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Synthesis and Preliminary Pharmacological Activity of Aminoalkoxy Isosteres of Glycolate Ester Anticholinergics

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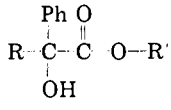
A series of 2-(N-substituted amino)alkoxy-1,1-diphenylethanols was synthesized and evaluated for anticholinergic activity. The compounds differ structurally from the glycolate ester-type anticholinergic compounds by the bioisosteric substitution of a methylene group for the ester carbonyl moiety. The ethers which result from this change have increased lipophilicity compared to their ester isosteres. Compounds in the series have significant anticholinergic activity when tested on isolated rat jejunum or for their ability to inhibit perphenazine-induced catatonia in rats. Structure–activity relationships of the compounds are discussed.

The glycolate esters 1 are a series of agents which have received considerable attention.[1-4] These agents produce a variety of pharmacological effects which are typical of peripheral and central muscarinic receptor blockage.[1,5] As a result of their activities, the glycolates have been reported effective as antispasmodic,[6,7] antidepressant,[8,9] antiparkinsonian,[10] and anticonvulsant[5] drugs.

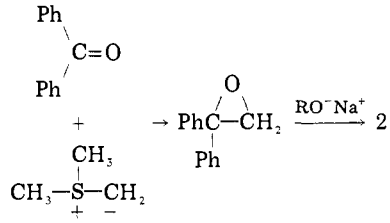


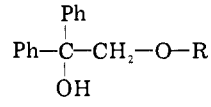
1, R = phenyl or cycloalkyl; R′ = dialkylaminoalkyl or alkyl heterocyclic amino

Despite their wide variety of activity, the central anticholinergic effects of the glycolates have not been applied clinically. Major problems associated with use of these agents are their unfavorable peripheral to central anticholinergic activity ratios[11] and probably more significant is their potential to produce psychotomimetic episodes.[1] The degree to which useful central activity is associated with the ability of the drugs to block peripheral muscarinic receptors is not clear. Compounds with potent antispasmodic activity will generally produce CNS effects;[12] however, the correlation between the peripheral and central activities is not good.[1,13] Furthermore, there are few studies which attempt to differentiate or separate the different types of CNS effects produced by anticholinergic agents. Thus, in designing new compounds with potentially useful central anticholinergic activity, one should attempt to prepare agents which possess a high degree of central activity compared to their peripheral activity and, if possible, a low degree of psychotomimetic activity.[10]

In an effort to investigate further the structure–activity relationships of anticholinergics we have synthesized and obtained preliminary pharmacological results on a series of substituted aminoalkoxy-1,1-diphenylethanol derivatives **2**. This series differs from the glycolate esters only in the replacement of the ester carbonyl with a methylene moiety. This bioisosteric replacement should result in (1) compounds of greater lipophilicity and thus greater ability to penetrate the blood brain barrier and (2) compounds with a greater duration of action resulting from the inability of serum and tissue esterases to metabolize the ethers. It is conceivable that agents with a longer biological half-life and a greater potential to reach the CNS might result in a favorable shift in their peripheral to central activity ratio.

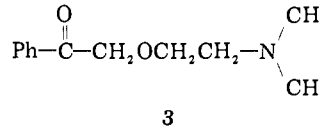
Scheme I





2, R = dialkylaminoalkyl or alkyl heterocyclic amino

Chemistry. Previous attempts to synthesize these ethers by the classical Williamson method or by addition of phenyllithium to **3**, although partially successful, were tedious and produced poor yields.[14] The alternative route outlined in Scheme I was used to prepare the compounds. The near quantitative yield of 2,2-diphenyloxirane, obtained by reacting trimethylsulfonium ylide[15] with benzophenone, and the commercial availability of a number of amino alcohols made this route extremely attractive. When the alkoxide opening of the oxirane intermediate was carried out at temperatures above 70 °C considerable methylsulfinyl methylide addition occurred to give **4**. The opening of the oxirane to give tertiary alcohols was confirmed by the failure of the products (**2**) to be oxidized by chromic acid[16] and by the singlet carbinol peak observed when the NMR spectra of **2** were determined in anhydrous Me_2SO-d_6.[17]



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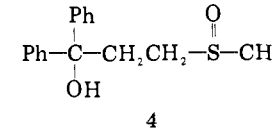

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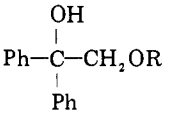
Pharmacology. Peripheral anticholinergic (antispasmodic) activity was determined on isolated rat jejunum.

Table I. Antispasmodic and Anticataleptic Activities of 2-[(N-Substituted amino)alkoxy]-1,1-diphenylethanols



		pD′$_2$ value, isolated rat jejunum[a]		% inhibn of perphenazine-induced catatonia[b]			
				0.5 h	1 h	2 h	3 h
Scopolamine hydrobromide		5.31		96	96	83	71
Atropine hydrobromide		7.3		87	56	30	27
Benztropine mesylate		5.35		60	56	27	19
No.	R	Methiodide[c]	HCl				
5	$CH_2CH_2N(CH_3)_2$	5.49	4.68	75	21	21	8
6	$CH_2CH_2N(C_2H_5)_2$	6.92	4.92	38	0	0	0
7	$CH_2CH_2CH_2N(CH_3)_2$		5.02	100	71	54	17
8	$CH_2CH_2N(CH_3)(CH_2CH=CH_2)$		4.09	79	25	17	0
9	$CH_2CH_2N(C_2H_5)(CH_2CH=CH_2)$		5.13	8	0	0	0
10	*N*-Methyl-3-pyrrolidyl		5.58	50	21	8	0
11	*N*-Methyl-3-piperidyl	5.68	4.90	92	67	54	17
12	*N*-Ethyl-3-piperidyl	5.00	4.95	12	0	0	0
13	*N*-Methyl-4-piperidyl	7.26	6.24	80	37	7	0
14	3-Quinuclidyl	6.18	6.58	96	85	56	48

[a] Determined by single dose of agonist method (ref 18). [b] The ability of a 2 mg/kg (ip) dose of test agent (as HCl salt) to inhibit the catatonia induced by a standard 5 mg/kg (ip) dose of perphenazine (ref 19). [c] A blank indicates that samples were not prepared or tested.

Table II. Ranking of Inhibition of Perphenazine-Induced Catatonia by 2 mg/kg Dose of Test Agent[a]

0.5 h	1 h	2 h	3 h
7	Scopolamine	Scopolamine	Scopolamine
Scopolamine	14	14	14
14	7	11	Atropine
11	11	7	Benztropine
13	Benztropine	Atropine	11
8	Atropine	Benztropine	7
5	12	5	5
Atropine	8	8	6
Benztropine	5	10	13
10	10	13	10
6	6	6	12
12	12	12	8
9	9	9	9

[a] Brackets designate values which are not statistically different from each other as determined by Duncan's multiple range test ($p < 0.05$; ref 20).

The pD′$_2$ values reported are averages of from four to six determinations performed on fresh jejunum strips.[18] An analysis of variance was run on the pD′$_2$ values. The statistical analysis revealed that the observed differences between the activities of the various compounds were highly significant when based on a probability level (p) less than 0.01. Results are listed in Table I.

The agents were screened in rats for their ability to relieve the catatonia which was induced by perphenazine. The procedure described by Morpurgo[19] was followed. The activities (Table I) are reported as the percent to which the test agents inhibit the catatonia caused by perphenazine when compared to rats injected with perphenazine alone. An analysis of variance run on the catatonia-inhibition values revealed that there are highly significant ($p < 0.01$) differences among the observed activities at each time period. To determine which of the compounds possessed statistically different activities, a Duncan's multiple range test[20] was used ($p < 0.05$). The results of this test are given in Table II.

It is possible that the reversal of the perphenazine catatonia could be due to a dopaminergic action of the test compounds; however, the known peripheral anticholinergic activity of these compounds, coupled with the known ability of cholinolytics to reverse neuroleptic-induced catatonia,[19] suggests that the agents are acting by a central anticholinergic mechanism. To further eliminate the possibility of a dopaminergic mechanism, the compounds were tested in rabbits for their ability to alter colonic temperature. These experiments were carried out on male New Zealand rabbits (J. E. Nicely Rabbitry, Greenfield, Ind.) weighing 2.0–2.5 kg and restrained in wooden stanchions. The colonic temperatures were recorded at 15-min intervals after drug administration, using a telethermometer with thermistor probe attachments. The rabbits (two per drug) were given intravenous doses of 5 mg/kg of benactyzine hydrochloride, **6**·HCl, and **14**·HCl. All three drugs failed to alter colonic temperature over a 2-h time period. Both direct and indirect acting dopaminergic agents are known to cause hyperthermia in rabbits.[21] Thus, it is likely that the compounds have no central dopaminergic activity.

Partition Coefficients. Partition coefficients (K_p, octanol–pH 7.4 phosphate buffer) were determined for two of the ethers and their ester isosteres. The partition coefficient of ether **6** (K_p = 5.6) is 20 times that of the corresponding ester, benactyzine, (K_p = 0.26). *N*-Methyl-4-piperidinyl ether **13** (K_p = 3.1) is about twice as soluble in the oil phase as its isosteric piperidinyl ester (K_p = 1.8). The partition coefficients demonstrate that replacement of the ester carbonyl with a methylene group results in compounds with increased lipophilicity as had

been expected; however, it cannot be stated for certain at this time that increased lipophilicity results in increased brain levels of the compounds.

Structure–Activity Relationships. The pharmacological results show that most of the compounds tested have a moderate degree of anticholinergic activity. It is difficult to make meaningful comparisons of the results obtained for the ethers with the activities observed for similar anticholinergics evaluated in different test systems. Because of this difficulty no attempt will be made to compare the results in Table I with those reported for the corresponding esters. However, comparison of the activities observed within the ether series is valid and on this basis certain structure–activity relationships may be made in relation to previously observed structure–activity trends.[1]

The central and peripheral anticholinergic activity displayed by members of the ether series indicates that the carbonyl moiety is not necessary for activity.

Quaternization of the tertiary amines resulted in an increase in antispasmodic activity with all of the compounds except the quinuclidinoxy derivative **14**. The quaternary salts of the diphenylacetic and benzilic esters of 3-quinuclidinol are also reported to be less active than the free base.[22]

In general, like changes in the amino alcohol portions of the ether and ester series gave parallel changes in pharmacological activity. Thus, the *N,N*-diethylaminoethoxy congener **6** is more potent as an antispasmodic than its *N,N*-dimethyl homologue **5**. Increasing the chain length to propoxy (**7**) resulted in an unusual (from the SAR standpoint) increase in both antispasmodic and antiparkinsonian activity. Among the cyclic amino representatives of the series, the *N*-methyl-4-piperidinoxy (**13**) and 3-quinuclidinoxy (**14**) derivatives displayed maximal antispasmodic activity, results which are consistent with observations in the ester series.

The *N*-allyl analogues **8** and **9** were prepared to investigate the suggestions that this substitution may confer useful antiparkinsonian activity in anticholinergic agents.[23] The activities demonstrated by these two compounds do not reveal any special characteristics; however, further investigation is required to determine whether any specificity in CNS activity exists.

Preliminary evaluation of compounds **13** and **14** indicates that they are about one-tenth as potent as their ester counterparts in producing behavioral disturbancy (psychotomimetic) effects in cats.[24] It cannot be assessed at this time whether the decreased behavioral effects produced by the ethers occur by virtue of a selective mode of pharmacological action or simply by a lower degree of activity. It is also possible that the total concentration or relative distribution of the different agents within the brain is responsible for part or all of the differences in activity. Additional and more specific tests, directly comparing the ether and ester isosteres, will be required before more definitive statements concerning the relative activities of these agents can be made.

In summary, this study has shown that the ester carbonyl moiety of the glycolate ester type of anticholinergics can be replaced with a methylene group and the resulting compounds retain significant central and peripheral biological activity. The bioisosteric change results in ethers which have greater lipophilicity, and thus they may reach higher brain levels than the corresponding ester isosteres. Preliminary results show the ethers to be less psychotomimetic than the corresponding esters. Further pharmacological testing (e.g., oxotremorine-induced tremor, etc.) will be required to determine whether the ethereal compounds have properties which are worthy of consideration for clinical use.

Experimental Section

Chemical. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill., or by the microanalytical laboratory at the Medical College of Virginia. Where analyses are indicated only by symbols of elements, they are within ±0.4% of the theorectical values. IR spectra were obtained with the Perkin-Elmer Model 257 spectrophotometer as liquid films or KBr disks. NMR data (δ) were recorded with a Varian A-60A spectrophotometer in $CDCl_3$ (Me_4Si), Me_2SO-d_6 (Me_4Si), or D_2O (DDS). All IR and NMR spectra were consistent with the assigned structures. A Coleman-Hitachi EPS-3T recording spectrophotometer was used in determining the partition coefficients.

The agents used as standards in the antiparkinsonian screen were perphenazine (supplied by Schering Co.), benztropine mesylate (1 mg/mL) (MSD), and scopolamine hydrobromide (0.65 mg/mL) (Vitran Co.).

Trimethylsulfonium Iodide. A modified procedure of that described by Emeleus and Heal was used.[25] Methyl iodide (0.5 mol, 71 g) and methyl sulfide (0.5 mol, 31 g) were added to 200 mL of absolute EtOH and allowed to stand 14 h with stirring. The mixture was cooled (5 °C) and the precipitate which formed was removed by vacuum filtration and was washed (200 mL of petroleum ether): mp 200–202 °C dec (lit.[24] mp 200 °C dec).

2,2-Diphenyloxirane (15). Dimethylsulfonium methylide was prepared in Me_2SO–THF solution under nitrogen atmosphere as described by Corey and Chaykovsky.[15] To the ylide (10% molar excess) solution was added immediately 27 g (0.15 mol) of benzophenone in 75 mL of dry THF. The stirred reaction mixture was held below 10 °C during the addition and for an additional 30 min. Stirring was continued at 25 °C for 1 h and then an equal volume of H_2O was added slowly (Me_2S apparent). The mixture was transferred to a separatory funnel and extracted with Et_2O (3 × 100 mL), the extract was washed with H_2O (2 × 50 mL), dried ($MgSO_4$), and filtered, and the solvent was removed. The remaining oil crystallized from 100 mL of absolute EtOH and was recrystallized from Me_2CO to give 26.5 g (93%) of **15**: mp 55–56 °C (lit.[15] mp 55–56 °C).

General Procedure. Preparation of 2-[(N-Substituted amino)alkoxy]-1,1-diphenylethanols. Alkoxides were formed from the appropriate amino alcohols by proton abstraction with NaH in dry Me_2SO solution and under an N_2 atmosphere. Heating the stirred solution to 60 °C for 10–20 min or until H_2 evolution ceased was generally sufficient to ensure alkoxide formation. A Me_2SO solution of 2,2-diphenyloxirane was added to heated alkoxide solution and the resulting mixture allowed to stir for 1 h. The mixture was extracted with Et_2O (3 × 50 mL). The combined extracts were washed with H_2O, dried (Na_2SO_4), and filtered, and the ether was removed to leave the impure product as an oil. The desired products were crystallized from the solvents indicated. The HCl and MeI salts were prepared from the free bases by standard procedures.

Care should be taken in the above procedure to avoid a molar excess of NaH or reaction temperatures above 70 °C. In either of these cases considerable amounts of methylsulfinyl methylide addition product (generated from the Me_2SO solvent) with the oxirane [3,3-diphenyl-3-hydroxypropylmethyl sulfoxide. Anal. ($C_{16}H_{18}O_2S$) C, H] were isolated.

2-(Dimethylaminoethoxy)-1,1-diphenylethanol (5). The aminoalkoxide was prepared from 1.7 g (0.07 mol) of NaH and 15 mL (0.15 mol) of 2-dimethylaminoethanol and allowed to react with 4.0 g (0.02 mol) of oxirane **15**. Crystallization of the product (from 2-butanone) gave 4.6 g (75%) of **5**, mp 54–55 °C. Anal. ($C_{18}H_{23}NO_2$) C, H. **5**·MeI (from absolute EtOH) had mp 192 °C. Anal. ($C_{19}H_{26}INO_2$) C, H, N. **5**·HCl had mp 167–168 °C (from absolute EtOH). Anal. ($C_{18}H_{24}ClNO_2$) C, H.

2-(Diethylaminoethoxy)-1,1-diphenylethanol (6). The aminoalkoxide was prepared from 1.7 g (0.07 mol) of **15**. Work-up of the oil was modified by dissolution of the amine fraction into 5% HCl, extraction with ether, basification (10% NaOH) of the acid solution, and extraction of **6** into ether. Removal of the ether

and crystallization from 2-butanone gave 5.3 g (52%) of **6**, mp 53–54 °C. Anal. ($C_{20}H_{27}NO_2$) C, H, N. **6**·MeI had mp 212 °C (from absolute EtOH). Anal. ($C_{21}H_{30}INO_2$) C, H. **6**·HCl had mp 177–178 °C (absolute EtOH). Anal. ($C_{20}H_{28}ClNO_2$) C, H.

2-[3-(Dimethylamino)propoxy]-1,1-diphenylethanol (7). The aminopropoxide was prepared by reacting 1.0 g (0.04 mol) of NaH with 5 g (0.05 mol) of 3-dimethylaminopropanol and then reacting with 7.2 g (0.037 mol) of **15**. The oil from the reaction mixture gave crystals, 7.6 g (68%) from absolute EtOH. Further recrystallization from 2-butanone gave pure **7**, mp 69–70 °C. Anal. ($C_{19}H_{25}NO_2$) C, H. **7**·MeI [from absolute EtOH–Et_2O (1:1)] had mp 180–181 °C. Anal. ($C_{20}H_{28}INO_2$) C, H, N. **7**·HCl [from absolute EtOH–Et_2O (1:1)] had mp 124–125 °C. Anal. ($C_{19}H_{26}ClNO_2$) C, H, N.

2-(*N*-Allyl-*N*-methylaminoethoxy)-1,1-diphenylethanol Hydrochloride (8·HCl). *N*-Allyl-*N*-methylethanolamine (**16**) was prepared by addition of allyl bromide (0.5 mol) to methylaminoethanol (0.53 mol) in refluxing benzene. After 3 h the solution was cooled and work-up gave **16** (11.1 g, 20%), bp 64 °C (20 mm). The alkoxide was prepared by reaction of **16** (6.9 g, 0.06 mol) with NaH (1.44 g, 0.06 mol), and subsequent reaction of the alkoxide with **15** (5 g, 0.025 mol) and work-up gave crude **8** which was precipitated as its HCl salt (3.2 g) by adding an Et_2O–HCl solution to an Et_2O solution of the free base. Recrystallization from EtOAc gave pure **8**·HCl, mp 125–126 °C. Anal. ($C_{20}H_{26}ClNO_2$) C, H.

2-(*N*-Allyl-*N*-ethylaminoethoxy)-1,1-diphenylethanol Hydrochloride (9·HCl). *N*-Allyl-*N*-methylaminoethanol [**17**, bp 68 °C (20 mm)] was prepared by the procedure described above for **16**. The amino alkoxide was prepared from **17** (7.0 g, 0.06 mol) and NaH (1.44 g, 0.06 mol) and allowed to react with **15** (8.0 g, 0.04 mol) to afford crude **9**. The oil was dissolved in anhydrous Et_2O and Et_2O–HCl solution added until precipitation of **9**·HCl (5.9 g) was complete. Recrystallization from EtOAc gave **9**·HCl, mp 143–145 °C. Anal. ($C_{21}H_{28}ClNO_2$) C, H.

2-(*N*-Methyl-3-pyrrolidinoxy)-1,1-diphenylethanol Hydrochloride (10·HCl). Sodium *N*-methyl-3-pyrrolidinoxide was prepared from *N*-methyl-3-pyrrolidinol (5.0 g, 0.05 mol) and NaH (1.2 g, 0.05 mol) and allowed to react with 6.0 g (0.03 mol) of **15**. The oil obtained from the reaction failed to crystallize from a variety of solvents. The oil from the reaction was further purified by column chromatography (2 × 70 cm column packed with 60–100 mesh Florisil). The column was eluted with 200-mL quantities of benzene, 1% acetone in benzene, 2% acetone in benzene, 5% acetone in benzene, 10% acetone in benzene, and finally 100% acetone. The major component was eluted in the 10% acetone in benzene fraction. The oil obtained from this fraction was dissolved in anhydrous Et_2O and Et_2O–HCl solution added until no additional precipitate formed. The highly hygroscopic precipitate was isolated by filtration, washed with several portions of petroleum ether, dried, and recrystallized from absolute ethanol to give 1.2 g of **10**·HCl as white platelets, mp 96–97 °C. Anal. ($C_{19}H_{24}ClNO_2$) H, N; C: calcd, 68.35; found, 67.36. NMR and IR spectra are consistent with the assigned structure. **10**·MeI had mp 181–182 °C (from absolute EtOH). Anal. ($C_{20}H_{26}INO_2$) C, H.

2-(*N*-Methyl-3-piperidinoxy)-1,1-diphenylethanol (11). Sodium *N*-methyl-3-piperidinoxide, prepared from the piperidinol (9.2 g, 0.08 mol) and 1.7 g (0.07 mol) of NaH, was allowed to react with 4.0 g (0.02 mol) of **15**. The oil obtained from work-up of the reaction mixture crystallized from Et_2O solution when stored 12 h at −5 °C. Recrystallization from 2-butanone gave **11** (4.2 g, 65%), mp 135–136 °C. Anal. ($C_{20}H_{25}NO_2$) C, H, N. **11**·MeI was prepared and recrystallized from Et_2O–EtOH (1:1): mp 185–186 °C. Anal. ($C_{21}H_{28}INO_2$) C, H. **11**·HCl was prepared and recrystallized from EtOH: mp 173–174 °C. Anal. ($C_{20}H_{26}ClNO_2$) C, H.

2-(*N*-Ethyl-3-piperidinoxy)-1,1-diphenylethanol (12). Sodium *N*-ethyl-3-piperidinoxide, prepared from 1.1 g (0.047 mol) and NaH and 5.0 g (0.047 mol) of *N*-ethyl-3-piperidinol, was allowed to react with 8.0 g (0.04 mol) of **15**. Crystallization of the reaction residue from 2-butanone at −10 °C gave 6.5 g (46%) of solid which was recrystallized to yield pure **12**, mp 81–82 °C. Anal. ($C_{21}H_{27}NO_2$) C, H, N. **12**·MeI had mp 184–186 °C (from absolute EtOH). Anal. ($C_{22}H_{30}INO_2$) C, H. **12**·HCl had mp 93–95 °C (from absolute EtOH–Et_2O). Anal. ($C_{21}H_{28}ClNO_2$) C, H.

2-(*N*-Methyl-4-piperidinoxy)-1,1-diphenylethanol (13). Sodium *N*-methyl-4-piperidinoxide, prepared from the piperidinol (0.07 mol) and NaH (0.07 mol), was allowed to react with **15**. Work-up and crystallization of the reaction mixture gave **13** (6.6 g, 84%), mp 122 °C. Anal. ($C_{20}H_{25}NO_2$) C, H, N. **13**·HCl had mp 201–202 °C (from absolute EtOH). Anal. ($C_{20}H_{26}ClNO_2$) C, H. **13**·MeI had mp 212–213 °C (from absolute EtOH). Anal. ($C_{21}H_{28}INO_2$) C, H.

2-(3-Quinuclidinoxy)-1,1-diphenylethanol (14). The quinuclidinoxide was prepared from 1.1 g (0.047 mol) of NaH and 6.0 g (0.047 mol) of 3-quinuclidinol and allowed to react with 8 g (0.041 mol) of **15**. The oil obtained from the reaction work-up crystallized from Me_2CO and was recrystallized from 2-butanone to yield 6.9 g (52%) of **14**, mp 153–154 °C. Anal. ($C_{21}H_{25}NO_2$) C, H, N. **14**·MeI had mp 206–207 °C (from absolute ethanol). Anal. ($C_{22}H_{28}INO_2$) C, H. **14**·HCl had mp 181–182 °C (from absolute EtOH–Et_2O). Anal. ($C_{21}H_{26}ClNO_2$) C, H.

Pharmacology. Determination of pD'_2 Values by Single Dose Method.[18] The jejunum was removed from a freshly killed male Wistar rat and was placed in a petri dish containing Tyrode's solution into which O_2–CO_2 (95–5%) was bubbled. The jejunum was cut into four equal parts of about 1.5 cm each and one end of the muscle tissue was attached at the end of a stainless-steel rod. The tissue was placed in a tissue bath filled with 10 mL of Tyrode's solution (25 °C) and aerated continuously with 95% oxygen and 5% carbon dioxide. The other end of the tissue segment was attached to a Fourier transform 0.03 force transducer. A Grass Model 5D polygraph was used to record the response of the jejunum to stimulation by AcCh and inhibition by the cholinergic antagonist. After allowing 1 h for the system to rest, the muscle was primed with 10^{-5} M AcCh until reproducible contractions were obtained. The muscle was washed several times with Tyrode's solution after each application of agonist.

A concentration of 10^{-5} M AcCh was used as the submaximal standard dose of agonist against which the pD'_2 value of the antagonist was determined. The muscle contraction resulting from a 10^{-5} M dose of AcCh was measured and recorded on the polygraph. The muscle was washed by rinsing with Tyrode's solution and the bath was refilled with Tyrode's solution. After the baseline had stabilized, the antagonist was added. The system was allowed 2 min of contact time with each agent before AcCh (10^{-5} M) was added. The responses of the muscle tissue to the agonists were then recorded. The ratio of the response observed to the standard dose of AcCh in the presence of antagonist to the response observed in the absence of antagonist was calculated. The muscle tissue was washed with Tyrode's solution and primed with 10^{-5} M AcCh until the original response of the muscle was observed.

The above procedure was repeated with different concentrations of the potential antagonist until points above and below the 50% inhibition point of the standard dose of AcCh were observed. A plot of the negative logarithm of the concentration of antagonist vs. the percent inhibition of the standard dose of AcCh was prepared. The pD'_2 was determined as the intercept of the line connecting the observed experimental values with the 50% inhibition. The final pD'_2 value was taken as the average of four to six such determinations.

Determination of Antiparkinsonian Activity Based on Inhibition of Perphenazine-Induced Catatonia. Male albino Wistar rats which weighed 150–300 g were used. Groups of four rats were pretreated with a 2 mg/kg ip dose of one of the standard drugs (scopolamine hydrobromide, atropine hydrobromide, or benztropine mesylate) or the hydrochloride salt of the test compound. The same rats were injected intraperitoneally with 5 mg/kg doses of perphenazine 15 min after the potential antagonists were given.

Evaluation of the ability of the test drug to relieve the induced catatonia was made according to stages III and IV of the catatonic response as described by Wirth and co-workers.[26] For a positive catatonic response in stage III the rat fails to correct the imposed posture within 10 s when it is placed on the table with one front paw resting on a cork 3 cm high. The stage III response is measured on both the right and left sides and one-half point is scored for each positive catatonic response. A positive response in stage IV requires that the rat not correct the imposed posture within 10 s when one of its front paws is placed on a cork 9 cm

high and the other front paw is permitted to hang free. The head of the rat is not allowed to rest on top of the cork. The stage IV response is determined on both right and left sides and one point is scored for each positive catatonic response. The maximum possible catatonic response for stage III or IV is three points.

The catatonic response was determined on each rat at 0.5-, 1-, 2-, and 3-h intervals after injection of the perphenazine. The percentage which the test drugs inhibited the catatonic response was calculated against the test scores of rats injected with a 5 mg/kg ip dose of perphenazine at the same time. The results of these tests are given in Table II.

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β-Adrenergic Blocking Agents. 16. 1-(Acylaminomethyl-, ureidomethyl-, and ureidoethylphenoxy)-3-amino-2-propanols

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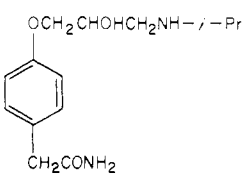
The synthesis of a series of 1-(acylaminomethyl-, ureidomethyl-, and ureidoethylphenoxy)-3-amino-2-propanols is described. The compounds were screened as β-adrenergic receptor antagonists in cats and their partial agonist activity was evaluated in rats depleted of circulating catecholamines. Some of the compounds have a pharmacological profile similar to atenolol. Their structure–activity relationships are discussed.

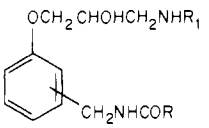
The addition of a methylene bridge between a carbamoyl moiety and the aromatic ring of an aryloxypropanolamine gave a β-blocking agent, atenolol (1, Tenormin[1]), that was potent, cardioselective, and without partial agonist activity.[2]



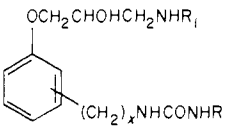
1

In an extension of this work we have synthesized a series of compounds that have a methylene or ethylene bridge interposed between the aromatic ring and an acylamino (**2**)[3] or ureido (**3**)[4] moiety.

The potency and selectivity of action found throughout the series was, in general, of a lower order than that observed with the parent acylamino[5] and ureido analogues.[6] Many of the compounds were similar to atenolol in that they had little or no partial agonist activity when examined in rats depleted of catecholamines. This paper describes the synthesis and discusses the structure–activity relationships found within this series of analogues.



2, R, R_1, see Tables I–IV



3, x = 1 or 2; R, R_1, see Tables I–IV

Chemistry. The compounds listed in Tables I–IV were prepared by previously described methods[5,7] and therefore the Experimental Section is limited to a typical example of each of the methods (A–C) outlined in Scheme I.

The various acylaminomethyl-, ureidomethyl-, and ureidoethylphenols used in the synthesis were made by