Parasympatholytic (Anticholinergic) Esters of the Isomeric 2-Tropanols. 1. Glycolates

Edward R. Atkinson,* Donna D. McRitchie, Linda F. Shoer,

Arthur D. Little, Inc., Cambridge, Massachusetts 02140

Louis S. Harris,[1] Sydney Archer,[2] Mario D. Aceto,[1] J. Pearl, and F. P. Luduena

Sterling-Winthrop Research Institute, Rensselaer, New York 12144. *Received May 20, 1977*

The 38 esters in Table I were prepared from the four isomeric 2-tropanols and a variety of racemic glycolic acids and their optical isomers. Anticholinergic activity in mice was measured in the peripheral nervous system (mydriasis) and in the central nervous system (anti-tremorine) and compared with that of atropine, scopolamine, and racemic 2-quinuclidinyl benzilate. The results (Table III) showed that several esters (such as **8**, **12**, **14**, and **21**) had significantly greater activity in both the peripheral and central nervous systems than did the reference compounds. Esters of (+)-2α-tropanol were more potent than those of either its epimer (−)-2β-tropanol or its optical isomer (−)-2α-tropanol. Esters derived from (−)-glycolic acids were uniformly more potent than those from the (+)-glycolic acids. Esters of (+)-2α-nortropanol and five of its N-substituted derivatives had markedly decreased activity. Peripheral/central activity ratios and time–activity profiles for five active compounds are discussed and compared with those of the reference compounds.

Anticholinergic drugs[3] have had for many years a variety of therapeutic applications, among which the best known is perhaps their use in the treatment of Parkinsonism.[4] The greatest peripheral and central anticholinergic activity appears to be that shown by the esters of certain amino alcohols and disubstituted glycolic acids such as benzilic acid. Originally,[3] interest in synthesis centered on glycolates derived from acyclic amino alcohols but subsequently much greater potency was discovered in the derivatives of cyclic amino alcohols such as 3-tropanol, the methylpiperidinols, and 3-quinuclidinol,[5] many of which are much more potent than atropine or scopolamine.

Our interest in this field was stimulated by the availability of (+)-2α-tropanol.[6] We realized that (+)-2α-tropanyl benzilate, as an ester of a β-hydroxyalkylamine, would be a weaker base than the corresponding 3-tropanyl benzilate and should therefore enter the CNS more readily. Clinical trials of (+)-2α-tropanyl benzilate in the treatment of Parkinsonism were carried out because the compound had low toxicity and the anticipated favorable ratio of central to peripheral activity. The trials, which involved oral doses as low as 0.005–0.007 mg/kg, were discontinued because of the appearance of characteristic side effects[7] such as intoxication and hallucinations.

The purpose of our work was to prepare the compounds shown in Table I to determine the effect structural and stereochemical changes had on the peripheral and CNS effects in the series.

The important relation between the stereochemistry and the biological activity of anticholinergic compounds is well known.[8] In the specific case of the amino alcohol esters, the importance of amino alcohol stereochemistry is shown by the fact that (−)-3-quinuclidinyl benzilate[9] is 20 times more potent than the (+) isomer and that esters of 3α-tropanol (such as atropine) are more potent than their 3β-epimers.[10,11] Similar stereochemical effects have been observed in our laboratories with other tropane alkaloids.[12-14]

The importance of the glycolic acid stereochemistry is illustrated by the fact that the 2-dimethylaminoethyl ester of (*R*)-(−)-cyclohexylphenylglycolic acid is 100 times more potent than the ester of the (*S*)-(+)-acid[15] and similar significant differences have been reported for other esters of these acids.[16,17]

The specific glycolic acids used by us were selected primarily because earlier workers had observed anticholinergic activity in esters of these acids with other amino alcohols.[3] The benzilate esters of (+)-2α-nortropanol and five of its N-substituted derivatives were examined because of references to the modified peripheral and CNS effects of N-substituted noratropines.[18,19] The times of onset and duration of peripheral and CNS anticholinergic effects were observed for five of the most active compounds and compared with those for racemic quinuclidinyl benzilate.

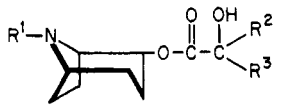
Chemistry. The 2-tropanyl glycolates in Table I were prepared by a conventional transesterification reaction between the appropriate 2-tropanol isomer and the methyl ester of the desired glycolic acid isomer; an example of the procedure is given in the Experimental Section. In the early part of the work, which was restricted to the preparation of esters of (+)-2α-tropanol, it was customary to react (+)-2α-tropanol with the methyl ester of the racemic glycolic acids and to work up the reaction mixture so as to obtain a mixture of both diastereoisomeric esters formed. In this way we were able to obtain preliminary pharmacological data for the ester and make it unnecessary to carry out optical resolutions of those acids whose esters had low potency. In the later part of the work, when it was apparent that tropanyl esters of specific glycolic acid stereoisomers were important, the preliminary preparation of tropanyl glycolates from racemic acids was omitted.

While working up (+)-2α-tropanyl esters of racemic glycolic acids, it soon became apparent that in most cases there was a great tendency for the diastereoisomers to separate; footnotes for compounds **5** and **6** describe specific examples of the tendency. As a rule, esters derived from (+)-2α-tropanol and (+)-glycolic acids could be recrystallized from *n*-hexane or *n*-heptane but were much too soluble in MeOH and EtOH. Conversely, esters derived from (+)-2α-tropanol and (−)-glycolic acids were easily recrystallized from the alcohols but were too soluble in hydrocarbon solvents. Thus, by appropriate use of solvents, it might have been possible to prepare each diastereoisomeric ester in high optical purity. We avoided this route in order to minimize handling of the very potent esters by laboratory personnel.

Optical resolution of the racemic glycolic acids was achieved by way of the (+)- and (−)-amphetamine salts (see Table II and Experimental Section). In the few cases where a comparison was possible the optical rotations observed were self-consistent. For example, compound **9**, derived from (+)-2α-tropanol and (+)-cyclopentylphenylglycolic acid, and compound **28**, derived from (−)-2α-tropanol and (−)-cyclopentylphenylglycolic acid, had equal rotations of opposite algebraic sign.

Pharmacology.[20] From among the pharmacological

Table I. 2-Tropanyl Glycolates[a]



Compd	R^1	R^2	R^3	2-Tropanol isomer	Glycolic acid isomer	Formula	Mp, °C	$[\alpha]_D$[b]
1	CH_3	C_6H_5	C_6H_5	(+)-2α		$C_{22}H_{25}NO_3$	135-137	+9.2
1a						$C_{22}H_{25}NO_3 \cdot HCl$	224-226	0[c]
2	CH_3	C_6H_5	C_6H_{11}	(+)-2α	(±)	$C_{22}H_{31}NO_3$	60-90	+18.5
3	CH_3	C_6H_5	C_6H_{11}	(+)-2α	(−)	$C_{22}H_{31}NO_3$	134-135	+4.8
4	CH_3	C_6H_5	C_6H_{11}	(+)-2α	(+)	$C_{22}H_{31}NO_3$	113-114	+37.0
5	CH_3	C_6H_5	C_4H_3S[d]	(+)-2α	(−)[e]	$C_{20}H_{23}NO_3S$	130-145	−2.3
6[f]	CH_3	C_6H_5	C_4H_3S[d]	(+)-2α	(+)	$C_{20}H_{23}NO_3S$	137-138	+21.4
7	CH_3	C_6H_5	C_5H_9	(+)-2α	(±)	$C_{21}H_{29}NO_3$	103-104	+25.0
8	CH_3	C_6H_5	C_5H_9	(+)-2α	(−)	$C_{21}H_{29}NO_3$	118-120	+12.3
9	CH_3	C_6H_5	C_5H_9	(+)-2α	(+)	$C_{21}H_{29}NO_3$	138-140	+33.2
10	CH_3	C_6H_5	C_4H_7	(+)-2α	(±)[g]	$C_{20}H_{27}NO_3$	120-124	+20.4
11	CH_3	C_6H_5	2-C_3H_7	(+)-2α	(±)	$C_{19}H_{27}NO_3$	113-115	+21.8
12	CH_3	C_6H_5	2-C_3H_7	(+)-2α	(−)	$C_{19}H_{27}NO_3$	134-136	−5.5
13	CH_3	C_6H_5	C_3H_5	(+)-2α	(±)[h]	$C_{19}H_{25}NO_3$	91-116	+18.0
14	CH_3	C_6H_5	C_3H_5	(+)-2α	(−)	$C_{19}H_{25}NO_3$	129-130	+7.5
15	CH_3	C_6H_5	C_3H_5[i]	(+)-2α	(±)	$C_{19}H_{25}NO_3$	102-118	+17.0
16	CH_3	C_6H_5	C_5H_7[j]	(+)-2α	(±)	$C_{21}H_{25}NO_3$	120-140	+24.0
17	CH_3	C_6H_5	$C_6H_3Cl_2$[k]	(+)-2α	(±)	$C_{22}H_{23}Cl_2NO_3$	132-135	±0.5
18	CH_3	C_6H_{11}	C_4H_3S[d]	(+)-2α	(−)	$C_{20}H_{29}NO_3S$	175-177	+12.3
19	CH_3	C_6H_{11}	C_4H_3S[d]	(+)-2α	(+)	$C_{20}H_{29}NO_3S$	139-145	+30.8
20	CH_3	C_5H_9	C_4H_3S[d]	(+)-2α	(±)	$C_{19}H_{27}NO_3S$	135-137	+24.2
21	CH_3	C_5H_9	C_4H_3S[d]	(+)-2α	(−)	$C_{19}H_{27}NO_3S$	150-152	+18.9
22	CH_3	C_5H_9	C_4H_3S[d]	(+)-2α	(+)	$C_{19}H_{27}NO_3S$	163-165	+29.8
23	CH_3	C_5H_9	C_3H_3[l]	(+)-2α	(±)	$C_{18}H_{27}NO_3$	110-137	+25.0
24	CH_3	C_6H_5	C_6H_5	(−)-2β		$C_{22}H_{25}NO_3 \cdot H_2O$[m]	60-80	−17.5
25	CH_3	C_6H_5	C_4H_3S[d]	(−)-2β	(±)	$C_{20}H_{23}NO_3S \cdot HCl$	272-277	+15.1[c]
26	CH_3	C_6H_5	C_5H_9	(−)-2β	(±)	$C_{21}H_{29}NO_3 \cdot HCl$	204-208	+11.5[n]
27	CH_3	C_6H_5	C_6H_5	(−)-2α		$C_{22}H_{25}NO_3$	137-139	−9.3
28	CH_3	C_6H_5	C_5H_9	(−)-2α	(−)	$C_{21}H_{29}NO_3$	138-140	−32.3
29	CH_3	C_6H_5	C_5H_9	(−)-2α	(+)	$C_{21}H_{29}NO_3$	118-120	−13.0
30	CH_3	C_6H_5	C_6H_5	(+)-2β		$C_{22}H_{25}NO_3 \cdot H_2O$	76-82	+16.5
31	CH_3	C_5H_9	C_4H_3S[d]	(+)-2β	(−)	$C_{19}H_{27}NO_3 \cdot HCl$	236-238	−5.0[n]
32	CH_3	C_5H_9	C_4H_3S[d]	(+)-2β	(+)	$C_{19}H_{27}NO_3S \cdot HCl$	223-235	−10.0[n]
33	H	C_6H_5	C_6H_5	(+)-2α		$C_{21}H_{23}NO_3$	158-159	+10.4
34	n-C_3H_7	C_6H_5	C_6H_5	(+)-2α		$C_{24}H_{29}NO_3$	69-71	−3.3
35	*o*	C_6H_5	C_6H_5	(+)-2α		$C_{24}H_{27}NO_3$	148-150	−2.8
36	*p*	C_6H_5	C_6H_5	(+)-2α		$C_{24}H_{25}NO_3$	128-129	−24.5
37	*q*	C_6H_5	C_6H_5	(+)-2α		$C_{24}H_{26}ClNO_3$	184-185	−19.5
38	*r*	C_6H_5	C_6H_5	(+)-2α		$C_{26}H_{29}NO_3$	99-101	−4.8

[a] With the exception of compounds **1**, **1a**, **20**, and **24** (ref 6), all compounds in the table are described for the first time. All compounds gave analytical values within 0.4% of theoretical values for C, H, and N and, where appropriate, for Cl and S. [b] Unless otherwise noted, rotations were observed in 1-dm tubes at ambient temperatures in dry CH_2Cl_2 at concentrations of 2-5%. [c] In H_2O. [d] 2-Thienyl. [e] Hydrolysis of **5** gave acid, $[\alpha]_D$ −11.5°, indicating additional enrichment in (−)-acid portion. [f] Prepared from racemic acid (ref 6); hydrolysis of **6** gave acid, $[\alpha]_D$ +14.2°, indicating significant enrichment in (+)-acid portion. [g] Hydrolysis of **10** gave acid, $[\alpha]_D$ +2.9°, indicating some enrichment in (+)-acid portion; the yield of **10** was almost quantitative so that its acid portion must have been essentially racemic. [h] Hydrolysis of **13** gave acid, $[\alpha]_D$ +2.5°, indicating some enrichment in (+)-acid portion; the yield of **13** was almost quantitative so that its acid portion must have been essentially racemic. [i] Isopropenyl. [j] 2-Methyl-1-buten-3-ynyl. [k] 3,4-Dichlorophenyl. [l] 1-Propynyl. [m] Hydrate stable at 20 °C (1 mm); anhydrous material could not be crystallized; for tosylate salt see ref 6. [n] In MeOH. [o] Allyl. [p] 2-Propynyl. [q] *trans*-3-Chloro-2-propenyl. [r] Cyclopropylmethyl.

data collected using the glycolates in Table I (for some compounds extensive preclinical pharmacology and toxicology data were collected), we have selected LD_{50} values, mydriasis ED_{50} values (as a measure of peripheral effects), and anti-tremorine[21] ND values (as a measure of CNS effects).[7a] Test protocols are described in the Experimental Section.

The data in Table III support the following conclusions.

(1) Glycolates of (+)-2α-tropanol are considerably more potent, both peripherally and centrally, than those derived from its epimer, (−)-2β-tropanol; compare **1** vs. **24**, **5** or **6** vs. **25**, and **7** vs. **26**.

(2) Glycolates derived from (+)-2α-tropanol are more potent mydriatics than those derived from its optical isomer, (−)-2α-tropanol; compare **1** vs. **27**, **8** vs. **28**, and **9** vs. **29**.

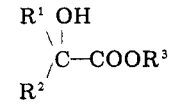
(3) In the single case observed, (+)-2β-tropanyl benzilate (**30**) is a stronger mydriatic than its epimer, (−)-2α-tropanyl benzilate (**27**); it is unfortunate that no analogous comparison can be made for the active compound **31**.

(4) Compound **30** is also a stronger mydriatic than its optical isomer, compound **24**.

(5) In all cases where a comparison is possible, esters derived from levorotatory glycolic acids are considerably more potent than those from racemic acids, which in turn are more potent than those derived from dextrorotatory acids. A similar observation has been made[15] for esters of (*R*)-(−)-cyclohexylphenylglycolic acid.

(6) Several compounds have significantly greater mydriatic activity than **1**, racemic quinuclidinyl benzilate, and atropine and have CNS activity equal or superior to these or to scopolamine. The therapeutic indices (in the CNS)

Table II. Glycolic Acids, Amphetamine Salts, and Methyl Esters



R^1	R^2	R^3	Ref	Acid isomer	Mp or bp (mm), °C	Formula	$[\alpha]_D$[a]
C_6H_5	C_6H_5	CH_3	b		71-72	$C_{15}H_{14}O_3$	
C_6H_5	C_6H_{11}	H	b	(±)	164-166	$C_{14}H_{18}O_3$	
(−)-Acid (−)-amphetamine salt			c			$C_{23}H_{31}NO_3$[d]	−27.5
(+)-Acid (+)-amphetamine salt			c			$C_{23}H_{31}NO_3$[d]	+27.2
C_6H_5	C_6H_{11}	H	c,e	(−)	140-142	$C_{14}H_{18}O_3$	−23.3
C_6H_5	C_6H_{11}	CH_3	c	(−)	51-52	$C_{15}H_{20}O_3$	−3.0
C_6H_5	C_6H_{11}	H	c,e	(+)	139-142	$C_{14}H_{18}O_3$	+24.6
C_6H_5	C_6H_{11}	CH_3	c	(+)	50-51	$C_{15}H_{20}O_3$	+1.0
C_6H_5	C_4H_3S[f]	H	g	(±)	120-123 dec	$C_{12}H_{10}O_3S$	
(−)-Acid (−)-amphetamine salt			c			$C_{21}H_{23}NO_3S$	−17.7
C_6H_5	C_4H_3S[f]	H	c,g	(−)	115-117	$C_{12}H_{10}O_3S$	−7.4
C_6H_5	C_4H_3S[f]	CH_3	c	(−)	51-55	$C_{13}H_{12}O_3S$	−5.0
C_6H_5	C_5H_9[h]	H	b	(±)	145-147	$C_{13}H_{16}O_3$	
C_6H_5	C_5H_9[h]	CH_3	b	(±)	109-110 (0.5)	$C_{14}H_{18}O_3$	
(−)-Acid (−)-amphetamine salt			c		193-195	$C_{22}H_{29}NO_3$[i]	−16.8
(+)-Acid (+)-amphetamine salt			c			$C_{22}H_{29}NO_3$[i]	+15.3
C_6H_5	C_5H_9[h]	H	c	(−)	119-120	$C_{13}H_{16}O_3$	−2.0
C_6H_5	C_5H_9[h]	CH_3	c	(−)	Oil	$C_{14}H_{18}O_3$	+9.3[j]
C_6H_5	C_5H_9[h]	H	c	(+)	115-116	$C_{13}H_{16}O_3$	+2.0
C_6H_5	C_5H_9[h]	CH_3	c	(+)	Oil	$C_{14}H_{18}O_3$	−9.5[j]
C_6H_5	C_4H_7[k]	CH_3	b	(±)	55-55.5	$C_{13}H_{16}O_3$	
C_6H_5	2-C_3H_7	H	l	(±)	145-150	$C_{11}H_{14}O_3$	
C_6H_5	2-C_3H_7	CH_3	l	(±)	34-38	$C_{12}H_{16}O_3$	
(−)-Acid (−)-amphetamine salt			c		189-192	$C_{20}H_{27}NO_3$[m]	−29.4
C_6H_5	2-C_3H_7	H	c	(−)	111-117	$C_{11}H_{14}O_3$	−27.0
C_6H_5	2-C_3H_7	CH_3	c	(−)	Oil	$C_{12}H_{16}O_3$	
C_6H_5	C_3H_5[n]	H	b	(±)	93-94	$C_{11}H_{12}O_3$	
C_6H_5	C_3H_5[n]	CH_3	c	(±)	Oil	$C_{12}H_{14}O_3$	
(−)-Acid (−)-amphetamine salt			c		180-181	$C_{20}H_{25}NO_3$[o]	−14.0
C_6H_5	C_3H_5[n]	H	c	(−)	75-81	$C_{11}H_{12}O_3$	−21.0
C_6H_5	C_3H_5[n]	CH_3	c	(−)	Oil	$C_{12}H_{14}O_3$	
C_6H_5	C_3H_5[p]	CH_3	q	(±)		$C_{12}H_{14}O_3$	
C_6H_5	C_5H_5[r]	CH_3	q	(±)	109-122 (0.003)	$C_{14}H_{14}O_3$	
C_6H_5	$C_6H_3Cl_2$[s]	H	c	(±)	118-121	$C_{14}H_{10}Cl_2O_3$[t]	
C_6H_5	$C_6H_3Cl_2$[s]	CH_3	c	(±)	79-84	$C_{15}H_{12}Cl_2O_3$[u]	
C_6H_{11}	C_4H_3S[f]	H	v	(±)	119-122	$C_{12}H_{16}O_3S$	
(+)-Acid (+)-amphetamine salt			c			$C_{21}H_{29}NO_3S$[w]	+11.6
(−)-Acid (−)-amphetamine salt			c			$C_{21}H_{29}NO_3S$[w]	−12.5
C_6H_{11}	C_4H_3S[f]	H	c	(−)	115-116	$C_{12}H_{16}O_3S$	−10.0
C_6H_{11}	C_4H_3S[f]	CH_3	c	(−)	Oil	$C_{13}H_{18}O_3S$	−2.4
C_6H_{11}	C_4H_3S[f]	H	c	(+)	118-119	$C_{12}H_{16}O_3S$	+10.5
C_6H_{11}	C_4H_3S[f]	CH_3	c	(+)	Oil	$C_{13}H_{18}O_3S$	+2.4
C_5H_9[h]	C_4H_3S[f]	H	x	(±)	120-121	$C_{11}H_{14}O_3S$	
C_5H_9[h]	C_4H_3S[f]	CH_3	c	(±)	106-117 (0.3)	$C_{12}H_{16}O_3S$	
(+)-Acid (+)-amphetamine salt			c		192-193 dec	$C_{20}H_{27}NO_3S$[y]	+2.0
(−)-Acid (−)-amphetamine salt			c		192-193 dec	$C_{20}H_{27}NO_3S$	−2.1
C_5H_9[h]	C_4H_3S[f]	H	c	(−)	95-97	$C_{11}H_{14}O_3S$	−51.0[z]
C_5H_9[h]	C_4H_3S[f]	CH_3	c	(−)	Oil	$C_{12}H_{16}O_3S$	+4.8
C_5H_9[h]	C_4H_3S[f]	H	c	(+)	94-100	$C_{11}H_{14}O_3S$	+51.3[z]
C_5H_9[h]	C_4H_3S[f]	CH_3	c	(+)	Oil	$C_{12}H_{16}O_3S$	−4.9
C_5H_9[h]	C_3H_3[aa]	C_2H_5	q	(±)	Oil	$C_{12}H_{18}O_3$	

[a] Rotations were observed in 1-dm tubes at ambient temperature in dry MeOH at concentrations of 2-5%; an exception was the isomers of cyclohexylphenylglycolic acid, whose rotations were observed in EtOH at 5% in order to duplicate literature values. [b] Commercially available. [c] Procedure in Experimental Section. [d] Anal. C, H. [e] Previously resolved by S. G. Kuznetsov and Z. I. Bolysheva, *Zh. Obshch. Khim.*, 32, 3779 (1962), and in ref 16 where other earlier resolutions are cited and where the *R* configuration is assigned to the (−) isomer. [f] 2-Thienyl. [g] A. Fredga, K. Aejmalaeus, and B. Tollander, *Ark. Kemi*, 3, 331 (1951); we confirm the authors' caution against exposing the compound to light. The completely resolved (−) isomer was reported to have $[\alpha]_D$ −28° (EtOAc). [h] Cyclopentyl. [i] Anal. C, H, N. [j] The rotations of the acid and its methyl ester have opposite algebraic signs. [k] Cyclobutyl. [l] H. Najer and R. Guidicelli, *Bull. Soc. Chim. Fr.*, 1907 (1961). [m] Anal. C, H, N. [n] Cyclopropyl. [o] Anal. C, H, N. [p] Isopropenyl. [q] Gift from Dr. Hugo Stange, FMC Corp. [r] 3-Methyl-3-buten-1-ynyl. [s] 3,4-Dichlorophenyl. [t] Prepared by hydrolysis of methyl ester; neutral equiv, 300. [u] Anal. C, H, Cl. [v] F. F. Blicke and M. U. Tsao, *J. Am. Chem. Soc.*, 66, 1645 (1944). [w] Anal. C, H, N. [x] F. F. Blicke, U.S. Patent 2 541 634 (1951). [y] Anal. C, H, N. [z] Rotations were observed at 350 nm because $[\alpha]_D$ values were zero within experimental error. [aa] 1-Propynyl.

of compounds **8**, **12**, **14**, and **21** are much higher than those of **1**, atropine, and scopolamine. The activity of **12** shows that at least one radical in the glycolic acid portion may be alkyl.

(7) Benzilates of (+)-2α-nortropanol (**33**) and its N-substituted derivatives **34–38** are significantly less active than that of (+)-2α-tropanol (**1**).

(8) While the data for compound **1** and a few others are in accord with a generalization[22,23] that anticholinergic glycolates are two to three times more active in the CNS

Table III. Peripheral and Central Effects of 2-Tropanyl Glycolates

Compd in Table I	Mydriasis, ED_{50}, mg/kg (sc), mouse[a]	Anti-tremorine, ND, mg/kg (sc), mouse[a]	LD_{50}, mg/kg (iv), mouse[a] (fiducial limits)
1, 1a	0.05	0.03	14 (12-18)
2	0.17	0.12	
3	0.07	0.03	50 (32-80)
4	1.1	0.77	40 (18-89)
5	0.02	0.02	20 (16-25)
6	0.03	0.03	20 (16-25)
7	0.04	0.05	71 (56-89)
8	0.016	0.03	50 (40-63)
9	0.76	0.35	36 (25-50)
10	0.04		56 (40-79)
11	0.04		56 (45-71)
12	0.023	0.027	63 (50-79)
13	0.02	0.04	50 (40-63)
14	0.016	0.029	63 (50-79)
15	0.077	0.16	50 (40-63)
16	0.14		25 (20-32)
17	1.8	2.0	36 (28-45)
18	0.05	0.03	56 (40-79)
19	0.18	0.20	56 (45-71)
20	0.04	0.03	56 (45-71)
21	0.015	0.02	71 (56-89)
22	0.15	0.5-1.0	36 (28-45)
23	0.14		79 (63-100)
24	1.4	1.75	32 (25-40)
25	0.57	0.72	40 (32-50)
26	14.4	0.8	71 (56-89)
27	0.52		32 (25-40)
28	0.05		32 (25-40)
29	6.1		56 (18-180)
30	0.33		18 (14-22)
31	0.02		63 (50-79)
32	0.77		36 (28-45)
33	0.08		22 (16-32)
34	0.1		16 (13-20)
35	0.3	0.56	20 (16-25)
36	1.7		71 (50-100)
37	>8	>10	1 (great)
38	0.1		11 (8.9-14.0)
(±)-Quinuclidinyl benzilate	0.05	0.16	25 (20-32)
Atropine	0.061	2.2	32 (10-100)
Scopolamine	0.012	1.3	100 (32-316)

[a] Dose calculated as free base.

than peripherally,[24] some of our most active compounds (such as 8 and 21) have reversed activity, as does quinuclidinyl benzilate. None of the compounds shows the large peripheral/central ratios of atropine and scopolamine. The variations have been ascribed[24] to differing abilities of the esters to penetrate to active sites. A more detailed analysis of peripheral/central ratios requires consideration of the fact that the time–activity profiles for the compounds also vary (see Table IV) so that a comparison of the ratios based on activity at a fixed time may be misleading.

Time–activity profiles for five compounds and for quinuclidinyl benzilate are reported in Table IV. It is apparent that compounds 1, 12, and 14 have shorter times to onset and shorter durations than do the other three, which require about 1 h to reach peak activity. No significant differences in times to onset were observed between mydriatic and anti-tremorine effects; a similar observation with 30 other anticholinergic compounds has been reported,[25] where the important feature was said to be the affinity constant of the drug rather than its partition properties. Following the testing described in Table IV, all animals were normal when next examined 24 h post-administration.

Experimental Section

Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and by the late Dr. S. M. Nagy (Belmont, Mass.). Analyses indicated only by symbols of the elements were within 0.4% of the theoretical values; satisfactory analyses were obtained for all compounds in Table I and for all novel compounds in Table II. In the case of some intermediates, analyses were omitted when satisfactory analytical data were obtained for derived products. Satisfactory IR, UV, and NMR spectra were recorded for all novel compounds synthesized in this work.

2-Tropanols. (+)-2α-Tropanol and (−)-2β-tropanol were prepared from cocaine.[26] (−)-2α-Tropanol and (+)-2β-tropanol were derived from racemic 2α-tropanol by optical resolution and epimerization.[27]

(+)-2α-Tropanyl Acetate. A modified literature procedure[28] gave the free base (94%) as a colorless oil: bp 72–76 °C (1.3 mm); $[\alpha]^{21}_D$ +47.5° (c 2, EtOH). Anal. ($C_{10}H_{17}NO_2$) C, H, N.

(−)-*N*-Cyanonor-2α-tropanyl Acetate. The crude product of a von Braun procedure[29] was distilled at 0.6 mm to give an 84% yield of material, bp 137–143 °C. Recrystallization from hexane gave colorless plates: mp 53–53.5 °C; $[\alpha]_D$ −68.4° (c 2, $CHCl_3$). Anal. ($C_{10}H_{14}N_2O_2$) C, H, N.

(+)-2α-Nortropanol. Acidic hydrolysis of the cyano compound was avoided in order to prevent possible racemization. In a typical run 10 g (0.052 mol) of (−)-*N*-cyanonor-2α-tropanol was dissolved under N_2 in 200 mL of a 2 N solution of KOH in 50% aqueous EtOH. After standing for 2 h at room temperature the mixture was refluxed under N_2 for 20 h. A conventional work-up gave 75%: mp 169–179 °C (CH_2Cl_2); $[\alpha]^{20}_D$ +16.8° (c 1, $CHCl_3$). Anal. ($C_7H_{13}NO$) C, H, N.

The optical integrity of (+)-2α-nortropanol was established by its reconversion to (+)-2α-tropanol, identical with an authentic sample, using a modified[30] Clark–Eschweiler methylation procedure.

(+)-*N*-*n*-Propyl-2α-nortropanol. A mixture of 3 g (0.024 mol) of (+)-2α-nortropanol, 2.8 g (0.023 mol) of *n*-propyl bromide, 3 g of anhydrous Na_2CO_3, and 100 mL of absolute EtOH was refluxed under N_2 for 24 h. The mixture was filtered and evaporated to give 6 g of a semisolid residue, which was leached with 3 × 50 mL of boiling hexane. The leachings were evaporated and the residual oil was distilled to give 2.94 g of a colorless oil: bp 75–76 °C (0.2 mm); $[\alpha]^{24}_D$ +1.4° (c 1, $CHCl_3$). Anal. ($C_{10}H_{19}NO$) C, H, N.

Table IV. Onset and Duration of Mydriasis and Anti-tremorine Effects

Min, post-medication	Mydriasis, ED_{50}, mg/kg (sc), mouse[a]						Anti-tremorine, ND, mg/kg (sc), mouse[a]					
	1	8	12	14	21	(±)-Quinuclidinyl benzilate	1	8	12	14	21	(±)-Quinuclidinyl benzilate
15	0.10	0.042	0.024	0.016	0.027	0.078						
30	0.12	0.021	0.022	0.022	0.014	0.042	0.025	0.027	0.027	0.029	0.018	0.16
60	0.25	0.012	0.040	0.062	0.011	0.040	0.24	0.017	0.14	0.56	0.013	0.046
120	1.04	0.010	0.16	0.31	0.011	0.041	1.5	0.016	0.33	0.57	0.010	0.059
240	⩾1.6	0.009	>0.80	>0.80	0.012	0.047	5.0	0.012	1.7	5.7	0.15	0.14
360		0.022			0.02	0.066						

[a] Dose calculated as free base.

(+)-*N*-Allyl-2α-nortropanol was prepared similarly and obtained (67%) as a light-sensitive oil: bp 86–87 °C (0.1 mm); $[\alpha]^{22}_D$ +16.9° (*c* 1, $CHCl_3$). Anal. ($C_{10}H_{17}NO$) C, H, N. A picrate salt had mp 90–91 °C (hexane). Anal. ($C_{16}H_{20}N_4O_8$) C, H, N.

(-)-*N*-(2-Propynyl)-2α-nortropanol was prepared similarly and obtained (55%) as a pale yellow solid: mp 92–94 °C (hexane); $[\alpha]^{21}_D$ -1.0° (*c* 1, $CHCl_3$). Anal. ($C_{10}H_{15}NO$) C, H, N.

(-)-*N*-(*trans*-3-Chloro-2-propenyl)-2α-nortropanol was prepared similarly using a sample of 1,3-dichloro-1-propene (90% trans) that was available from other work. The crude solid product was sublimed at 0.1 mm and a crop, mp 117–120 °C, was recrystallized from hexane to give colorless solid (60%): mp 120–120.5 °C; $[\alpha]^{22}_D$ -5.0° (*c* 1, $CHCl_3$). Anal. ($C_{10}H_{16}ClNO$) C, H, Cl, N.

***N*-Cyclopropanecarbonyl-2α-nortropanyl Cyclopropanecarboxylate.** (+)-2α-Nortropanol was acylated by excess cyclopropanecarbonyl chloride in benzene–pyridine in a conventional process to give (81%) a colorless solid: mp 51–52 °C (hexane). Anal. ($C_{15}H_{21}NO_3$) C, H, N.

(+)-*N*-Cyclopropylmethyl-2α-nortropanol. The preceding compound was reduced by $LiAlH_4$ in dry ether to give (69%) a colorless solid: mp 73–74 °C; $[\alpha]^{25}_D$ +12.2° (*c* 1, CH_2Cl_2). Anal. ($C_{11}H_{19}NO$) C, H, N.

Glycolic Acids and Methyl Esters. The racemic acids listed in Table II were obtained from the sources indicated there or as follows.

Methyl 3,4-Dichlorobenzilate. Ethyloxalyl chloride and *o*-dichlorobenzene were allowed to react under conventional Friedel–Crafts conditions, using excess *o*-dichlorobenzene as a solvent, to give **3,4-dichlorophenylglyoxylic acid** (73%) obtained either as a monohydrate (mp 50–52 °C, neutral equiv 242) or as a hemihydrate (mp 92–94 °C, neutral equiv 230). Ethereal diazomethane converted the acid to **methyl 3,4-dichlorophenylglyoxylate,** mp 53–57 °C (petroleum ether).

A Grignard reagent prepared from 6.8 g (0.28 mol) of Mg, 47 g (0.30 mol) of C_6H_5Br, and 200 mL of Et_2O was stirred into a solution of 50 g (0.21 mol) of methyl 3,4-dichlorophenylglyoxylate in 200 mL of Et_2O at 0 °C. The mixture was stirred overnight at room temperature, refluxed for 1 h, and then worked up in the usual way to give 16 g (25%), mp 79–84 °C (EtOH).

Optical Resolution of Glycolic Acids. In a typical resolution procedure a solution of 40 g (0.182 mol) of racemic cyclopentylphenylglycolic acid in 500 mL of EtOAc was neutralized at the boil with a solution of 25 g (0.185 mol) of (+)-amphetamine in 200 mL of EtOAc. The (+)-acid (+)-amphetamine salt was collected after standing overnight at room temperature. The 34 g so obtained was recrystallized to constant optical rotation from EtOH (12 mL/g) to give 13.7 g, which was then suspended in 100 mL of H_2O and treated with 6 N NaOH to decompose it. The basic solution was extracted with ether to recover (+)-amphetamine and then acidified with 6 N HCl to precipitate the (+)-cyclopentylphenylglycolic acid.

The mother liquors from the preparation of the (+)-acid (+)-amphetamine salt were evaporated to dryness and the crude (-)-acid (+)-amphetamine salt so obtained was decomposed as above to give crude (-)-acid. This was in turn converted to the (-)-acid (-)-amphetamine salt by neutralization with (-)-amphetamine; the salt was recrystallized to constant rotation and then was decomposed to give optically pure (-)-acid.

Methyl Glycolates. In all cases listed in Table II the methyl esters were prepared by adding a slight excess of ethereal diazomethane to an ether solution of the acid and then evaporating the mixture to dryness. The esters so obtained were used without additional purification.

2-Tropanyl Glycolates. In a typical transesterification reaction methyl (-)-cyclopentylphenylglycolate (55 g, 0.23 mol) was dissolved in 500 mL of dry *n*-heptane and 50 mL of the solvent was distilled off to remove any moisture present. To the cooled solution there was added 34 g (0.24 mol) of (+)-2α-tropanol, 250 mL of dry *n*-heptane, and 1.3 g (0.024 mol) of 85% NaOMe. The mixture was heated to reflux and MeOH evolved was collected as the overhead temperature rose from 64 to 98 °C during 45 min. *n*-Heptane was then allowed to distil freely until the volume of the reaction mixture decreased to about 450 mL. The mixture was cooled and then stirred into a cold mixture of 80 mL of concentrated HCl and 320 mL of H_2O. The *n*-heptane layer was additionally extracted with two 50-mL portions of cold dilute acid. The combined acid layers were cooled, made basic by adding cold 2 N NaOH, and extracted with four 150-mL portions of CH_2Cl_2. The extract was washed with two 150-mL portions of water, was dried over Na_2SO_4, and was then evaporated until crystallization of the tropanyl ester began. Boiling *n*-hexane (800 mL) was added and the homogeneous solution allowed to stand overnight until crystallization was complete. The first crop pf crystals was 53.8 g, mp 118–120 °C, and a second crop, obtained by concentrating the filtrate to 300 mL, was 11.5 g, mp 117–119 °C. The combined crops represented an 83% conversion.

The original *n*-heptane layer contained unreacted methyl ester. It was evaporated to dryness and the residual oil hydrolyzed to recover 4 g of (-)-cyclopentylphenylglycolic acid. The yield of 2-tropanyl ester thus became 90%.

In smaller scale work no attempt was made to follow the evolution of MeOH by means of the overhead temperature. Slow distillation of the reaction mixture was continued until the expected volume of MeOH was collected in a Dean-Stark trap and then for an additional 1–2 h until the reaction mixture decreased to about half its original volume. In a few cases, ten times the stated amount of NaOMe was used to hasten the conversion.

When it was desirable to check the optical integrity of the 2-tropanyl esters, samples were hydrolyzed by refluxing in dilute NaOH or dilute Na_2CO_3 and worked up in the usual way. In no case was racemization or epimerization involved in either the recovered 2-tropanol (by GC and $[\alpha]_D$) or in the recovered glycolic acid (by melting point and $[\alpha]_D$).

Animal Test Procedures. The LD_{50} values reported in Table III were collected as part of a modified[31] Irwin mouse profile,[32] in which the reactive sign at the minimum effective dose was mydriasis in almost all cases. More exact mydriatic data (Table III) were obtained using male albino mice, the drug being administered in normal saline at pH 4–5 to ten animals per dose at each of three logarithmically spaced doses. The pupillary diameter was measured at 5-min intervals for 30 min with a binocular microscope having a scale in the eyepiece. A standard 10 mg/kg dose of atropine was similarly administered to a control group and gave the maximum dilation. The maximum dilation caused by each dose of the drug during the 30-min period was compared to the maximum observed in the atropine controls and results were recorded as percent maximum dilation. The ED_{50}, the dose causing 50% of maximum dilation, was determined by the Miller–Tainter probit method.[33]

The reversal of tremorine-induced psychomotor depression in mice (Table III, anti-tremorine, ND) was measured using a photocell activity cage[34] containing five male albino mice. Nonmedicated control animals gave a cumulative 30-min group count of approximately 260 beam crossings. A standard 10 mg/kg sc dose of tremorine decreased the spontaneous activity by approximately 80%. The drug under test was given to a total of ten mice per dose at each of three or more logarithmically spaced doses, the drug being administered sc immediately following administration of tremorine. After a standard 10-min waiting period, activity was measured in the activity cage for 30 min and was plotted against the logarithm of the dose administered. The ND (normalizing dose), which was needed to reverse completely the tremorine-induced depression, was estimated from the graph.

For the mydriatic time–activity profile data reported in Table IV, the pupillary diameter was measured before medication and then at the subsequent indicated times. Maximum observed dilation was plotted against the logarithm of the dose administered. The ED_{50} value (the dose producing half-maximum dilation) was estimated from the graph.

For the anti-tremorine time–activity profile data reported in Table IV, animals were challenged with 10 mg/kg sc of tremorine at the stated times and their activity during 30 min was observed following a standard 10-min waiting period as described above.

Acknowledgment. We wish to thank Jacqueline K. Keller, Pamela L. Russ, Dr. Robert Stern, Dr. Richard N. Macnair, and William C. Lumma for assistance in chemical synthesis. Professor Robert E. Lyle was a consultant to the program.

References and Notes

(1) Present address: Department of Pharmacology, Medical College of Virginia, Richmond, Va.
(2) Present address: Department of Chemistry, Rensselaer Polytechnic Institute, Troy, N.Y.
(3) For reviews see (a) B. V. Rama Sastry in "Medicinal Chemistry", A. Burger, Ed., 3rd ed, Wiley-Interscience, New York, N.Y., 1970, p 1544; (b) R. W. Brimblecombe, "Drug Actions on Cholinergic Systems", University Park Press, Baltimore, Md., 1974.
(4) E. L. Engelhardt and C. A. Stone in ref 3a, p 1538.
(5) For summaries see L. Albanus, *Acta Pharmacol. Toxicol.*, **28**, 305 (1970); M. D. Mashkovsky and L. N. Yakhontov, *Drug Res.*, **13**, 293 (1969).
(6) S. Archer and M. R. Bell, U.S. Patent 3 145 210 (1964).
(7) (a) R. W. Brimblecombe and R. M. Pinder, "Hallucinogenic Agents", Wright-Scientechnica, Bristol, 1975, p 44; (b) p 185; (c) p 250.
(8) A. F. Casy in ref 3a, p 81.
(9) A. Meyerhöffer, *J. Med. Chem.*, **15**, 994 (1972).
(10) R. J. Hunt and J. B. Robinson, *J. Pharm. Pharmacol.*, **24**, 324 (1972).
(11) D. F. Biggs, A. F. Casy, and W. K. Jeffery, *J. Med. Chem.*, **15**, 506 (1972).
(12) S. J. Daum, M. D. Aceto, and R. L. Clarke, *J. Med. Chem.*, **16**, 667 (1973).
(13) R. L. Clarke, S. J. Daum, A. J. Gambino, M. D. Aceto, J. Pearl, M. Levitt, W. R. Cumiskey, and E. F. Bogado, *J. Med. Chem.*, **16**, 1260 (1973).
(14) S. J. Daum, C. M. Martini, R. K. Kullnig, and R. L. Clarke, *J. Med. Chem.*, **18**, 496 (1975).
(15) R. W. Brimblecombe, D. M. Green, T. D. Inch, and P. B. J. Thompson, *J. Pharm. Pharmacol.*, **23**, 745 (1971).
(16) R. B. Barlow, F. M. Franks, and J. D. M. Pearson, *J. Med. Chem.*, **16**, 439 (1973).
(17) T. D. Inch and R. W. Brimblecombe, *J. Pharm. Pharmacol.*, **23**, 813 (1971).
(18) L. Decsi and K. Nador, *Arzneim.-Forsch.*, **13**, 567 (1963).
(19) R. Banholzer, A. Hausner, O. Korndoeffer, W. Schulz, G. Walther, and K. Zeite (to Boehringer Ingelheim G.m.b.H.), S. African Patent 67 05 252 (1968).
(20) In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals", as promulgated by the Committee on Revision of the "Guide for Laboratory Animals, Facilities and Care" of the Institute of Laboratory Animal Resources, National Research Council.
(21) Merck Index, 8th ed, Merck and Co., Rahway, N.J., 1968, p 1064.
(22) S. N. Golikov, E. P. Zatsepin, M. A. Levshunova, and S. I. Loktinov, *Farmakol. Tsentr. Kholinolitikov Drugikh Neirotropnykh Sredstv.*, 10 (1969); *Chem. Abstr.*, **73**, 118697 (1970).
(23) S. N. Golikov, *Aktual, Probl. Farmakol. Farm., Vses. Nauchn. Konf.*, 33 (1971); *Chem. Abstr.*, **76**, 4 (1972).
(24) R. W. Brimblecombe and D. M. Green, *Int. J. Neuropharmacol.*, **7**, 15 (1968), report that *N*-ethyl-3-piperidyl benzilate is in this category.
(25) T. D. Inch, D. M. Green, and P. B. J. Thompson, *J. Pharm. Pharmacol.*, **25**, 359 (1973).
(26) M. R. Bell and S. Archer, *J. Am. Chem. Soc.*, **82**, 4642 (1960).
(27) E. R. Atkinson and D. D. McRitchie, *J. Org. Chem.*, **36**, 3240 (1971); Chemical Abstracts currently indexes the isomers as 8-azabicyclo[3.2.1]octan-2-ol, 8-methyl; (+)-2α-tropanol is 1*R*, endo; (−)-2α-tropanol is 1*S*, endo; (−)-2β-tropanol is 1*R*, exo; (+)-2β-tropanol is 1*S*, exo.
(28) S. Archer, T. R. Lewis, M. R. Bell, and J. W. Schulenberg, *J. Am. Chem. Soc.*, **83**, 2386 (1961).
(29) H. A. Hageman, *Org. React.*, **7**, 229 (1953).
(30) M. L. Moore, *Org. React.*, **5**, 232 (1949).
(31) W. J. Lennox, *U.S.C.F.S.T.I., AD Rep.*, 852897 (1969).
(32) S. Irwin, *Psychopharmacologia*, **13**, 222 (1968).
(33) L. C. Miller and M. L. Tainter, *Proc. Soc. Exp. Biol. Med.*, **57**, 261 (1944).
(34) L. S. Harris and F. C. Uhle, *J. Pharmacol.*, **132**, 251 (1961).

Potent Reversible Anticholinesterase Agents. Bis- and Mono-N-substituted Benzoquinolinium Halides

Wen-Sherng Chen, George H. Cocolas,* Chester J. Cavallito, and Kyung Ja Chai

School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina 27514. *Received July 7, 1975*

A number of bis- and mono-N-substituted benzoquinolinium salts and their analogues were prepared and evaluated as inhibitors of acetylcholinesterase (AcChE) and butyrylcholinesterase (BuChE). These compounds were also used to help identify some of the morphologic characteristics of the surface at or near the active sites of the cholinesterases. The shape, size, configuration, and conformation of the onium moieties of the quaternary ammonium compounds were found to be the important factors in their anticholinesterase activity. A high concentration of the positive charge of the quaternary ammonium compound is not a critical factor for the cholinesterase inhibitory activity. The order of decreasing potency of cholinesterase inhibition of the benzoquinolinium compounds was found to be acridinium > phenanthridinium > 5,6-benzoquinolinium > 7,8-benzoquinolinium. The inhibitory activity of the monobenzoquinolinium halides against cholinesterases is influenced by the N-substituent. A bis-quaternary ammonium compound with a flexible bridge that links the two nitrogen atoms was found to be more potent in inhibiting AcChE and less potent in inhibiting BuChE than a bis-quaternary ammonium compound with a rigid bridge. The acridinium and phenanthridinium derivatives of the benzoquinolinium compounds are very potent reversible inhibitors against both AcChE and BuChE.

A variety of mono- and bis-quaternary ammonium compounds has been described as reversible inhibitors of the esterolytic activity of both acetylcholinesterase (AcChE) and butyrylcholinesterase (BuChE).[1] It is assumed that these compounds interact by coulombic attraction with one or more of the anionic sites that exist on the enzymes. The more potent inhibitors are believed[1-4] to interact with the anionic site associated with the esteratic site while other inhibitors such as decamethonium, *d*-tubocurarine, and gallamine have been indicated to act on other sites on AcChE designated as β- or γ-anionic sites.[5-7] The mono-quaternary compounds are generally weaker inhibitors than their bis-quaternary counterparts. This lends support to the view that more than one anionic site may exist on the cholinesterases. In general, polymethylene bis-quaternary ammonium salts, **1**, show an increase in anticholinesterase activity as the length of the methylene chain separating the nitrogen atoms increas-