the atmosphere, and absorbed 5 moles of water, forming the stable crystalline pentahydrate. Reaction of R-(+)-tropic acid with 2-*N,N*-diethylaminoethylchloride hydrochloride (K_2CO_3-DMF, 70°C) gave the 2-*N,N*-diethylaminoethyl ester (**11**) in 93% yield. Reaction with MeI gave the product, which was recrystallized from *iso*-propanol-methyl ethyl ketone to give the methoiodide (**12**) as white crystals (83%).

The synthesis of **15** (Scheme 3) followed closely that of **12**. Reaction of (±)-4-methoxy-tropic acid (**13**)[16] with 2-*N,N*-dimethylaminoethylchloride hydrochloride (K_2CO_3-DMF, 70°C) gave the 2-*N,N*-dimethylaminoethyl ester (**14**) as a pale oil that crystallized on standing in the freezer in 32% yield. Treatment of **14** with ethereal HCl gave the product as a white solid (94%).

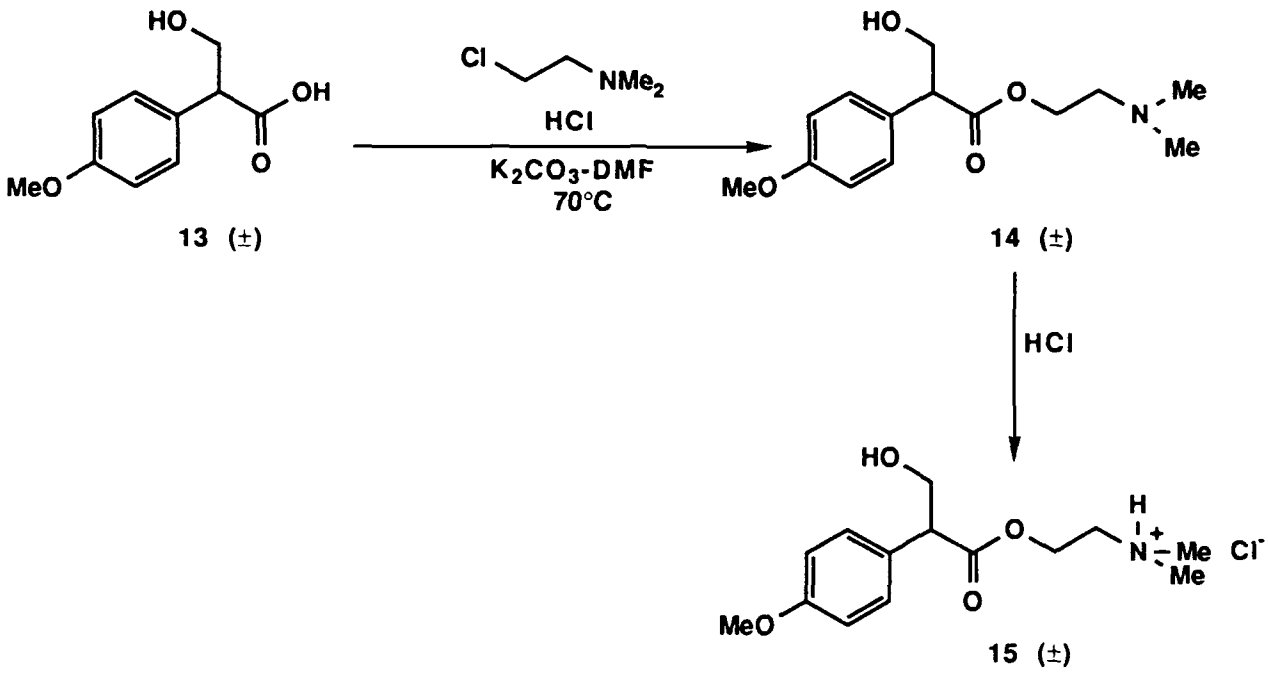
The resynthesis of R-(-)-α-(hydroxy)benzeneacetic acid, 2-*N,N*-dimethylaminoethyl ester ethoiodide (**17**), shown in Scheme 4, was tried on several occasions, but the product could never be obtained in crystalline form. A check of the original data sheet showed that the compound had originally been submitted to USAMRDC in a gumlike form. The 2-*N,N*-dimethylaminoethyl ester (**16**) was prepared in the usual manner (K_2CO_3-DMF, 70°C) as a pale yellow oil and was chromatographed very carefully until pure by HPLC and by elemental analysis. Attempted conversion of **16** into the ethoiodide (**17**) gave a pale yellow-orange oil that would not crystallize. All manipulation of the oil led to decomposition and to a darkening of the color. Several different approaches were tried but without success. Barlow *et al.*[17] had been unable to obtain pure quaternary salts of R-(-)-α-(hydroxy)benzeneacetic acid, 2-*N,N*-dimethylaminoethyl esters because of problems with their stability.

The five completed crystalline solids were sent to USAMRDC to be tested *in vivo*.

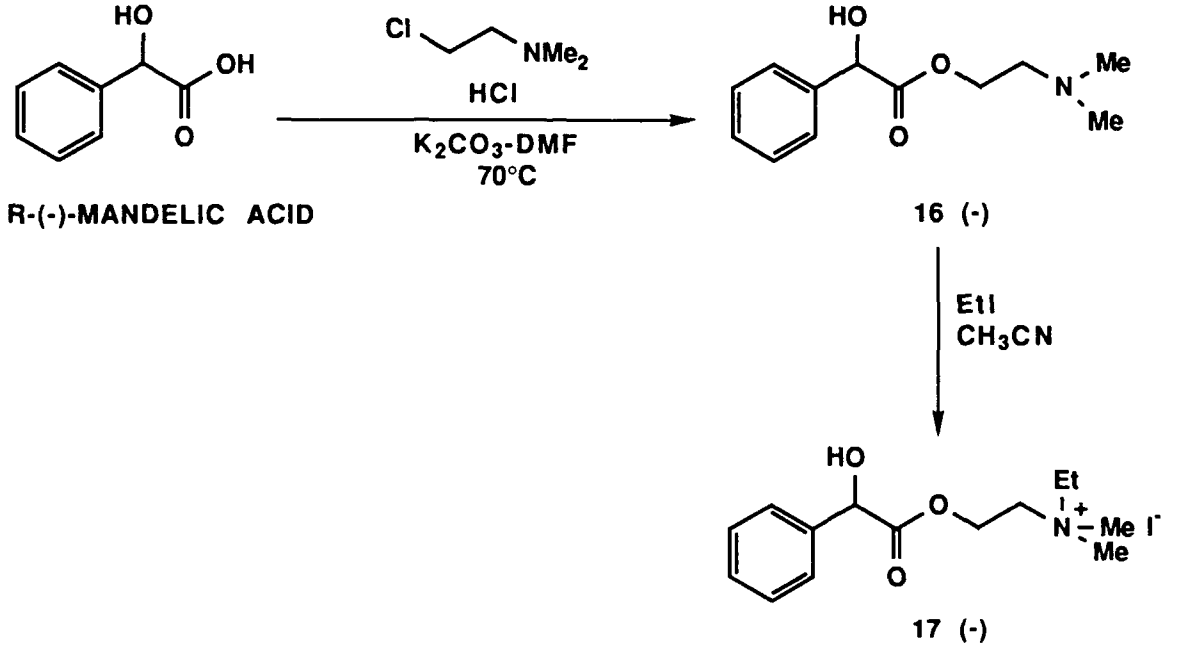
Novel Synthesis

The data from the *in vitro* muscarinic binding studies shown in Table 1 clearly demonstrate the stereoselective specificity of the muscarinic receptor for the S-(-)-isomers of the quaternary salts of the 2-*N,N*-dialkylaminoethyl esters of tropic acid. The presence of the extra methylene group in tropic acid, compared with 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.

Because a considerable amount of the research we conducted was focused on the



Scheme 3



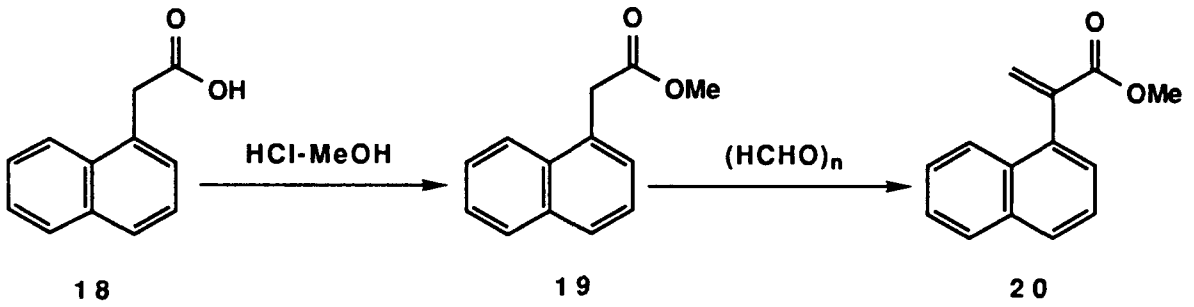
Scheme 4

onium terminal end of the esters we were attempting to potentiate, we examined how changes in the aromatic portion of the molecule would affect both the muscarinic receptor binding affinity and the rate of cholinesterase hydrolysis. The initial targets were modified by the introduction of a naphthyl ring rather than a benzene ring into the tropic acid moiety, because the initial *in vitro* results for the muscarinic receptor binding of (±)-α-(hydroxymethyl)-1-naphthaleneacetic acid, 2-*N*,*N*-dimethylaminoethyl ester methoiodide (Table 1: K_i (nM) = 40) appeared promising.

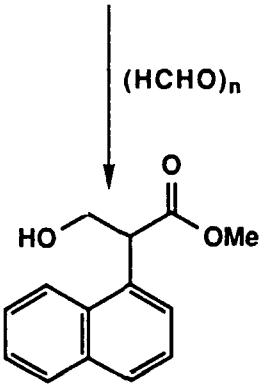
Synthesis of (±)-α-(hydroxymethyl)-1-naphthaleneacetic acid (**22**), using methodology previously developed at SRI International for the synthesis of (±)-tropic acid, is outlined in Scheme 5. 1-Naphthaleneacetic acid (**18**) was converted into the methyl ester (**19**) by treatment with gaseous HCl in methanol (100%). Reaction with paraformaldehyde in DMSO using 5% NaOMe as base introduced the hydroxymethyl moiety, and cleavage of the ester with NaOH gave (±)-α-(hydroxymethyl)-1-naphthaleneacetic acid (**22**) in good overall yield. The quantity of NaOMe used for the introduction of the hydroxymethyl moiety was critical; use of too much base led to dehydration of the product, giving large quantities of the styryl derivative (**20**), while use of too little base led to incomplete product formation, yielding mixtures of **21** and **19**. No resolution of the racemic mixture was performed and the pure (±) acid was directly converted into esters.

Conversion of (±)-α-(hydroxymethyl)-1-naphthaleneacetic acid (**22**) to the 2-*N*,*N*-dimethylaminoethyl ester (**23**) was carried out in 57% yield using the normal reaction conditions outlined in Scheme 6. Treatment of the ester with ethereal HCl gave the hydrochloride (**24**) as a pale yellow oil that could not be crystallized. Quaternization with either methyl iodide or ethyl iodide in methyl ethyl ketone gave yellow gums (**26** and **27**), which also could not be crystallized. Careful resynthesis and chromatographic purification of the 2-*N*,*N*-dimethylaminoethyl ester (**23**) and further attempts to obtain quaternary salts failed to yield any crystalline material. Passage of the methoiodide (**26**) down an IRA 400 (Cl^-) gave the methochloride, but again all attempts to crystallize the product failed. Treatment of the ester (**23**) with one equivalent of oxalic acid gave the oxalate (**25**) as a nonhygroscopic, white solid gum, which could be recrystallized to give white needles. Attempted quaternization with other organic acids to obtain salts more appropriate for testing drugs *in vivo* failed to yield any crystalline products.

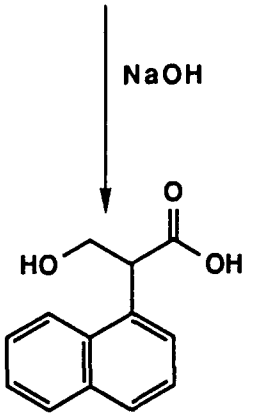
Conversion of (±)-α-(hydroxymethyl)-1-naphthaleneacetic acid (**22**) into the 2-*N*,*N*-diethylaminoethyl ester (**28**; Scheme 7) was carried out in 98% yield using the same reaction



18 19 20

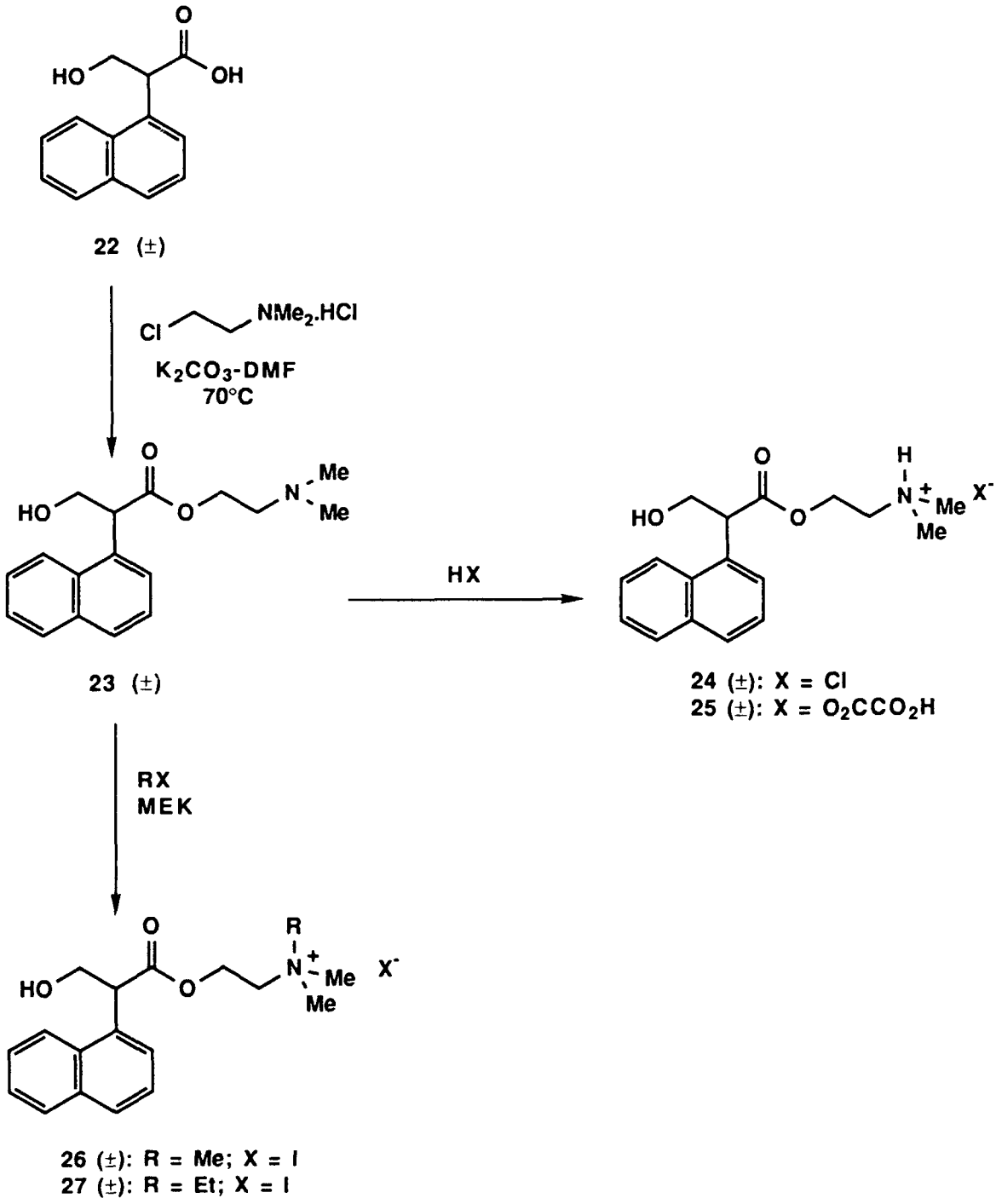


21 (±)

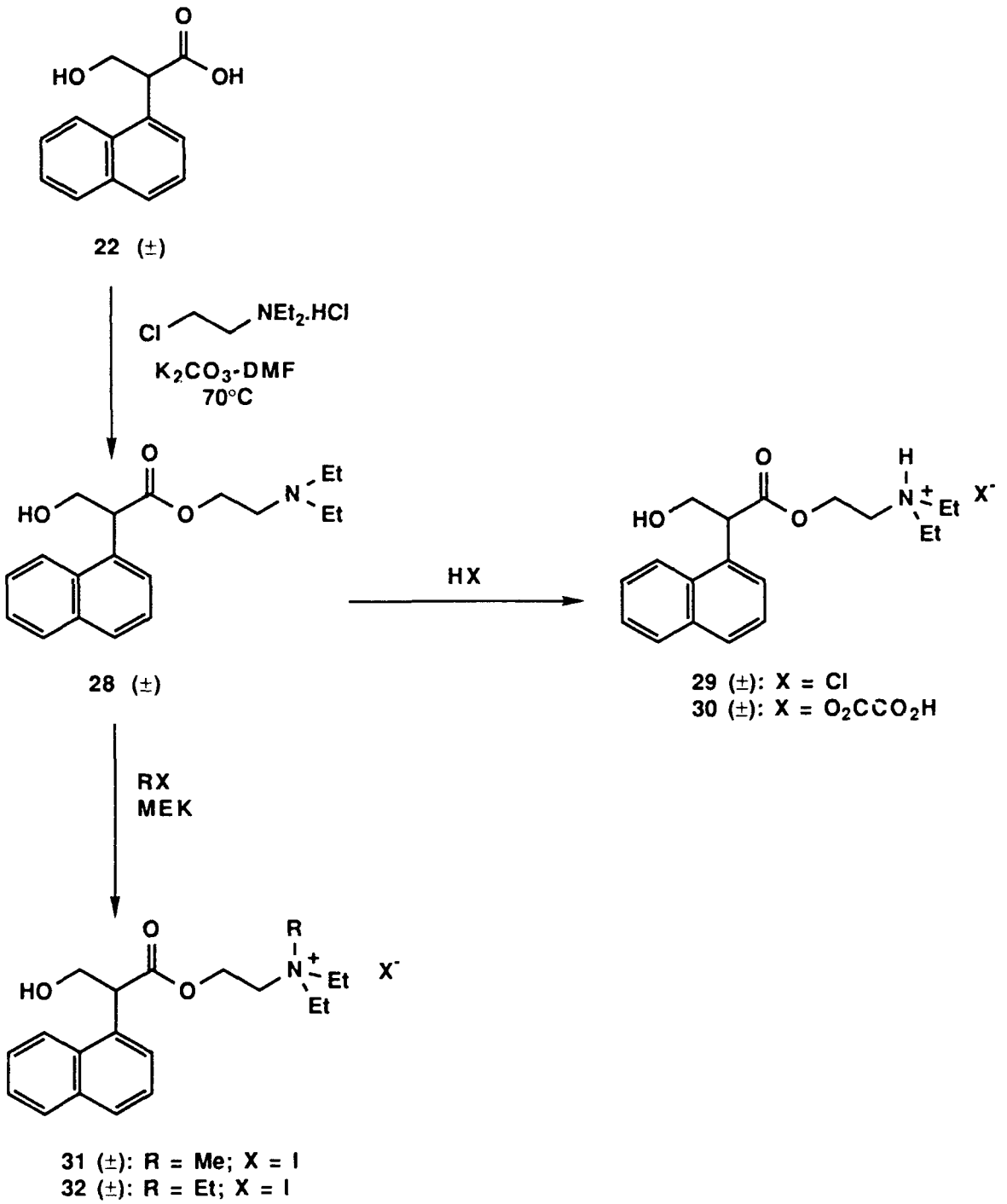


22 (±)

Scheme 5

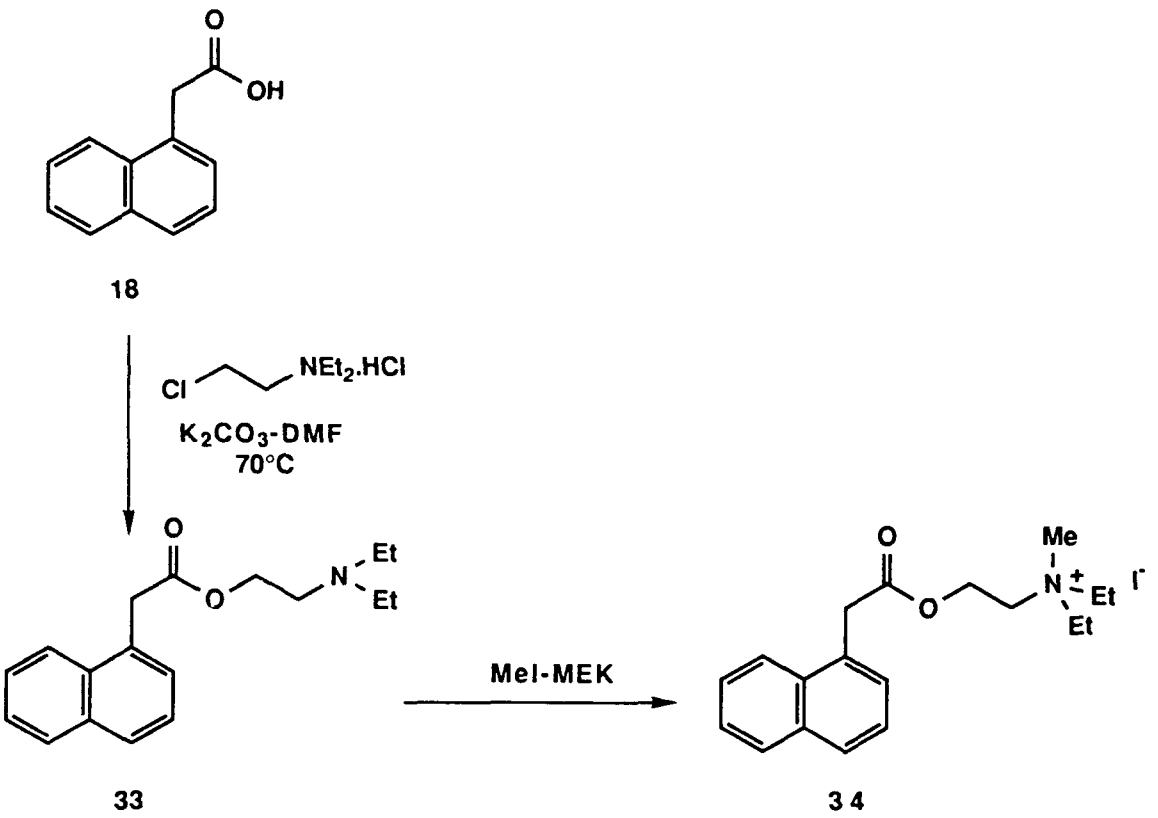

HO
O
OH
22 (±)
Cl
NMe2.HCl
K2CO3-DMF
70°C
HO
O
O
N
Me
Me
23 (±)
HX
HO
O
O
H
N
Me
Me
X-
24 (±): X = Cl
25 (±): X = O2CCO2H
RX
MEK
HO
O
O
R
N
Me
Me
X-
26 (±): R = Me; X = I
27 (±): R = Et; X = I

Scheme 6


HO
O
OH
22 (±)
Cl
NEt2.HCl
K2CO3-DMF
70°C
HO
O
O
N
Et
Et
28 (±)
HX
HO
O
O
H
N
Et
Et
X-
29 (±): X = Cl
30 (±): X = O2CCO2H
RX
MEK
HO
O
O
R
N
Et
Et
X-
31 (±): R = Me; X = I
32 (±): R = Et; X = I

Scheme 7

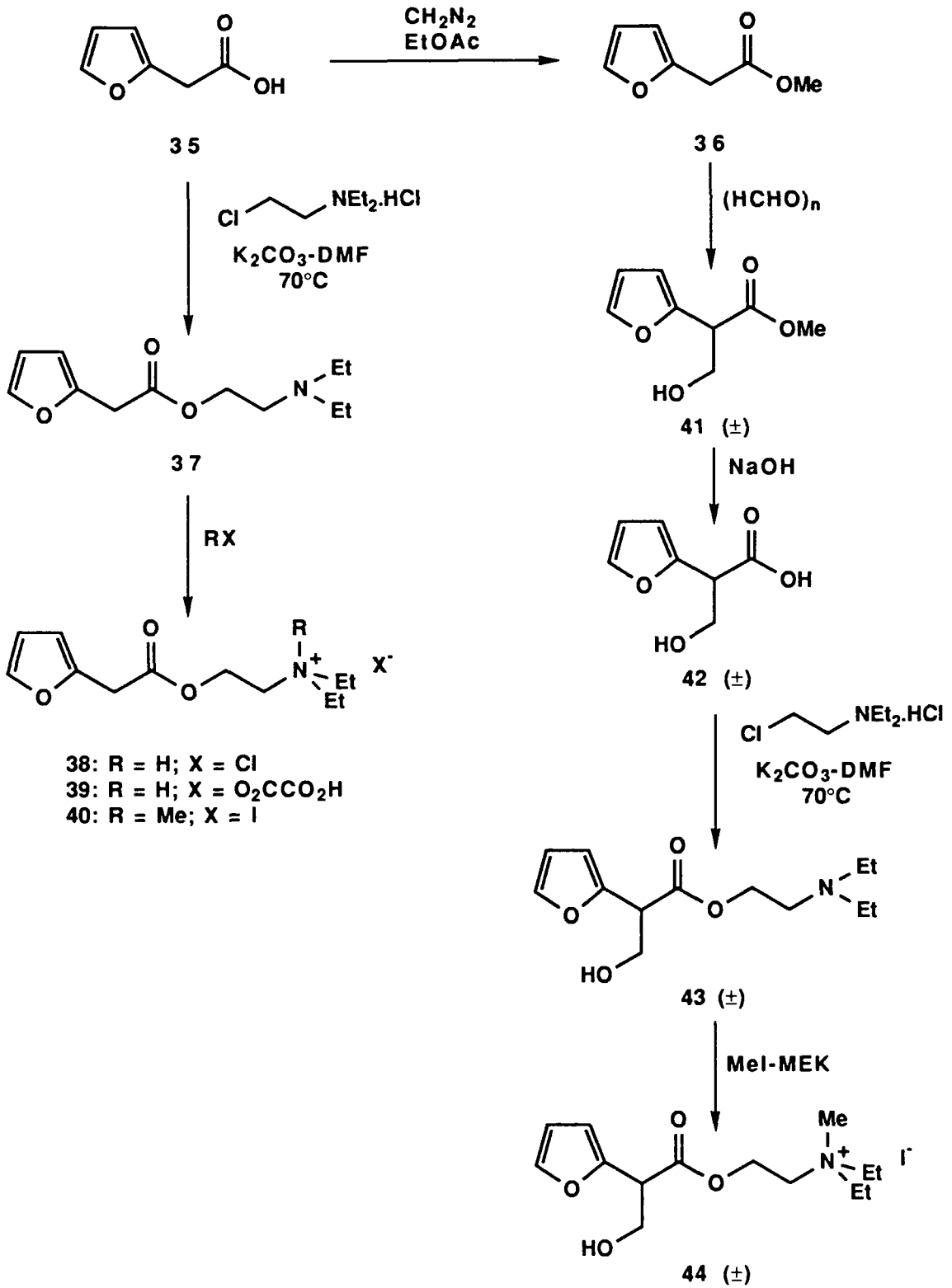
conditions used to obtain (**23**). Again, all attempts to obtain crystalline quaternary salts (**29**, **31** and **32**), except for the oxalate (**30**), were unsuccessful. Treatment of the ester (**28**) with one equivalent of oxalic acid gave the oxalate (**29**), which was recrystallized as white needles.



Scheme 8

1-Naphthaleneacetic acid (**18**) was readily converted to the 2-*N*,*N*-diethylaminoethyl ester (**33**), which, after treatment with methyl iodide in methyl ethyl ketone, gave the methoiodide (**34**) as a pale yellow crystalline solid (Scheme 8). This result clearly demonstrates that the presence of the hydroxymethyl moiety in the case of the (±)-α-(hydroxymethyl)-1-naphthaleneacetic acid derivatives prevents ready crystallization of the quaternary products.

Methodology similar to that used for synthesizing (±)-α-(hydroxymethyl)-1-naphthaleneacetic acid (**22**) has been used to synthesize (±)-α-(hydroxymethyl)-2-furanacetic acid (**42**; Scheme 9).[18] 2-Furanacetic acid (**35**) was converted into the methyl ester (**36**) by treatment with diazomethane in ethyl acetate (90%). Reaction with paraformaldehyde in DMSO using 5% NaOMe as base introduced the hydroxymethyl moiety, and cleavage of the ester with NaOH gave


CH2N2
EtOAc
OH
OMe
35
36
NEt2.HCl
Cl
K2CO3-DMF
70°C
(HCHO)n
Et
N
Et
37
41 (±)
NaOH
RX
R
X-
38: R = H; X = Cl
39: R = H; X = O2CCO2H
40: R = Me; X = I
42 (±)
43 (±)
Mel-MEK
Me
I-
44 (±)

Scheme 9

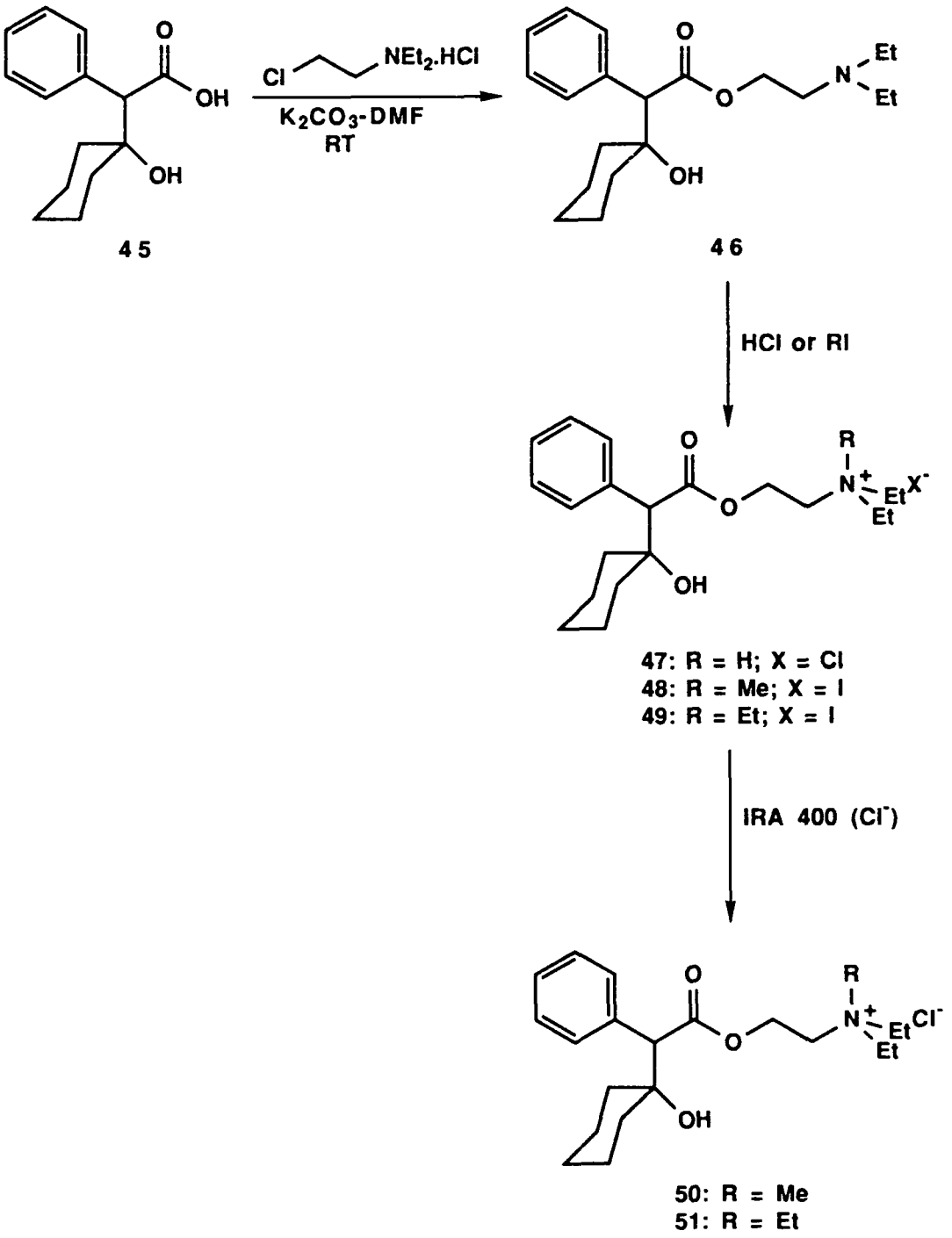
(±)-α-(hydroxymethyl)-2-furanacetic acid (**42**) in good overall yield. No resolution of the racemic mixture was carried out. Conversion of (±)-α-(hydroxymethyl)-2-furanacetic acid (**42**) to the 2-*N,N*-diethylaminoethyl ester (**43**) was carried out in 68% yield using the normal reaction conditions outlined in Scheme 9. Quaternization of **43** with methyl iodide in methyl ethyl ketone gave the methoiodide (**44**) as a white solid after careful washing with ether. Conversion of 2-furanacetic acid (**35**) into the 2-*N,N*-diethylaminoethyl ester (**37**) was carried out in the usual manner in 71% yield, and conversion into a series of crystalline quaternary salts (**38-40**) proceeded as expected.

Analysis by Abramson *et al.*[5] of several series of quaternary salts of 2-*N,N*-diethyl-aminoethyl esters of different aromatic acid derivatives showed that compounds containing one phenyl group and one cyclohexyl group in that part of the molecule bound more strongly than tropic acid derivatives to the postganglionic ("muscarine-sensitive") acetylcholine receptors in the guinea pig ileum. To determine whether this enhancement in binding might have a significant effect on enhancing the anticholinergic efficacy of a compound we synthesized three series of derivatives, two incorporating a phenyl and cyclohexyl moiety (Scheme 10 and 11) and one incorporating a phenyl and cyclopentyl moiety (Scheme 12).

Conversion of α-(1-hydroxycyclohexyl)benzeneacetic acid (**45**)[19] into the 2-*N,N*-diethyl-aminoethyl ester (**46**; Scheme 10) was carried out under optimized conditions (K_2CO_3-DMF, RT) in very high yield (100%). Treatment with ethereal HCl and recrystallization of the white precipitate from methyl ethyl ketone gave the hydrochloride (**47**) as white needles. Quaternization of the ester with methyl iodide gave the methoiodide (**48**) as a pale yellow solid that readily crystallized on standing. Passage down an IRA 400 (Cl^-) ion exchange resin gave the methochloride (**50**), which was recrystallized from *iso*-propanol-methyl ethyl ketone as a white, analytically pure, nonhygroscopic solid in high yield. Formation of the ethoiodide (**49**) employing a similar route with ethyl iodide gave the product far more slowly (7 days). Conversion to the ethochloride went smoothly in high yield (85%).

Quaternary analogues (**53-57**, Scheme 11: and **60-64**, Scheme 12) of the 2-*N,N*-dimethylaminoethyl ester of α-(1-hydroxycyclohexyl)benzene acetic acid (**52**) and the 2-*N,N*-diethylaminoethyl ester of α-(1-hydroxycyclopentyl)benzene acetic acid (**59**) were prepared in a similar fashion in high yield.

All crystalline solids were submitted to USAMRDC for biological testing *in vivo*.



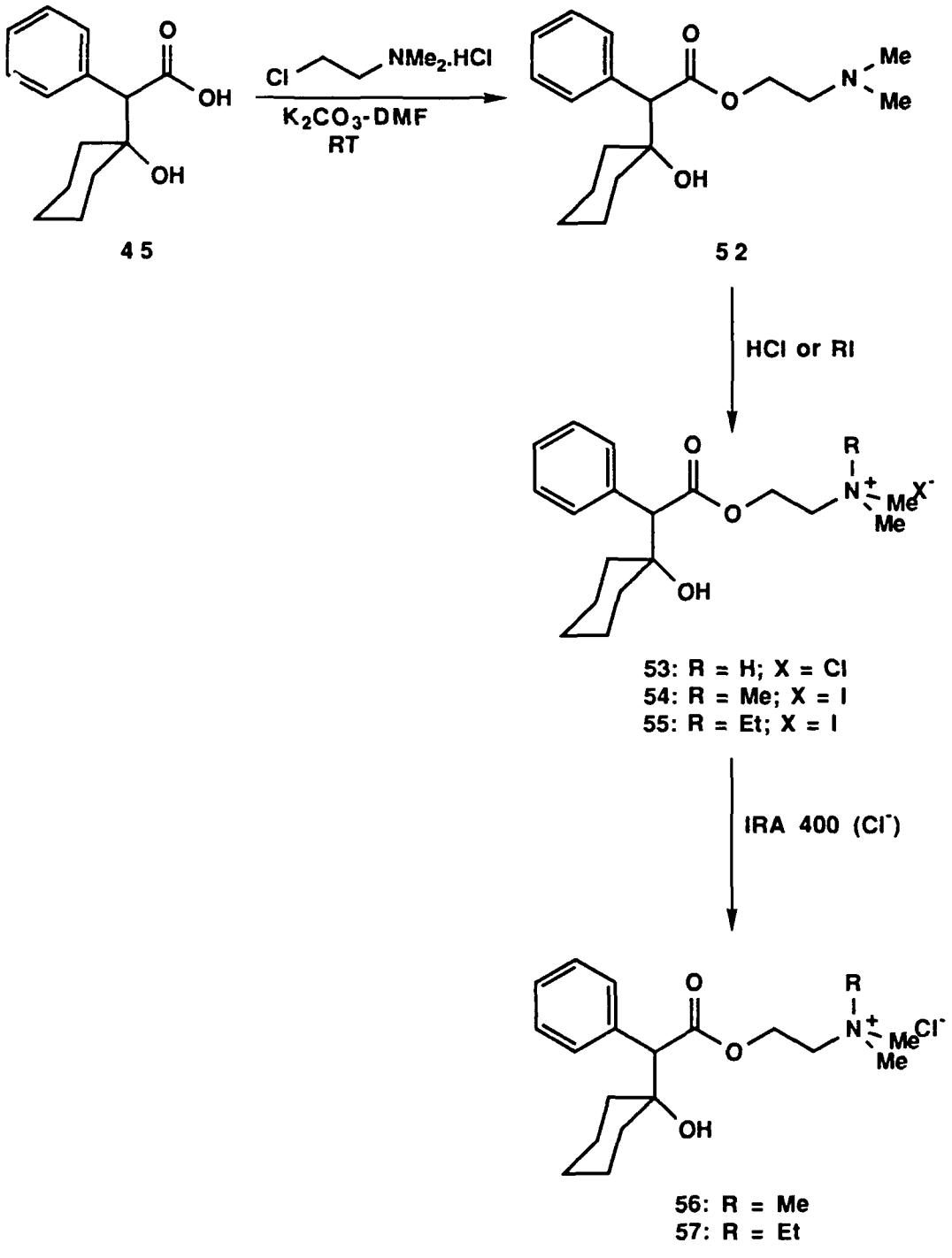
45

46

47: R = H; X = Cl
48: R = Me; X = I
49: R = Et; X = I

50: R = Me
51: R = Et

Scheme 10



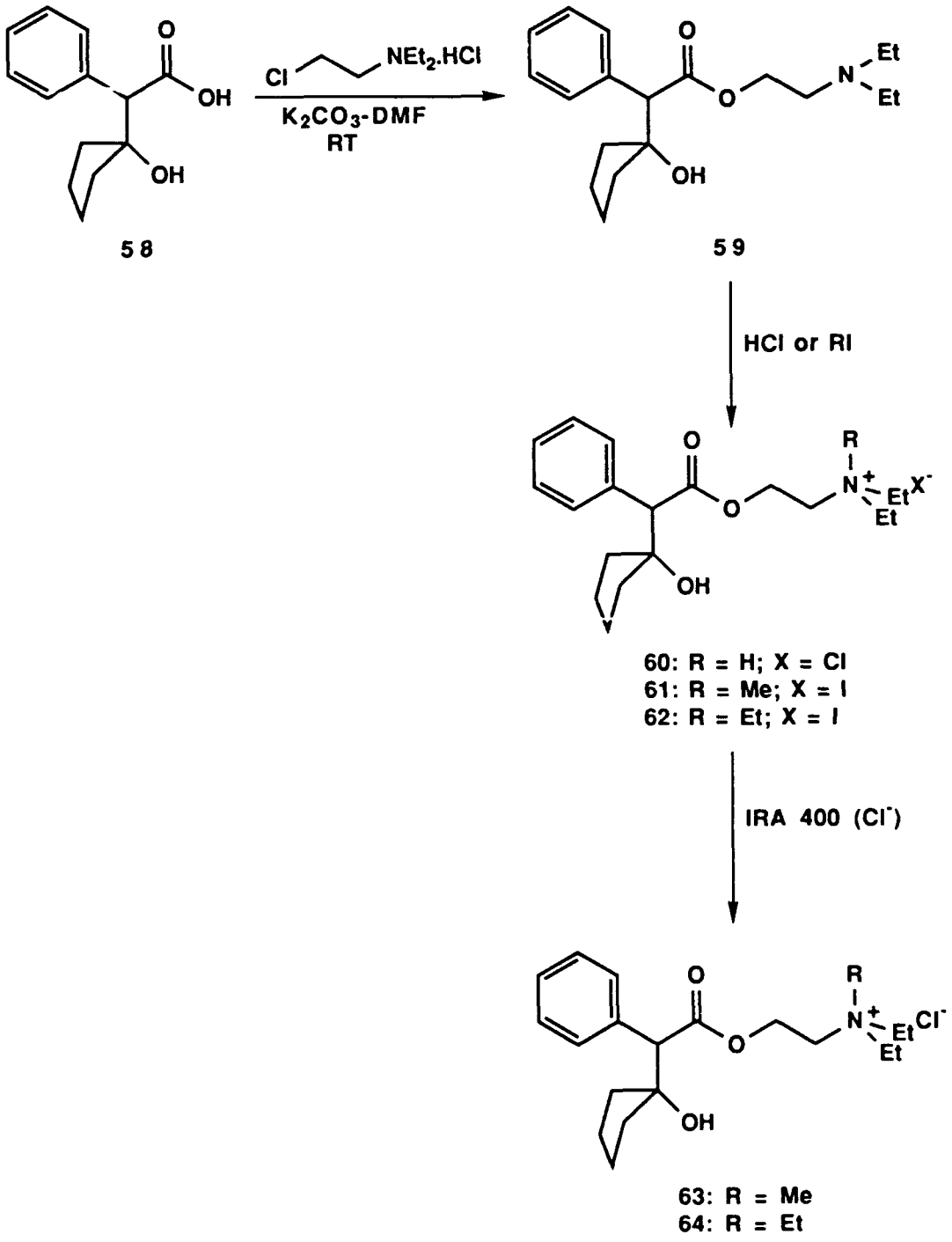
45

52

53: R = H; X = Cl
54: R = Me; X = I
55: R = Et; X = I

56: R = Me
57: R = Et

Scheme 11



58

59

60: R = H; X = Cl
61: R = Me; X = I
62: R = Et; X = I

63: R = Me
64: R = Et

Scheme 12

BIOLOGY

In vitro Pharmacology

In vitro assays to determine muscarinic receptor binding affinity and rates of cholinesterase hydrolysis were deleted from the contract during this period.

In vivo Testing by USAMRICD

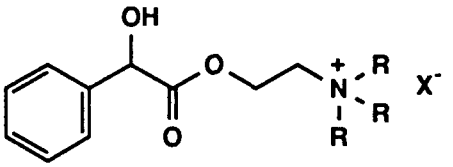
In vivo test results for compounds synthesized and submitted to USAMRICD during this contract period are shown in Tables 4 through 9.

Tables 4 and 5 summarize all the data, both *in vitro* and *in vivo*, for the quaternary salts of the 2-*N*,*N*-dialkylaminoethyl esters of mandelic and tropic acid. The results are disappointing and demonstrated few of the trends we had hoped to establish. Retesting the methoiodide of the 2-*N*,*N*-diethylaminoethyl ester of (+)-tropic acid, the most potent derivative previously examined, at different dose levels gave inconclusive results. None of the new derivatives tested in the anticholinergic efficacy screen (Table 6) showed promise.

Unfortunately many of the compounds submitted during the latter part of the contract period were tested in the pretreatment survival efficacy screens (Tables 7 through 9), not in the mode for which they were designed as substitutes for atropine in the appropriate anticholinergic efficacy screen. This difference in mode of administration makes analysis and comparison of these data with those previously obtained very difficult.

Table 4

Comparison of *In vitro* data with *In vivo* Intramuscular Anticholinergic Survival Efficacy data[a] for 2-*N*,*N*-Dialkylaminoethyl Mandelic Acid Esters in the Mouse

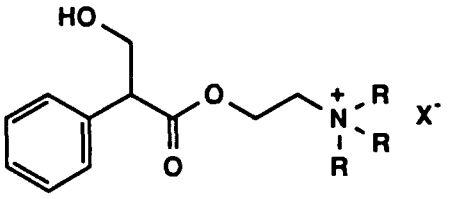


WR No.	Bottle No.	Amine	Isomer	Musc. Bind. K_i(nM)	Cholin. Hydrol. t($^1/_2$)min.	IM LD_{50} (mmol/kg)	1/16	1/8	1/4
251881	BK71552	NMe_2.HCl	(+)	42,000	NA	7.66	1	0	0
251866	BK71221	NMe_2.HCl	(-)	28,000	NA	5.89	0	0	2
254271	BL04261	NMe_2EtI	(-)	400	NA	NA	NA	NA	NA
251865	BK71230	NMe_3I	(+)	1,000	4	4.24	0	0	0
251882	BK71561	NMe_3I	(-)	2,000	4	0.31	0	0	0
254270	BL04305	NEt_2.HCl	(-)	18,000	NA	1.58	1	0	0
251884	BK71543	NEt_2MeI	(+)	800	27	0.68	0	0	1
251883	BK71472	NEt_2MeI	(-)	290	5	0.15	0	0	0
251886	BK71534	NEt_3I	(+)	NA	NA	1.08	0	1	1
251885	BK71481	NEt_3I	(-)	240	>120	0.34	0	0	0

[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.

Table 5

Comparison of *In vitro* data with *In vivo* Intramuscular Anticholinergic Survival Efficacy data[a] for 2-*N*,*N*-Dialkylaminoethyl Tropic Acid Esters in the Mouse



WR. No.	Bottle No.	Amine	Isomer	Musc. Bind. K_i(nM)	Cholin. Hydrol. t ($^1/_2$)min.	IM LD_{50} (mmol/kg)	1/16	1/8	1/4
251864	BK71249	NMe_2.HCl	(+)	280.0	>120	7.18	0	1	1
251863	BK71276	NMe_2.HCl	(-)	8.5	>120	0.36	0	0	0
251860	BK71267	NMe_2EtI	(+)	15.0	>120	4.00	0	)	0
251859	BK71294	NMe_2EtI	(-)	0.7	30	2.09	0	0	0
251862	BK71258	NMe_3I	(+)	52.5	5	1.94	0	0	0
251861	BK71285	NMe_3I	(-)	5.5	15	1.48	0	1	0
251887	BK71507	NEt_2MeI	(+)	37.0	>120	1.12	0	0	4
251887	BL35426	NEt_2MeI	(+)	37.0	>120	0.55	0[b]	1[b]	0[b]
251888	BK71525	NEt_2MeI	(-)	1.5	>120	0.60	2	2	2
251889	BK71490	NEt_3I	(+)	20.0	>120	3.83	0	0	0
251890	BK71516	NEt_3I	(-)	0.7	>120	0.67	1	1	3
254278	BL04298	pyrrolid.HCl	(+)	55.0	NA	7.07	1	1	0
254279	BL21002	pyrrolid.HCl	(-)	200.0	NA	>1.33	0[c]	0[c]	1[c]
254280	BL04252	piperid.HCl	(+)	NA	NA	8.78	1	0	0
254277	BL20998	morphol.HCl	(-)	66.0	NA	>1.11	0[b]	1[b]	0[b]

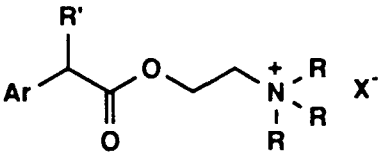
[a]Compound administered with 2-PAM after GD challenge at doses equal to the indicated fraction of the LD_{50}. Corrected number of survivors out of 10 is indicated.

[b,c]Different dose fractions ([b]1/64 1/16 1/4, [c]1/256 1/32 1/4).

Table 6

In vivo Intramuscular Anticholinergic Survival

Efficacy data[a] for Various Aromatic 2-*N*,*N*-Dialkylaminoethyl Esters in the Mouse



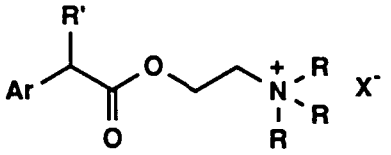
WR. No.	Bottle No.	Ar	Amine	R'	IM LD_{50} (mmol/kg)	1/16	1/8	1/4
254276	BL04270	4-MeOPh	NMe_2.HCl	CH_2OH	8.22	0	1	0
254276	BL35408	4-MeOPh	NMe_2.HCl	CH_2OH	1.34	0[b]	0[b]	0[b]
254273	BL04289	1-Naphthyl	NMe_2	H	5.40	0	0	1
256741	BL35417	1-Naphthyl	NEt_2MeI	H	>0.09	1[c]	2[c]	0[c]
256729	BL35337	2-Furanyl	NEt_2.Oxal.	H	>1.27	0[b]	0[b]	0[b]
256730	BL35346	2-Furanyl	NEt_2MeI	H	0.21	0[d]	0[d]	0[d]
256742	BL35435	2-Furanyl	NEt_2MeI	CH_2OH	0.04	0[d]	0[d]	1[d]

[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,d]Different dose fractions ([b]1/256 1/32 1/4, [c]1/128 1/32 1/2, [d]1/64 1/16 1/4).

Table 7

In vivo Intramuscular *Pretreatment* Survival Efficacy data[a] for Various Aromatic 2-*N,N*-Dialkylaminoethyl Esters Against GD in the Mouse



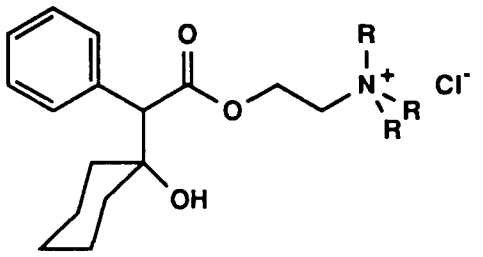
WR. No.	Bottle No.	Ar	Amine	R'	IM LD_{50} (mmol/kg)	15 min. 1/64	1/16	1/4	60 min. 1/64	1/16	1/4
251887	BL35426	Ph-(+)	NEt_2MeI	CH_2OH	0.55	0	0	0	1	1	0
254279	BL21002	Ph-(-)	pyrrolid.HCl	CH_2OH	>1.33	0^b	0^b	0^b	0^b	0^b	0^b
254276	BL35408	4-MeOPh	NMe_2.HCl	CH_2OH	1.34	0^b	0^b	0^b	0^b	2^b	1^b
257717	BL50512	1-Naphthyl	NEt_2.Oxal.	CH_2OH	>0.03	0^c	0^c	0^c	1^c	0^c	0^c
256729	BL35328	2-Furanyl	NEt_2.HCl	H	>1.53	1^b	0^b	0^b	3^b	0^b	1^b
256729	BL35337	2-Furanyl	NEt_2.Oxal.	H	>1.27	1^b	0^b	0^b	2^b	0^b	1^b
256730	BL35346	2-Furanyl	NEt_2MeI	H	0.21	0	0	0	0	1	1
256742	BL35435	2-Furanyl	NEt_2MeI	CH_2OH	0.04	0	1	0	0	0	1

[a]Pretreatment compound administered 15 or 60 minutes prior to GD challenge at doses equal to the indicated fraction of the LD_{50}, followed by atropine sulfate and 2-PAM intramuscularly 10 seconds after GD challenge. Corrected number of survivors out of 10 is indicated.

[b,c]Different dose fractions ([b]1/256 1/32 1/4, [c]1/64 1/4 1/2).

Table 8

In vivo Intramuscular *Pretreatment* Survival Efficacy data[a] for 2-*N*,*N*-Dialkylaminoethyl α-(1-Hydroxycyclohexyl)benzeneacetic Acid Esters Against GD in the Mouse

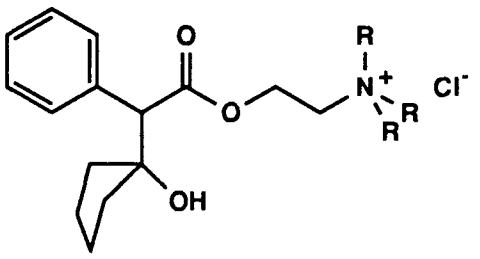


WR. No.	Bottle No.	Amine	IM LD_{50} (mmol/kg)	15 min. 1/64	15 min. 1/16	15 min. 1/4	60 min. 1/64	60 min. 1/16	60 min. 1/4
216854	BL50272	NMe_2.HCl	>1.02	0	1	1	0	0	0
257716	BL50503	NMe_2EtCl	0.48	0	0	0	0	0	0
257711	BL50450	NMe_3Cl	1.58	0	0	2	0	1	0
257701	BL50281	NEt_2.HCl	>0.91	0	2	0	0	0	0
257710	BL50441	NEt_2MeCl	0.54	0	0	0	0	0	0
257715	BL50496	NEt_3Cl	0.44	0	0	3	0	0	0

[a]Pretreatment compound administered 15 or 60 minutes prior to GD challenge at doses equal to the indicated fraction of the LD_{50}, followed by atropine sulfate and 2-PAM intramuscularly 10 seconds after GD challenge. Corrected number of survivors out of 10 is indicated.

Table 9

In vivo Intramuscular *Pretreatment* Survival Efficacy data[a] for 2-*N*,*N*-Dialkylaminoethyl α-(1-Hydroxycyclopentyl)benzeneacetic Acid Esters Against GD in the Mouse



WR. No.	Bottle No.	Amine	IM LD_{50} (mmol/kg)	15 min. 1/64	15 min. 1/16	15 min. 1/4	60 min. 1/64	60 min. 1/16	60 min. 1/4
216851	BL50432	$NEt_2.HCl$	>1.12	1	1	0	0	0	0
257712	BL50469	NEt_2MeCl	0.15	0	0	0	1	0	1
257714	BL50487	NEt_3Cl	>0.43	0	1	1	0	1	0

[a]Pretreatment compound administered 15 or 60 minutes prior to GD challenge at doses equal to the indicated fraction of the LD_{50}, followed by atropine sulfate and 2-PAM intramuscularly 10 seconds after GD challenge. Corrected number of survivors out of 10 is indicated.

EXPERIMENTAL DETAILS

Melting points were obtained on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. All solvents were purchased as AR grade and, when appropriate, were stored over 4Å molecular sieves. All anhydrous reactions were conducted under an atmosphere of argon. Flash chromatography was accomplished using silica gel 60 (230-400 mesh) purchased from EM Science. TLC analyses were performed on glass-backed Analtech Uniplates (250 μ, 2 x 8 in) with F-256. Visualization was performed by viewing under ultraviolet light, by exposure to iodine vapor, and by charring with H_2SO_4. ^{1}H-NMR analyses were obtained on a Varian XL-400 operating at 400 MHz or on either a JEOL FX90Q or Varian EM 390, both operating at 90 MHz, and were referenced to tetramethylsilane as an internal standard. IR spectra were recorded on a Perkin-Elmer 1310 spectrophotometer. Mass spectra were obtained on a Reibermag Model R10-10C operating in either chemical ionization or desorption-chemical ionization mode. Electron impact mass spectra (EIMS) were obtained on an LKB-9000. Microanalytical data were obtained from Desert Analytics (Tucson, AZ). Optical rotations were measured on a Perkin-Elmer 141 automatic polarimeter. Reverse-phase HPLC was performed on a Spectra-Physics SP8100 liquid chromatograph with an SP8440 UV/Vis detector and a Brownlee Labs "phenyl" reverse-phase column.

R-(+)-Tropic Acid Quinine Salt. To a solution of 200 g (0.616 mol) of quinine in 1 L of abs EtOH was added 102 g (0.614 mol) of (±)-tropic acid in 1 L of 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 of 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 of H_2SO_4 and 1 L of diethyl ether. After being stirred for 0.5 h, the ether layer was separated and the aqueous layer washed with ether (2 x 1 L). The combined ether fractions were washed with satd NaCl solution, dried over $MgSO_4$, filtered, and evaporated to give 38 g. This material was taken up in 50 mL of 60% EtOH and added to a hot solution of 38 g (0.229 mol) of l-(-)-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 (11.8 mmol) 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-(Pyrrolidin-1-yl)ethyl Ester (5). To 4.00 g (24.1 mmol) of S-(-)-tropic acid in 50 mL of anhydrous DMF under argon was added 6.20 g (45 mmol) of powdered K_2CO_3. The cloudy mixture was stirred at RT for 0.5 h, followed by the addition of 4.05 g (23.8 mmol) of 1-(2-chloroethyl)pyrrolidine hydrochloride. The mixture was stirred at 70°C for 4 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 3.75 g (59%) of **5** as a brown oil. This oil was chromatographed on a silica gel column and eluted with CH_2Cl_2, followed by 97% CH_2Cl_2/3% [MeOH/NH_3 (95/5)], then 95% CH_2Cl_2/5% [MeOH/NH_3(95/5)], to give 2.87 g (46%) of **5** as a pale yellow oil. 400 MHz ^{1}H-NMR ($CDCl_3$) δ 7.20 (s, 5H, aromatic), 4.40 (q, 2H, $CHC\underline{H}_2OH$), 4.1-3.6 (m, 4H, $CO_2C\underline{H}_2$, $C\underline{H}CH_2O\underline{H}$), 2.70 (t, 2H, $C\underline{H}_2N$), 2.6-2.45 (m, 4H, $N[C\underline{H}_2]_2$), 1.8-1.6 (m, 4H, $C\underline{H}_2C\underline{H}_2$). Anal calcd for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.27; H, 8.06; N, 5.16.

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(Pyrrolidin-1-yl)ethyl Ester Hydrochloride (6). To 2.75 g (10.45 mmol) of **5** in 100 mL of ether under argon at 0°C was added ethereal HCl until no more solid was formed. The ether was decanted, and recrystallization of the residue from ethanol-ether gave 2.81 g (90%) of **6** as white needles, mp 118-120°C. 90 MHz ^{1}H-NMR ($CDCl_3$) δ 7.35 (s, 5H, aromatic), 4.80-3.35 (m, 12H), 2.10 (m, 4H, $C\underline{H}_2C\underline{H}_2$). 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.

R-(+)-α-Hydroxymethyl)benzeneacetic Acid, 2-(Pyrrolidin-1-yl)ethyl Ester (7). Prepared from R-(+)-tropic acid (4.00 g, 24.1 mmol) and 1-(2-chloroethyl)pyrrolidine hydrochloride (4.05 g, 23.8 mmol) by the same method as **5** to give 2.29 g (36%) of **7** as a pale yellow oil. 400 MHz ^{1}H-NMR ($CDCl_3$) δ 7.20 (s, 5H, aromatic), 4.40 (q, 2H, $CHC\underline{H_2}OH$), 4.1-3.6 (m, 4H, $CO_2C\underline{H_2}$, $C\underline{H}CH_2O\underline{H}$), 2.70 (t, 2H, $C\underline{H_2}N$), 2.6-2.4 (m, 4H, $N[C\underline{H_2}]_2$), 1.8-1.6 (m, 4H, $C\underline{H_2}C\underline{H_2}$). Anal calcd for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.24; H, 8.11; N, 5.09.

R-(+)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(Pyrrolidin-1-yl)ethyl Ester Hydrochloride (8). Prepared from **7** (2.29 g, 8.7 mmol) and ethereal HCl by the same method as **6** to give 2.56 g (98%) of **6** as white needles, mp 130-132°C. 90 MHz ^{1}H-NMR ($CDCl_3$) δ 7.35 (s, 5H, aromatic), 4.80-3.35 (m, 12H), 2.10 (m, 4H, $C\underline{H_2}C\underline{H_2}$). 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, 11.99.

S-(-)-α-Hydroxymethyl)benzeneacetic Acid, 2-(Morpholin-4-yl)ethyl Ester (9). Prepared from S-(-)-tropic acid (2.97 g, 17.9 mmol) and 1-(2-chloroethyl)morpholine hydrochloride (3.50 g, 18.81 mmol) by the same method as **5** to give 2.80 g (56%) of **9** as a pale yellow oil. 90 MHz ^{1}H-NMR ($CDCl_3$) δ 7.30 (s, 5H, aromatic), 4.50-3.55 (m, 10H), 2.90-2.35 (m, 6H). Anal calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.58; H, 7.46; N, 5.18.

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(Morpholin-4-yl)ethyl Ester Hydrochloride (10). Prepared from **9** (2.31 g, 8.7 mmol) and ethereal HCl by the same method as **6**, without recrystallization, to give 1.89 g (72%) of **10** as a white solid. 90 MHz ^{1}H-NMR ($CDCl_3$) δ 7.32 (s, 5H, aromatic), 4.80-2.75 (m, 17H). Anal calcd for $C_{15}H_{22}ClNO_4$: C, 57.05; H, 7.02; N, 4.44; Cl, 11.23. Found: C, 57.15; H, 7.00; N, 4.29; Cl, 10.84.

R-(+)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester (11). To 5.00 g (30.1 mmol) of R-(+)-tropic acid in 100 mL of anhydrous DMF under argon was added 8.30 g (60.4 mmol) of powdered K_2CO_3. The cloudy mixture was stirred at RT for 0.5 h, followed by the addition of 5.30 g (30.7 mmol) of 2-*N*,*N*-diethylaminoethylchloride hydrochloride. The mixture was stirred at 70°C for 3 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 7.39 g (93%) of **11** as an oil,

R_f = 0. 25 (95% CH_2Cl_2/5% [MeOH/NH_3(95/5)]). 90 MHz ^{1}H-NMR ($CDCl_3$) δ 7.31 (s, 5H, aromatic), 4.51-3.72 (m, 5H, C<u>H</u>C<u>H</u>$_2$OH, OC<u>H</u>$_2$), 2.75 (t, 2H, C<u>H</u>$_2$N), 2.56 (q, 4H, N[C<u>H</u>$_2$CH$_3$]$_2$), 1.02 (t, 6H, N[CH$_2$C<u>H</u>$_3$]$_2$). $[\alpha]_D$ = -25° (1.38% in 95% EtOH.).

R-(+)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester Methoiodide (12). To 5.91 g (22.3 mmol) of **11** in 50 mL of anhydrous CH_3CN was slowly added 10 mL of CH_3I (161 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 solid was filtered and recrystallized from *iso*-propanol-methyl ethyl ketone to give 7.52 g (83%) of **12**, mp 85-87°C. $[\alpha]_D$ = 16.5 ° (2.5% in 95% EtOH.) 400 MHz ^{1}H-NMR (CD_3CN) δ 7.33 (s, 5H, aromatic), 4.44 (m, 2H, C<u>H</u>$_2$N), 4.2-3.6 (m, 6H, C<u>H</u>C<u>H</u>$_2$O<u>H</u>, CO_2C<u>H</u>$_2$), 3.26 (q, 4H, [C<u>H</u>$_2$CH$_3$]$_2$), 2.88 (s, 3H, NC<u>H</u>$_3$), 1.19 (t, 6H, N[CH$_2$C<u>H</u>$_3$]$_2$). Anal calcd for $C_{16}H_{26}INO_3$: C, 47.18; H, 6.43; N, 3.44; I, 31.16. Found: C, 47.52; H, 6.68; N, 3.29; I, 30.24.

(±)-α-(Hydroxymethyl)-4'-methoxybenzeneacetic Acid, 2-(*N*,*N*-Dimethylamino)ethyl Ester (14). Prepared from 4-methoxytropic acid (**13**)[16] (4.0 g, 20.4 mmol) and 2-*N*,*N*-dimethylaminoethylchloride hydrochloride (3.14 g, 21.80 mmol) in the same manner as **11** to give 2.34 g (38%) of an oil. This oil was chromatographed on silica gel, eluting with 95% CH_2Cl_2/5% ([MeOH/NH_3(95/5)] to give 1.93 g (32%) of **14** as an oil that crystallized on storage in a freezer. 400 MHz ^{1}H-NMR ($CDCl_3$) δ 7.26 (m, 2H, aromatic H-2', H-6'), 6.87 (m, 2H, aromatic H-3', H-5'), 4.19 (t, 2H, CO_2C<u>H</u>$_2$), 4.1-3.6 (m, 4H, C<u>H</u>C<u>H</u>$_2$O<u>H</u>), 3.75 (s, 3H, OC<u>H</u>$_3$), 2.62 (t, 2H, C<u>H</u>$_2$N), 2.28 (s, 6H, N[C<u>H</u>$_3$]$_2$).

(±)-α-(Hydroxymethyl)-4'-methoxybenzeneacetic Acid, 2-(*N*,*N*-Dimethylamino)ethyl Ester Hydrochloride (15). Prepared from **14** (2.55 g, 9.55 mmol) and ethereal HCl by the same method as **6**, without recrystallization, to give 2.72 g (94%) of **15** as a white solid, mp 118°C. 90 MHz ^{1}H-NMR (DMSO) δ 7.25 (m, 2H, H-2', H-6'), 6.85 (m, 2H, H-3', H-5'), 4.90-3.25 (m, 9H), 3.75 (s, 3H, OC<u>H</u>$_3$), 2.75 (s, 6H, N[C<u>H</u>$_3$]$_2$). Anal calcd for $C_{14}H_{22}ClNO_4$: C, 55.35; H, 7.30; N, 4.61; Cl, 11.67. Found: C, 55.42; H, 7.31; N, 4.57; Cl, 11.82.

R-(-)-α-(Hydroxy)benzeneacetic Acid, 2-(*N*,*N*-Dimethylamino)ethyl Ester (16). To 10.0 g (65.7 mmol) of R-(-)-mandelic acid in 125 mL of anhydrous DMF under argon was added 20.0 g (145 mmol) of powdered K_2CO_3. The cloudy mixture was stirred at RT for 1.5 h, followed by the addition of 10.0 g (69.4 mmol) of 2-*N*,*N*-dimethylaminoethylchloride

hydrochloride. The mixture was stirred at 70°C for 4 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 13.83 g (94%) of crude **16** as an oil. The residue was purified by flash chromatography elution with 95% CH_2Cl_2/5% [MeOH/NH_3(95/5)] to give 6.20 g (42%) of **16** as a pale yellow oil. R_f = 0.22 (95% CH_2Cl_2/5% [MeOH/NH_3(95/5)]). 90 MHz ^{1}H-NMR ($CDCl_3$) δ 7.40 (m, 5H, aromatic), 5.30 (s, 1H, C<u>H</u>OH), 4.80 (s, 1H, CHO<u>H</u>) 4.25 (t, 2H, OC<u>H</u>$_2$CH$_2$), 2.50 (t, 2H, C<u>H</u>$_2$N), 2.20 (s, 6H, N[C<u>H</u>$_3$]$_2$). Anal. calcd. for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.68; N, 6.27. Found: C, 64.42; H, 7.57; N, 6.23.

1-Naphthaleneacetic Acid, Methyl Ester (19). To 37.2 g (0.20 mol) of 1-naphthaleneacetic acid (**18**) in 125 mL of MeOH at 0°C was added 125 mL of MeOH saturated with HCl gas. The solution was stirred for 22 h, then evaporated to an oil. This oil 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 36.4 g (98%) of **19** as a colorless liquid. 90 MHz ^{1}H-NMR ($CDCl_3$) δ 8.05-7.35 (m, 7H, aromatic), 4.10 (s, 2H, C<u>H</u>$_2$), 3.69 (s, 3H, OC<u>H</u>$_3$).

(±)-α-Hydroxymethyl-1-naphthaleneacetic Acid, Methyl Ester (21). Into a flask, flame-dried under argon, was placed a solution of 7.55 g (37.8 mmol) of **19** and 1.40 g of paraformaldehyde in 40 mL of anhydrous DMSO, followed by the addition of 0.12 g (2.22 mmol) of sodium methoxide in one portion. This mixture was stirred for 1 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 2% MeOH in $CHCl_3$ to give 27 g (97%) of **21** as a colorless oil that crystallized on standing. 90 MHz ^{1}H-NMR ($CDCl_3$) δ 8.20-7.37 (m 7H, aromatic), 4.85-3.80 (m, 3H, C<u>H</u>C<u>H</u>$_2$OH), 3.75 (s, 3H, OC<u>H</u>$_3$).

(±)-α-Hydroxymethyl-1-naphthaleneacetic Acid (22). To 26 g (0.113 mol) of **21** in 100 mL of THF was added 23 mL (0. 137 mmol) of 6 N NaOH, and this mixture was stirred for 8 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 22.4 g (92%) of **22.** 90 MHz ^{1}H-NMR (DMSO-d_6) δ 8.15-7.60 (m 7H, aromatic), 5.90 (br, 2H, CO$_2$<u>H</u>, O<u>H</u>), 4.10-3.60 (m, 3H, C<u>H</u>C<u>H</u>$_2$).

(±)-α-Hydroxymethyl-1-naphthaleneacetic Acid, 2-(*N,N*-Dimethylamino)ethyl Ester (23). To 10.0 g (46.3 mmol) of (±)-α-hydroxymethyl-1-naphthaleneacetic acid (**22**) in 150 mL of anhydrous DMF was added 6.40 g (46.3 mmol) of K_2CO_3 (dried *in vacuo*) and this mixture was stirred at room temperature for 1.5 h. To the cloudy mixture was added 33.3 g (230 mmol) of 2-*N,N*-dimethylaminoethylchloride hydrochloride, followed by stirring for 4 h at 70°C. The mixture was poured into 800 mL of ice water and extracted with Et_2O (3 x 250 mL). The ether layer was washed with 250 mL of satd NaCl soln, dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was taken up in 250 mL of CH_2Cl_2, dried over Na_2SO_4, filtered and evaporated to dryness to give 11.93 g (90%) of **23** as an oil. The residue was purified by flash chromatography elution with 95% CH_2Cl_2/5% [MeOH/NH_3(95/5)]) to give 7.55 g (57%) of **23.** R_f = 0.23 (95% CH_2Cl_2/5% [MeOH/NH_3(95/5)]). 90 MHz ^{1}H-NMR ($CDCl_3$) δ 8.16-7.20 (m, 7H, aromatic), 4.65 (dd, 1H, C$\underline{H}_2$OH), 4.20 (m, 3H, C$\underline{H}$, OC$\underline{H}_2$), 3.88 (dd, 1H, C$\underline{H}_2$OH), 2.40 (m, 2H, C$\underline{H}_2$N), 2.10 (s, 6H, N[C$\underline{H}_3$]$_2$). Anal calcd for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37; N, 4.87. Found: C, 71.16; H, 7.17; N, 4.83.

(±)-α-Hydroxymethyl-1-naphthaleneacetic Acid, 2-(*N,N*-Diethylamino)ethyl Ester (28). To 5.0 g (23.2 mmol) of (±)-α-hydroxymethyl-1-naphthaleneacetic acid (**22**) in 100 mL of anhydrous DMF was added 6.40 g (46.3 mmol) of K_2CO_3 (dried *in vacuo*) and this mixture was stirred at room temperature for 1.5 h. To the cloudy mixture was added 4.18 g (24.3 mmol) of 2-*N,N*-diethylaminoethylchloride hydrochloride, followed by stirring for 4 h at 70°C. The mixture was poured into 800 mL of ice water and extracted with Et_2O (3 x 250 mL). The ether layer was washed with 250 mL of satd NaCl soln, dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by flash chromatography elution with 95% CH_2Cl_2/5% [MeOH/NH_3(95/5)] to give 7.05 g (97%) of **28** as a pale yellow oil. R_f = 0.27 (95% CH_2Cl_2/5% [MeOH/NH_3(95/5)]). 90 MHz ^{1}H-NMR ($CDCl_3$) δ 8.15-7.20 (m, 7H, aromatic), 4.70 (dd, 1H, C$\underline{H}_2$OH), 4.30 (m, 3H, C$\underline{H}$, OC$\underline{H}_2$), 3.88 (dd, 1H, C$\underline{H}_2$OH), 2.65 (m, 2H, C$\underline{H}_2$N), 2.55 (q, 4H, N[C$\underline{H}_2$CH$_3$]$_2$), 1.00 (t, 6H, N[CH$_2$C$\underline{H}_3$]$_2$). Anal calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.16; H, 7.97; N, 4.43.

(±)-α-Hydroxymethyl-1-naphthaleneacetic Acid, 2-(*N,N*-Diethylamino)ethyl Ester Oxalate (30). To 3.16 g (10 mmol) of **28** in anhydrous diethyl ether (100 mL) was added 0.91 g (10.1 mmol) of oxalic acid in anhydrous diethyl ether (100 mL). The white precipitate that formed was collected, crushed, and washed with more ether. Recrystallization of the residue from abs EtOH-ether gave 2.70 g (66%) of **30** as a free-flowing, nonhygroscopic, white solid. Anal calcd for $C_{21}H_{27}NO_7$: C, 62.21; H, 6.71; N, 3.46. Found: C, 62.10; H, 6.89; N, 3.25.

1-Naphthaleneacetic Acid, 2-(*N,N*-Diethylamino)ethyl Ester (33). To 10.0 g (53.7 mmol) of 1-naphthaleneacetic acid **(18)** in 200 mL of anhydrous DMF was added 14.84 g (107 mmol) of K_2CO_3 (dried *in vacuo*) and this mixture was stirred at room temperature for 0.5 h. To the cloudy mixture was added 9.42 g (54.8 mmol) of 2-*N,N*-diethylaminoethylchloride hydrochloride, followed by stirring for 5 h at 70°C. The mixture was poured into 800 mL of ice water and extracted with Et_2O (3 x 250 mL). The ether layer was washed with 250 mL of satd NaCl soln, dried over Na_2SO_4, filtered, and evaporated to dryness. The brown residue was distilled by short-path distillation (154°C-0.025 mm) to give 5.60 g (37%) of **33** as a pale yellow oil. 90 MHz ^{1}H-NMR ($CDCl_3$) δ 8.00-7.30 (m, 7H, aromatic), 4.25 (t, 2H, $OC\underline{H}_2$), 4.03 (s, 2H, $C\underline{H}_2CO$), 2.60 (t, 2H, $C\underline{H}_2N$) 2.45 (q, 4H, $N[C\underline{H}_2CH_3]_2$), 0.90 (t, 6H, $N[CH_2C\underline{H}_3]_2$). Anal calcd for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.80; H, 7.97; N, 4.93.

1-Naphthaleneacetic Acid, 2-(*N,N*-Diethylamino)ethyl Ester Methoiodide (34). To 2.35 g (8.25 mmol) of **33** in 20 mL of anhydrous methyl ethyl ketone was slowly added 2.56 mL of CH_3I (41.1 mmol). The reaction, kept under argon and protected from light, was stirred at RT for 24 h, then chilled at -4°C for 24 h to give a white solid. This solid was filtered and recrystallized from *iso*-propanol-methyl ethyl ketone to give 3.02 g (86%) of **34**. 90 MHz ^{1}H-NMR (DMSO) δ 8.00-7.40 (m, 7H, aromatic), 4.40 (m, 2H, $OC\underline{H}_2$), 4.20 (s, 2H, $C\underline{H}_2CO$), 3.50 (t, 2H, $C\underline{H}_2N$) 3.20 (q, 4H, $N[C\underline{H}_2CH_3]_2$), 2.80 (s, 3H, $NC\underline{H}_3$), 1.06 (t, 6H, $N[CH_2C\underline{H}_3]_2$). Anal calcd for $C_{19}H_{26}INO_2$: C, 53.40; H, 6.13; N, 3.28; I, 29.70. Found: C, 53.33; H, 6.18; N, 3.40; I, 29.83.

2-Furanacetic Acid, 2-(*N,N*-Diethylamino)ethyl Ester (37). To 7.66 g (60 mmol) of 2-furanacetic acid **(35)** in 200 mL of dry DMF was added 16.8 g (120 mmol) of K_2CO_3 (dried *in vacuo*) and the mixture was stirred at room temp for 0.5 h. To the cloudy mixture was added 10.84 g (64 mmol) of 2-*N,N*-diethylaminoethylchloride hydrochloride, followed by stirring for 3 h at 70°C. The mixture was poured into 800 mL of ice water and extracted with Et_2O (3 x 250 mL). The ether layer was washed with 250 mL of satd NaCl soln, dried over Na_2SO_4, filtered, and evaporated to dryness. The brown residue was distilled by short-path distillation (70°C-0.15 mm) to give 9.70 g (71%) of **37** as a pale yellow oil. 90 MHz ^{1}H-NMR ($CDCl_3$) δ 7.30 (m, 1H, H-5'), 6.23 (m, 2H, H-3', H-4'), 4.19 (t, 2H, $OC\underline{H}_2$), 3.66 (s, 2H, $C\underline{H}_2CO$), 2.55 (t, 2H, $C\underline{H}_2N$) 2.45 (q, 4H, $N[C\underline{H}_2CH_3]_2$), 0.90 (t, 6H, $N[CH_2C\underline{H}_3]_2$). Anal calcd for $C_{12}H_{19}NO_3$: C, 63.97; H, 8.50; N, 6.22. Found: C, 63.80; H, 8.40; N, 6.31.

2-Furanacetic Acid, 2-(*N,N*-Diethylamino)ethyl Ester Hydrochloride (38). To 3.00 g (13 mmol) of **37** in 10 mL of methyl ethyl ketone under argon at 0°C was added ethereal HCl until no more solid was formed. The ether was decanted, and the residue was washed with pentane and dried to give 2.81 g (90%) of **38** as a white solid. 90 MHz ^{1}H-NMR ($CDCl_3$) δ 7.33 (m, 1H, H-5'), 6.26 (m, 2H, H-3', H-4'), 4.42 (m, 2H, $OC\underline{H}_2$), 3.70 (s, 2H, $C\underline{H}_2CO$), 3.30 (m, 2H, $C\underline{H}_2N$) 3.20 (q, 4H, $N[C\underline{H}_2CH_3]_2$, 1.27 (t, 6H, $N[CH_2C\underline{H}_3]_2$). Anal calcd for $C_{12}H_{20}ClNO_3$: C, 55.06; H, 7.70; N, 5.35. Found: C, 55.15; H, 8.00; N, 5.53.

2-Furanacetic Acid, 2-(*N,N*-Diethylamino)ethyl Ester Oxalate (39). To 2.50 g (10 mmol) of **37** in anhydrous diethyl ether (100 mL) was added 1.0 g (11 mmol) of oxalic acid in anhydrous diethyl ether (100 mL). The white precipitate that formed was collected, crushed, and washed with more ether to give 3.40 g (97%) of **39** as a free-flowing, nonhygroscopic, white solid. 90 MHz ^{1}H-NMR ($CDCl_3$) δ 10.37 (s, 2H, O<u>H</u>), 7.33 (m, 1H, H-5'), 6.26 (m, 2H, H-3', H-4'), 4.46 (m, 2H, $OC\underline{H}_2$), 3.72 (s, 2H, $C\underline{H}_2CO$), 3.33 (m, 2H, $C\underline{H}_2N$), 3.20 (q, 4H, $N[C\underline{H}_2CH_3]_2$), 1.27 (t, 6H, $N[CH_2C\underline{H}_3]_2$). Anal calcd for $C_{14}H_{21}NO_7$: C, 53.33; H, 6.71; N, 4.44. Found: C, 53.66; H, 6.83; N, 4.39.

2-Furanacetic Acid, 2-(*N,N*-Diethylamino)ethyl Ester Methoiodide (40). To 3.0 g (13 mmol) of **37** in 15 mL anhydrous methyl ethyl ketone was slowly added 4.15 mL of CH_3I (66 mmol). The reaction, kept under argon and protected from light, was stirred at RT for 24 h, then chilled at -4°C for 24 h to give a white solid. This was filtered to give 4.20 g (86%) of **40**. 90 MHz ^{1}H-NMR ($CDCl_3$) δ 7.35 (m, 1H, H-5'), 6.22 (m, 2H, H-3', H-4'), 4.63 (m, 2H, $OC\underline{H}_2$), 3.93 (m, 2H, $C\underline{H}_2N$), 3.85 (s, 2H, $C\underline{H}_2CO$), 3.60 (q, 4H, $N[C\underline{H}_2CH_3]_2$), 3.25 (s, 3H, $NC\underline{H}_3$), 1.38 (t, 6H, $N[CH_2C\underline{H}_3]_2$). Anal calcd for $C_{13}H_{22}INO_3$: C, 42.52; H, 6.04; N, 3.81; I, 34.56. Found: C, 42.28; H, 6.21; N, 3.82; I, 34.27.

(±)-α-Hydroxymethyl-2-furanacetic Acid, 2-(*N,N*-Diethylamino)ethyl Ester (43). To 2.29 g (14.7 mmol) of (±)-α-hydroxymethyl-2-furanacetic acid **(42)**[18] in 65 mL of anhydrous DMF was added 2.20 g (15.9 mmol) of K_2CO_3 (dried *in vacuo*) and this mixture was stirred at room temperature for 0.5 h. To the cloudy mixture was added 2.52 g (15 mmol) of 2-*N,N*-diethylaminoethylchloride hydrochloride, followed by stirring for 4 h at 70°C. The mixture was poured into 800 mL of ice water and extracted with Et_2O (3 x 250 mL). The ether layer was washed with 250 mL of satd NaCl soln, dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was chromatographed to give 2.50 g (68%) of **43** as a pale yellow oil. 90 MHz ^{1}H-NMR ($CDCl_3$) δ 7.28 (m, 1H, H-5'), 6.28 (m, 2H, H-3', H-4'), 4.30 (dd, 1H, $C\underline{H}_2OH$), 3.93

(m, 3H, C<u>H</u>, OC<u>H</u>$_2$), 3.88 (dd, 1H, C<u>H</u>$_2$OH), 2.60 (m, 6H, C<u>H</u>$_2$N, N[C<u>H</u>$_2$CH$_3$]$_2$), 1.00 (t, 6H, N[CH$_2$C<u>H</u>$_3$]$_2$). Anal calcd for $C_{13}H_{21}NO_4$: C, 61.15; H, 8.29; N, 5.49. Found: C, 61.15; H, 8.40; N, 5.31.

(±)-α-Hydroxymethyl-2-furanacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester Methoiodide (44). To 2.50 g (9.8 mmol) of **43** in 15 mL of anhydrous methyl ethyl ketone was slowly added 12.6 g of CH_3I (10.8 mmol). The reaction, kept under argon and protected from light, was stirred at RT for 24 h, then chilled at -4°C for 24 h to give a white solid. The solution was decanted from the precipitate and the residue recrystallized from *iso*-propanol-methyl ethyl ketone to give 3.20 g (57%) of **44**. 90 MHz ^{1}H-NMR ($CDCl_3$) δ 7.41 (m, 1H, H'-5), 6.27 (m, 2H, H-3', H-4'), 4.78 (dd, 1H, C<u>H</u>$_2$OH), 4.58-4.06 (m, 4H, C<u>H</u>, OC<u>H</u>$_2$, C<u>H</u>$_2$OH), 3.87 (m, 2H, C<u>H</u>$_2$N), 3.40 (q, 4H, N[C<u>H</u>$_2$CH$_3$]$_2$), 3.16 (s, 3H, NC<u>H</u>$_3$), 1.35 (t, 6H, N[CH$_2$C<u>H</u>$_3$]$_2$). Anal calcd for $C_{14}H_{24}INO_4$: C, 42.33; H, 6.09; N, 3.52; I, 31.94. Found: C, 42.75; H, 6.21; N, 3.45; I, 31.81.

α-(1-Hydroxycyclohexyl)benzeneacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester (46). To 7.02 g (30.0 mmol) of α-(1-hydroxycyclohexyl)benzeneacetic acid (**45**)[19] in 450 mL of dry DMF was added 4.35 g (31.4 mmol) of K_2CO_3 (dried *in vacuo*) and this mixture was stirred at room temperature for 1.5 h. To the cloudy mixture was added 5.17 g (30.0 mmol) of 2-*N*,*N*-diethylaminoethylchloride hydrochloride, followed by stirring for 18 h at RT. The mixture was poured into 800 mL of ice water and extracted with Et_2O (3 x 250 mL). The ether layer was washed with 250 mL of satd NaCl soln, dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was taken up in 50 mL of CH_2Cl_2, dried over Na_2SO_4, filtered, and evaporated to dryness to give 9.9 g (100%) of **46** as an oil, R_f = 0.25 (95% CH_2Cl_2/5% [MeOH/NH_3(95/5)]). 90 MHz ^{1}H-NMR ($CDCl_3$) δ 7.6-7.2 (m, 5H, aromatic), 4.20 (t, 2H, COC<u>H</u>$_2$), 3.61 (s, 2H, C<u>H</u>, O<u>H</u>), 2.64 (t, 2H, C<u>H</u>$_2$N), 2.52 (q, 4H, N[C<u>H</u>$_2$CH$_3$]$_2$), 1.9-1.1 (m, 10H, ring C<u>H</u>$_2$), 0.97 (t, 6H, N[CH$_2$C<u>H</u>$_3$]$_2$). Anal calcd for $C_{20}H_{31}NO_3$: C, 72.03; H, 9.37; N, 4.20. Found: C, 71.86; H, 9.17; N, 4.23.

α-(1-Hydroxycyclohexyl)benzeneacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester Hydrochloride (47). To 3.33 g (10.0 mmol) of 46 in 40 mL of Et_2O under argon at 0 °C was slowly added a solution of ethereal HCl until the formation of the precipitate stopped. This mixture was stirred at 0°C for 0.5 h, then filtered. The solid was washed with 300 mL of ether, then dried *in vacuo* to give 3.86 g (93%) of **47** as a white solid which was recrystallized from methyl ethyl ketone, mp 137-138°C. 90 MHz ^{1}H-NMR (DMSO-d_6) δ 7.5-7.2 (m, 5H, aromatic), 4.39 (br q,

2H, $COC\underline{H}_2$), 3.80 (m, 2H, $C\underline{H}_2N$), 3.75 (s, 1H, $C\underline{H}$), 3.02 (unresolved q, 4H, $N[C\underline{H}_2CH_3]_2$), 1.8-1.2 (m, 10H, ring $C\underline{H}_2$), 1.15 (t, 6H, $N[CH_2C\underline{H}_3]_2$). Anal calcd for $C_{20}H_{32}ClNO_3$: C, 64.94; H, 8.72; N, 3.78; Cl, 9.58. Found: C, 64.90; H, 8.62; N, 3.82; Cl, 9.37.

α-(1-Hydroxycyclohexyl)benzeneacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester Methoiodide (48). To 3.20 g (9.60 mmol) of **46** in 40 mL of methyl ethyl ketone was slowly added 3 mL of methyl iodide (under argon and protected from light), and this mixture was stirred overnight. The solid was collected by filtration, washed with ether, and dried *in vacuo* to give 3.2 g (70%) of **48** as a solid. 90 MHz ^{1}H-NMR ($CDCl_3$) δ 7.34 (m, 5H, aromatic), 4.59 (br q, 2H, $COC\underline{H}_2$), 3.90 (br q, 2H, $C\underline{H}_2N$), 3.69 (s, 1H, $C\underline{H}$), 3.40 (q, 2H, $NC\underline{H}_2CH_3$), 3.38 (q, 2H, $NC\underline{H}_2CH_3$), 3.11 (s, 3H, $NC\underline{H}_3$), 1.8-1.2 (m, 10H, ring $C\underline{H}_2$), 1.23 (t, 6H, $N[CH_2C\underline{H}_3]_2$).

α-(1-Hydroxycyclohexyl)benzeneacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester Ethoiodide (49). To 3.20 g (9.60 mmol) of **46** in 40 mL of methyl ethyl ketone was slowly added 4 mL of ethyl iodide (under argon and protected from light), and this mixture was stirred for 7 days. The solid was collected by filtration to give 2.0 g of a solid. The filtrate was reduced in volume and chilled to afford a second crop, which was filtered and combined with the first crop to give a combined yield of 4.0 g (85%) of **49**. 90 MHz ^{1}H-NMR ($CDCl_3$) δ 7.34 (br s, 5H, aromatic), 4.60 (br q, 2H, $COC\underline{H}_2$), 3.90 (br q, 2H, $C\underline{H}_2N$), 3.67 (s, 1H, $C\underline{H}$), 3.40 (q, 4H, $N[C\underline{H}_2CH_3]_2$), 3.37 (q, 2H, $NC\underline{H}_2CH_3$), 1.9-1.2 (m, 10H, ring $C\underline{H}_2$), 1.22 (t, 9H, $N[CH_2C\underline{H}_3]_3$).

α-(1-Hydroxycyclohexyl)benzeneacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester Methochloride (50). A solution of 3.6 g (7.57 mmol) of **48** in 40 mL of H_2O was loaded onto a column of IRA 400 (Cl-) resin (prewashed with 500 mL of 5% HCl, followed by H_2O [2 x 500 mL]) and eluted with ~1 L of water. The solvent was removed by lyophilization to give 3.2 g of a white foam. This foam was recrystallized from 40 mL of methyl ethyl ketone and 10 mL of chilled *iso*-propanol. Filtration gave 2.8 g (96%) of **50** as a white solid, mp 187-191°C. 90 MHz ^{1}H-NMR (DMSO-d_6) δ 7.5-7.2 (m, 5H, aromatic), 4.42 (br t, 2H, $COC\underline{H}_2$), 3.71 (s, 1H, $C\underline{H}$), 3.55 (br t, 2H, $C\underline{H}_2N$), 3.30 (q, 4H, $N[C\underline{H}_2CH_3]_2$), 2.94 (s, 3H, $NC\underline{H}_3$), 1.51 (t, 6H, $N[CH_2C\underline{H}_3]_2$), 1.45 (m, 10H, ring $C\underline{H}_2$). Anal calcd for $C_{21}H_{34}ClNO_3$: C, 65.69; H, 8.93; N, 3.65; Cl, 9.23. Found: C, 65.81; H, 9.04; N, 3.49; Cl, 9.08.

α-(1-Hydroxycyclohexyl)benzeneacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester Ethochloride (51). A solution of 4.00 g (8.17 mmol) of **49** in 40 mL of H_2O was loaded onto

a column of IRA 400 (Cl-) resin (prewashed with 500 mL of 5% HCl, followed by H_2O [2 x 500 mL]) and eluted with ~1 L of water. The solvent was removed by lyophilization to give a white foam. This foam was recrystallized from 40 mL of methyl ethyl ketone and 10 mL of chilled *iso*-propanol. Filtration gave 2.8 g (86%) of **51** as a white crystalline solid, mp 202-203°C. 90 MHz ^{1}H-NMR (DMSO-d_6) δ 7.5-7.2 (m, 5H, aromatic), 4.54 (br t, 2H, COC$\underline{H}_2$), 3.71 (s, 1H, C$\underline{H}$), 3.50 (br t, 2H, C$\underline{H}_2$N), 3.25 (q, 6H, N[C$\underline{H}_2$CH$_3$]$_3$), 1.45 (m, 10H, ring C$\underline{H}_2$), 1.12 (t, 9H, N[CH$_2$C$\underline{H}_3$]$_3$). Anal calcd for $C_{22}H_{36}ClNO_3$: C, 66.39; H, 9.12; N, 3.53; Cl, 8.91. Found: C, 66.14; H, 9.15; N, 3.49; Cl, 8.52.

α-(1-Hydroxycyclohexyl)benzeneacetic Acid, 2-(*N,N*-Dimethylamino)ethyl Ester (52). Prepared from α-(1-hydroxycyclohexyl)benzeneacetic acid (**45**)[19] (10.0 g, 42.6 mmol), powdered K_2CO_3 (6.5 g, 47 mmol), and 2-*N,N*-dimethylaminoethylchloride hydrochloride (6.5 g, 45.1 mmol) by the same method as **46** to give 9.1 g (70%) of **52** as a semisolid. 90 MHz ^{1}H-NMR ($CDCl_3$) δ 7.5-7.2 (m, 5H, aromatic), 4.29 (t, 2H, COC$\underline{H}_2$), 4.05 (s, 1H, O$\underline{H}$), 3.64 (s, 1H, C$\underline{H}$), 2.51 (t, 2H, C$\underline{H}_2$N), 2.22 (s, 6H, N[C$\underline{H}_3$]$_2$), 2.0-0.9 (br m, 10H, ring C$\underline{H}_2$).

α-(1-Hydroxycyclohexyl)benzeneaceticacid, 2-(*N,N*-Dimethylamino)ethyl Ester Hydrochloride (53). Prepared from **52** (2.66 g, 8.71 mmol) by the same method as **47** to give 2.8 g (97%) of **53** as a white solid, mp 129-131°C. 90 MHz ^{1}H-NMR (DMSO-d_6) δ 7.5-7.2 (m, 5H, aromatic), 4.30 (m, 2H, COC$\underline{H}_2$), 3.79 (s, 1H, C$\underline{H}$), 3.30 (br m, 2H, C$\underline{H}_2$N), 2.76 (s, 6H, N[C$\underline{H}_3$]$_2$), 1.8-0.8 (br m, 10H, ring C$\underline{H}_2$). Anal calcd for $C_{18}H_{28}ClNO_3$: C, 63.24; H, 8.26; N, 4.10; Cl, 10.30. Found: C, 63.25; H, 8.27; N, 3.93; Cl, 10.15.

α-(1-Hydroxycyclohexyl)benzeneacetic Acid, 2-(*N,N*-Dimethylamino)ethyl Ester Methoiodide (54). Prepared from **52** (3.15 g, 10.3 mmol) and methyl iodide (3.2 mL) by the same method as **48**. The solid was filtered and washed with ether to give 4.1 g (89%) of **54** as a white solid. 90 MHz ^{1}H-NMR ($CDCl_3$) δ 7.35 (d, 5H, aromatic), 4.55 (br t, 2H, COC$\underline{H}_2$), 4.00 (d x t, 2H, C$\underline{H}_2$N), 3.69 (s, 1H, C$\underline{H}$), 3.26 (s, 9H, N[C$\underline{H}_3$]$_3$), 1.9-1.0 (br m, 10H, ring C$\underline{H}_2$).

α-(1-Hydroxycyclohexyl)benzeneacetic Acid, 2-(*N,N*-Dimethylamino)ethyl Ester Ethoiodide (55). Prepared from **52** (3.0 g, 9.82 mmol) and ethyl iodide (4 mL) by the same method as **49**. The residue was triturated with hot methyl ethyl ketone and Et_2O and the solid filtered to give 4.1 g (89%) of **55** as a white solid. 90 MHz ^{1}H-NMR ($CDCl_3$) δ 7.32 (d, 5H, aromatic), 4.58 (br t, 2H, COC$\underline{H}_2$), 3.92 (br q, 2H, C$\underline{H}_2$N), 3.70 (s, 1H, C$\underline{H}$), 3.49 (q, 2H,

$NC\underline{H}_2CH_3$), 3.19 (s, 3H, $NC\underline{H}_3$), 3.16 (s, 3H, $NC\underline{H}_3$), 1.9-1.2 (m, 10H, ring $C\underline{H}_2$), 1.24 (t, 3H, $NCH_2C\underline{H}_3$).

α-(1-Hydroxycyclohexyl)benzeneacetic Acid, 2-(*N,N*-Dimethylamino)ethyl Ester Methochloride (56). Prepared from **54** (4.0 g, 8.94 mmol) by the same method as **50** to give 2.8 g (88%) of **56** as a white solid, mp 193-197°C. 90 MHz ^{1}H-NMR (DMSO-d_6) δ 7.55-7.20 (m, 5H, aromatic), 4.40 (br t, 2H, $COC\underline{H}_2$), 3.71 (s, 1H, C<u>H</u>), 3.63 (br t, 2H, $C\underline{H}_2N$), 3.08 (s, 9H, $N[C\underline{H}_3]_3$), 1.8-0.8 (br m, 10H, ring $C\underline{H}_2$). Anal calcd for $C_{19}H_{20}ClNO_3$: C, 64.12; H, 8.50; N, 3.94; Cl, 9.96. Found: C, 63.92; H, 8.51; N, 3.79; Cl, 9.56.

α-(1-Hydroxycyclohexyl)benzeneacetic Acid, 2-(*N,N*-Dimethylamino)ethyl Ester Ethochloride (57). Prepared from **55** (4.0 g, 8.67 mmol) dissolved in 40 mL of H_2O and 5 mL of MeOH by the same method as **51** to give 2.8 g (87%) of **57** as a white solid, mp 195-198°C. 90 MHz ^{1}H-NMR (DMSO-d_6) δ 7.5-7.2 (m, 5H, aromatic), 4.45 (br q, 2H, $COC\underline{H}_2$), 3.71 (s, 1H, C<u>H</u>), 3.61 (br q, 2H, $C\underline{H}_2N$), 3.29 (q, 2H, $NC\underline{H}_2CH_3$), 3.01 (s, 6H, $N[C\underline{H}_3]_2$), 1.45 (br m, 10H, ring $C\underline{H}_2$), 1.18 (t, 3H, $NCH_2C\underline{H}_3$). Anal calcd for $C_{20}H_{32}ClNO_3$: C, 64.94; H, 8.72; N, 3.78; Cl, 9.58. Found: C, 64.90; H, 8.86; N, 3.73; Cl, 9.42.

α-(1-Hydroxycyclopentyl)benzeneacetic Acid, 2-(*N,N*-Diethylamino)ethyl Ester (59). Prepared from α-(1-hydroxycyclopentyl)benzeneacetic acid (**58**)[19] (8.81 g, 40.0 mmol), powdered K_2CO_3 (5.80 g, 42.0 mmol), and 2-*N,N*-diethylaminoethylchloride hydrochloride (6.90 g, 40.1 mmol) by the same method as **46** to give 11.0 g (86%) of **59** as an oil. 90 MHz ^{1}H-NMR ($CDCl_3$) δ 7.5-7.2 (m, 5H, aromatic), 4.23 (t, 2H, $COC\underline{H}_2$), 3.66 (s, 1H, C<u>H</u>), 3.53 (q, 4H, $N[C\underline{H}_2CH_3]_2$), 2.57 (t, 2H, $C\underline{H}_2N$), 2.0-1.2 (m, 8H, ring $C\underline{H}_2$), 0.97 (t, 6H, $N[CH_2C\underline{H}_3]_2$).

α-(1-Hydroxycyclopentyl)benzeneacetic Acid, 2-(*N,N*-Diethylamino)ethyl Ester Hydrochloride (60). Prepared from **59** (2.85 g, 8.92 mmol) by the same method as **47** to give 3.0 g (94%) of **60** as a white solid, mp 115-118°C. 90 MHz ^{1}H-NMR (DMSO-d_6) δ 7.5-7.15 (m, 5H, aromatic), 4.40 (br t, 2H, $COC\underline{H}_2$), 3.92 (s, 1H, C<u>H</u>), 3.34 (br t, 2H, $C\underline{H}_2N$), 3.01 (q, 4H, $N[C\underline{H}_2CH_3]_2$), 1.55 (br d, 8H, ring $C\underline{H}_2$), 1.04 (t, 6H, $N[CH_2C\underline{H}_3]_2$). Anal calcd for $C_{19}H_{30}ClNO_3$: C, 64.12; H, 8.50; N, 3.94; Cl, 9.96. Found: C, 64.18; H, 8.45; N, 3.83; Cl, 9.86.

α-(1-Hydroxycyclopentyl)benzeneacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester Methoiodide (61). Prepared from **59** (3.5 g, 11.0 mmol) and methyl iodide (3.5 mL) by the same method as **48**. The methyl ethyl ketone was decanted from the gummy solid that formed, and the residue was taken up in 50 mL of MeOH and evaporated to dryness to give 5.0 g (98%) of **61** as a foam. 90 MHz ^{1}H-NMR ($CDCl_3$) δ 7.33 (d, 5H, aromatic), 4.60 (br t, 2H, $COC\underline{H}_2$), 3.85 (br t, 2H, $C\underline{H}_2N$), 3.81 (s, 1H, C<u>H</u>), 3.39 (q, 4H, $N[C\underline{H}_2CH_3]_2$), 3.09 (s, 3H, $NC\underline{H}_3$), 2.0-1.35 (m, 8H, ring $C\underline{H}_2$), 1.22 (t, 6H, $N[CH_2C\underline{H}_3]_2$).

α-(1-Hydroxycyclopentyl)benzeneacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester Ethoiodide (62). Prepared from **59** (3.5 g, 11.0 mmol) and ethyl iodide (4 mL) by the same method as **49**. Recrystallization from methyl ethyl ketone-Et_2O gave 4.9 g (94%) of **62** as a white solid. 90 MHz ^{1}H-NMR ($CDCl_3$) δ 7.34 (m, 5H, aromatic), 4.59 (br t, 2H, $COC\underline{H}_2$), 3.81 (s, 1H, C<u>H</u>), 3.70 (br t, 2H, $C\underline{H}_2N$), 3.30 (q, 6H, $N[C\underline{H}_2CH_3]_3$), 2.0-1.4 (m, 8H, ring $C\underline{H}_2$), 1.23 (t, 9H, $N[CH_2C\underline{H}_3]_3$).

α-(1-Hydroxycyclopentyl)benzeneacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester Methochloride (63). Prepared from **61** (5.0 g, 10.8 mmol) by the same method as **50** followed by recrystallization from methyl ethyl ketone-*iso*-propanol to give 2.8 g (70%) of **63** as a white solid, mp 165-168°C. 90 MHz ^{1}H-NMR (DMSO-d_6) δ 7.55-7.20 (m, 5H, aromatic), 4.40 (br t, 2H, $COC\underline{H}_2$), 3.88 (s, 1H, C<u>H</u>), 3.56 (br t, 2H, $C\underline{H}_2N$), 3.30 (q, 4H, $N[C\underline{H}_2CH_3]_2$), 2.93 (s, 3H, $NC\underline{H}_3$), 1.62 (br d, 8H, ring $C\underline{H}_2$), 1.13 (t, 6H, $N[CH_2C\underline{H}_3]_2$). Anal calcd for $C_{20}H_{32}ClNO_3$: C, 64.94; H, 8.72; N, 3.78; Cl, 9.58. Found: C, 65.07; H, 8.90; N, 3.71; Cl, 9.27.

α-(1-Hydroxycyclohexyl)benzeneacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester Ethochloride (64). Prepared from **62** (4.8 g, 10.1 mmol) dissolved in 50 mL of H_2O and 5 mL of MeOH by the same method as **51.** Recrystallization from methyl ethyl ketone-*iso*-propanol gave 2.7 g (69%) of **64** as a white hygroscopic solid, mp 177-180°C. 90 MHz ^{1}H-NMR (DMSO-d_6) δ 7.5-7.2 (m, 5H, aromatic), 4.41 (br t, 2H, $COC\underline{H}_2$), 3.89 (s, 1H, C<u>H</u>), 3.50 (br q, 2H, $C\underline{H}_2N$), 3.23 (q, 6H, $N[C\underline{H}_2CH_3]_3$), 1.55 (br d, 8H, ring $C\underline{H}_2$), 1.10 (t, 9H, $N[CH_2C\underline{H}_3]_3$). Anal calcd for $C_{21}H_{34}ClNO_3$: C, 65.69; H, 8.93; N, 3.65; Cl, 9.23. Found: C, 65.19; H, 8.87; N, 3.62; Cl, 8.52.

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