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Stereochemical Analogs of a Muscarinic, Ganglionic Stimulant. 2. Cis and Trans Olefinic, Epoxide, and Cyclopropane Analogs Related to 4-[*N*-(3-Chlorophenyl)carbamoyloxy]-2-butynyltrimethylammonium Chloride (McN-A-343)†,‡,[1,2]

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Preparation of analogs of 4-[*N*-(3-chlorophenyl)carbamoyloxy]-2-butynyltrimethylammonium chloride [**1** (McN-A-343)], *cis*- and *trans*-4-[*N*-(4-chlorophenyl)carbamoyloxy]-2-butenyltrimethylammonium iodides (**5** and **6**), and the corresponding epoxides and cyclopropanes is reported. Pharmacological testing for ganglion-stimulating activity demonstrated that the trans olefin **6** and trans epoxide **8** have properties similar to **1**, while the trans cyclopropane analog **10** was inactive. All cis compounds were inactive. The muscarinic ganglion-stimulating properties of the active compounds are interpreted in terms of similar fit at the receptor level by the alkyltrimethylammonium ion and the ether oxygen 5.7 Å distant, as well as an electron-rich center midway between these groups in the form of a double bond or unshared electron pairs. Comparison of smooth muscle and ganglion-stimulating properties of the compounds showed that trans epoxide **8** was the most selective for muscarinic ganglionic sites.

A detailed pharmacological study by Roszkowski[3] of 4-[*N*-(3-chlorophenyl)carbamoyloxy]-2-butynyltrimethylammonium chloride [**1** (McN-A-343)] demonstrated that this compound possessed unique ganglionic stimulant properties, exciting sympathetic ganglia at muscarinic (atropine sensitive) sites to produce an increase in blood pressure, after a short initial depressor effect. Other less important effects were noted including some classical muscarinic effects of vasodilitation and stimulation of intestinal smooth muscle. Recently, parasympathetic ganglion-stimulating effects have been noted[4,5] as well as nonmuscarinic effects including antagonism of the amine uptake pump of the sympathetic nerve terminal[6,7] and local anesthetic effects.[8]

In an earlier study[1] we demonstrated that the trans olefinic analog **4** possessed very similar muscarinic ganglion-stimulant properties, being about one-third as potent as **1**, in elevating blood pressure in anesthetized cats. Cis compound **3** was much less active. Neither olefinic analog showed significant muscarinic effects on smooth muscle similar to **1**. These results suggested that extended conformations of **1** and **4** are responsible for ganglion-stimulant activity, where the ether oxygen and quaternary nitrogen are 5.7 Å apart. Only in these conformations do **1** and **4** approximate each other in a spatial

† Dedicated to the memory of Edward E. Smissman.

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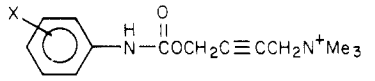
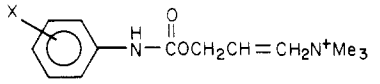
arrangement of ether oxygen, unsaturation between C-2 and C-3, and the quaternary nitrogen.

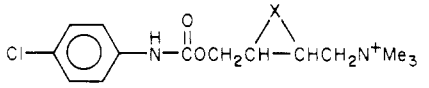
In this study we have extended our work to include olefinic, epoxide, and cyclopropane analogs in a series of 4-chlorophenylcarbamates related to **1**. Previously, it was demonstrated that the 4-chloro analog **2** was about 2.8 times as potent at **1**.[9] The present study was performed to determine whether a similar increase in potency would be noted for the olefinic analogs, and the epoxide and cyclopropane analogs provided the opportunity to assess the importance of the unsaturation in a molecule for this type of ganglionic stimulant activity.



1, X = 3-Cl (McN-A-343)
2, X = 4-Cl

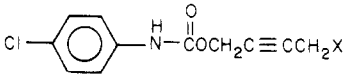


cis	trans
3, X = 3-Cl	**4**, X = 3-Cl
5, X = 4-Cl	**6**, X = 4-Cl

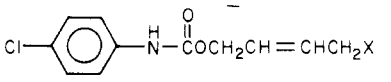


cis	trans
7, X = O	**8**, X = O
9, X = CH_2	**10**, X = CH_2

The 4-chlorophenyl cis and trans olefinic compounds, **5** and **6**, were synthesized via pathways similar to those previously reported for the 3-chlorophenyl derivatives, assuring the stereochemical purity of each.[1] The starting materials were 2-butyne-1,4-diol (**11**) for preparation of **5** and *trans*-2-butene-1,4-diol (**12**) for **6**.



13, X = OH
15, X = Br
17, X = NMe_2



trans
14, X = OH
16, X = Br
18, X = NMe_2

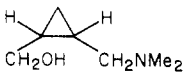
In order to suppress formation of biscarbamate, a 0.5–1 *M* excess of the respective diol was allowed to react with 4-chlorophenyl isocyanate. The monocarbamate alcohols **13** and **14** were converted to their respective halides **15** and **16** with phosphorus tribromide, which proved to be a more successful process than using thionyl chloride. The bromide was readily displaced upon reaction with dimethylamine providing good yields of amines **17** and **18**, which were converted to **2** and **6**, respectively, using methyl iodide. Catalytic hydrogenation of **2** using a Lindlar catalyst afforded **5**.

An attempted direct epoxidation route to **7** and **8** failed. Reaction of one of the olefinic carbamate derivatives, such as halide **16** or amine **18**, with 3-chloroperbenzoic acid produced only dark oils from which were obtained starting material, 4-chloroaniline, and unidentified by-products. Purification attempts were unsuccessful.

cis- and *trans*-2-butene-1,4-diols, **19** and **12**, were successfully used as starting materials for **7** and **8** (Scheme I). Peracid epoxidation was performed in acetonitrile because of lack of solubility of the starting diols in $CHCl_3$ or CH_2Cl_2. After removing the precipitated 3-chlorobenzoic acid, the remaining traces of 3-chlorobenzoic acid and unreacted peracid were removed by treating the filtrate with water and washing the aqueous phase with chloroform followed by removal of the water by lyophilization.

The epoxide diols **20** and **21** were treated as outlined in Scheme I, in sequential steps using first 4-chlorophenyl isocyanate to yield carbamates **22** and **23**, which were always contaminated with *N*,*N*'-di(4-chlorophenyl)urea, probably due to water of hydration in the lyophilized crude epoxide diols. Separation of this urea from carbamates **22** and **23** required several crystallizations. The tosyl derivatives **24** and **25** of the carbamates were allowed to react dimethylamine at room temperature (7 days) in order to avoid epoxide ring opening. Reaction of amines **26** and **27** with methyl iodide completed the synthesis of the cis and trans epoxide analogs **7** and **8**.

Initial synthetic efforts focused on converting one of the olefinic carbamate derivatives to the corresponding cyclopropane derivative by way of the Simmons–Smith reaction failed. However, the amino alcohols **28** and **29** necessary for the synthesis of the cyclopropane compounds are directly available from the work of Cannon,[10] who prepared each from the appropriate cyclopropanedicarboxylic acid. Carbamate formation followed by treatment with methyl iodide complete synthesis of **9** and **10**.



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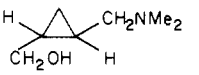
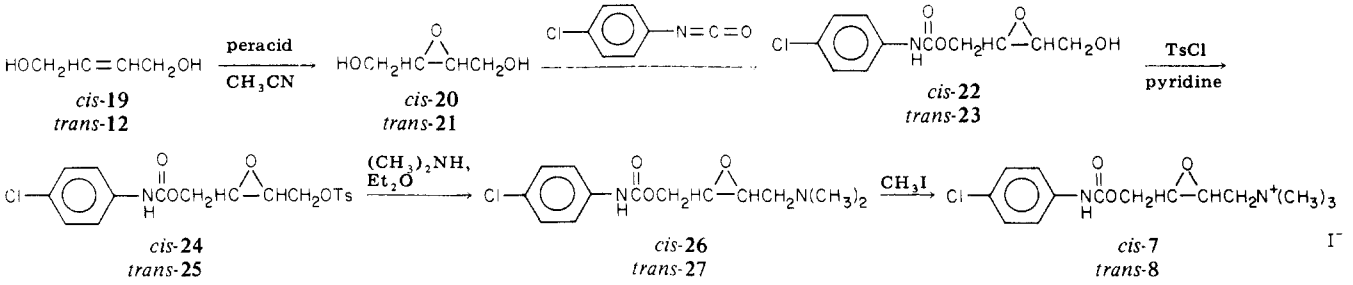


29

Pharmacology. The relative muscarinic ganglion-stimulant activity of **1** (McN-A-343) and its analogs was estimated from their pressor responses in cats.[1] The fact that pressor responses were blocked by atropine is consistent with the theory that the active analogs stimulate ganglia through muscarinic (i.e., atropine sensitive) mechanisms. Responses were decreased in cats pretreated

Scheme I



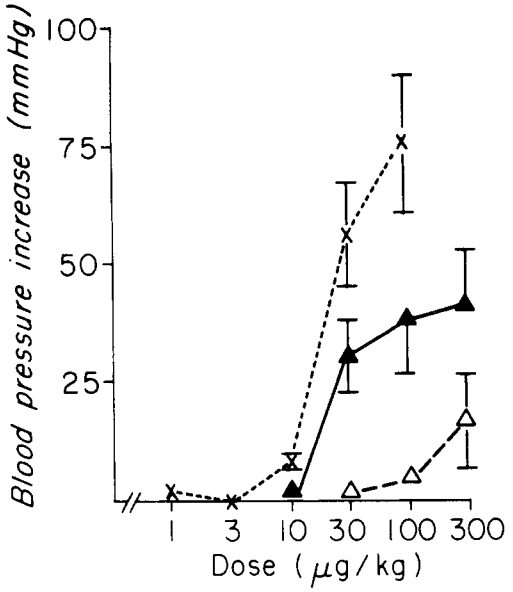


Figure 1. Influence of olefinic analogs **5** and **6** on arterial blood pressure. Semilogarithmic plots of maximum increase in systolic blood pressure vs. dose: (X) **1**, iodide salt (McN-A-343); (▲) trans olefin **6**; (△) cis olefin **5**. Each point is the mean of at least one determination in each of three animals. Vertical bars indicate ±SE.

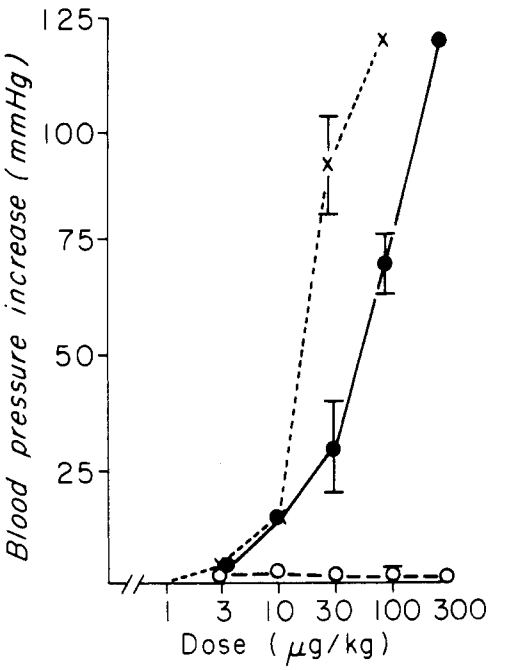


Figure 2. Influence of epoxide analogs **7** and **8** on arterial blood pressure. Semilogarithmic plots of maximum increase in systolic blood pressure vs. dose: (X) **1**, iodide salt (McN-A-343); (●) trans epoxide **8**; (○) cis epoxide **7**. Each point is the mean of at least one determination in each of three animals. Vertical bars indicate ±SE.

with phentolamine (an α-adrenergic blocking agent) but not by hexamethonium and are thus dependent on stores of sympathetic amines and appear to occur via atropine-sensitive sites at sympathetic ganglia, in agreement with the work of Roszkowski.[3]

A comparison of the pressor activities of the 4-chlorophenyl cis and trans olefinic analogs, **5** and **6**, and **1** (McN-A-343) is presented in Figure 1. The anticipated approximate threefold increase in pharmacological activity converting from 3-chlorophenyl analogs to the 4-chlorophenyl moiety similar to **1** and **2** was realized. The trans analog **6** is nearly equipotent with **1** and is two to three times as potent as previously reported for the 3-chlorophenyl trans analog **4**.[1] As was previously noted for the *cis*-3-chlorophenyl compound **3**, compound **5** also had only a small pressor response at high doses.

A comparison of pressor activity of **1** and the cis and trans epoxide analogs **7** and **8** is presented in Figure 2. Again, the trans isomer is much more potent than the cis isomer. The trans epoxide **8** is nearly equal in pressor activity to **1** and the cis epoxide **7** has only minor pressor activity.

Preliminary testing of the *cis*- and *trans*-cyclopropane analogs **9** and **10** showed both to be inactive as pressor agents. None of the cyclopropane isomers **9** and **10**, the cis olefinic isomers **3** and **5**, or the cis epoxide isomer **7** was an antagonist to the muscarinic ganglion-stimulant activity of **1** or of **2**.

Muscarinic effects of the 4-chlorophenyl cis and trans olefinic analogs **5** and **6** on rabbit ileum are compared with ACh in Figure 3. The trans olefin **6** is approximately 1% as potent as ACh and the cis olefin **5** is almost inactive in this assay at the concentrations employed.

Muscarinic effects of ACh and the cis and trans epoxide analogs **7** and **8** on rabbit ileum are compared in Figure 4. Neither analog is an effective muscarinic agonist at the concentrations used in this system. The cyclopropanes were also inactive in this classical muscarinic assay system, as are the acetate esters of **28** and **29**.[10]

The 4-chlorophenyl trans olefinic analog **6** shows the least selectivity between classical muscarinic receptors and ganglionic muscarinic receptors since it is also an active

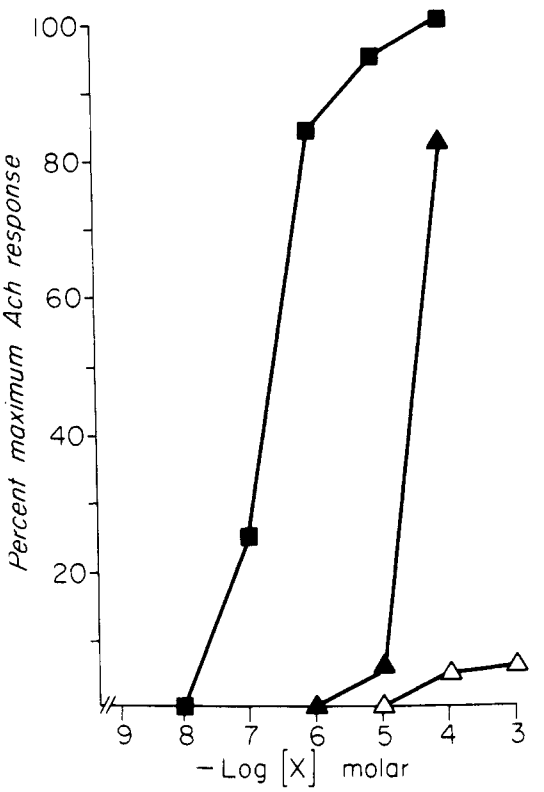
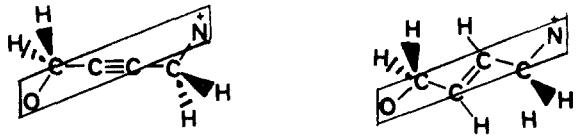


Figure 3. Influence of olefinic analogs **5** and **6** on isolated rabbit ileum. Semilogarithmic plots of isotonic contraction vs. molar concentration: (■) ACh; (▲) trans olefin **6**; (△) trans olefin **6**; (△) cis olefin **5**. Each point represents the mean of at least four responses in two tissues.

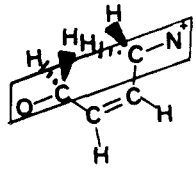
classical muscarinic agonist. The trans epoxide **8** appears to be the most selective among the muscarinic ganglion stimulants (including **1**, McN-A-343[1]) since **8** has only minimal muscarinic activity on smooth muscle (Figure 4).

The pharmacological similarities of 1 and 2, and the corresponding trans olefinic analogs 4 and 6 are interpreted in terms of a similar distribution of functional groups in the drug–receptor complex. The quaternary nitrogen, the unsaturation at C-2, and the ether oxygen are three groups whose spatial relationship to one another is controlled by the stereochemistry at C-2 and C-3. Models show that when 1 and the trans analogs 4 and 6 are in their fully extended conformations, the quaternary ammonium ion and the carbamate ether oxygen are approximately 5.7 Å apart with the triple or double bond, respectively, occupying similar spatial positions along a plane.

Attempting to fit the cis analogs 3 and 5 to this pattern shows that in order for the quaternary nitrogen and ether oxygen to be approximately 5.7 Å apart, the double bond must be above or below the plane defined by the three functional groups in 1. The fact that the 4-chlorophenyl trans olefin 6 is approximately three times more potent than the 3-chlorophenyl trans olefin 4, which parallels the increase in potency observed for the 4-chlorophenylacetylene 2 over 1,[9] indicates the trans analogs 4 and 6 and alkynes 1 and 2 probably form similar drug–receptor complexes at muscarinic ganglionic sites.



trans



cis

Since the epoxide analogs 7 and 8 show the same relationship between cis and trans isomers as in the olefinic analogs, they also must be accommodated in the proposed drug–receptor fit. The nonbonding electrons of the oxygen bridge in the trans epoxide analog 8 appear to play a similar role in the drug–receptor complex as the π electrons in the acetylenic or trans olefinic analogs. This is supported by the lack of pressor activity found for both the *cis*- and *trans*-cyclopropane analogs 9 and 10. Since the trans olefinic, epoxide, and cyclopropane analogs can all have similar spatial relationships between their phenylcarbamate and quaternary ammonium side chains, the inactivity of the *trans*-cyclopropane 10 may be due to the absence of the free electron pairs in the vicinity between C-2 and C-3.

In conformational models, the oxygen bridge in the trans epoxide 8 may be made to closely coincide with the position of unsaturation in the acetylenic and trans olefinic compounds or may be placed in conformations where it is above or below the plane. The former arrangement requires the C-1 and C-4 methylenes to assume positions only slightly different than in conformations of trans compounds 4 or 6. This conformation is capable of defining a drug–receptor space accommodating the ether oxygen and quaternary nitrogen about 5.7 Å apart and also accommodating an electron-rich site from the drug molecule about midway between. These tentative requirements for receptor fit are compatible with this small sample of related compounds but may be insufficient to predict activity, or lack of activity, of yet untested molecules.

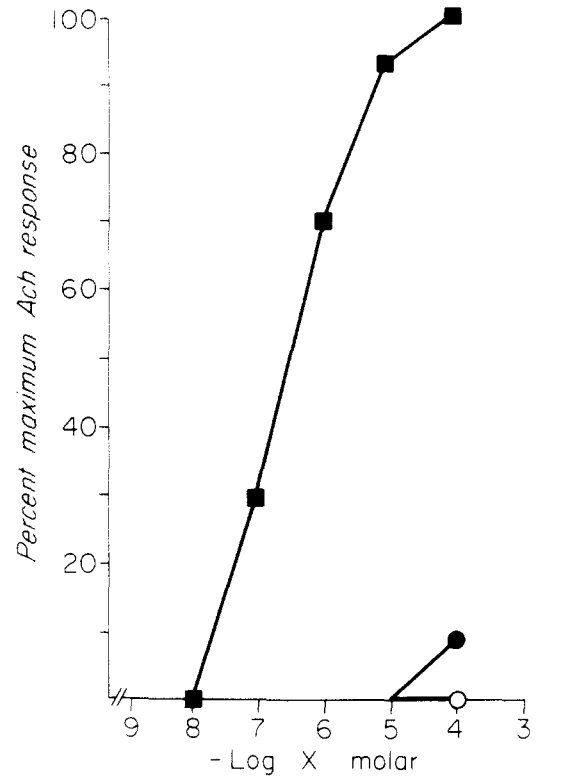


Figure 4. Influence of epoxide analogs 7 and 8 on isolated rabbit ileum. Semilogarithmic plots of isotonic contraction vs. molar concentration; (■) ACh; (●) trans epoxide 8; (○) cis epoxide 7. Each point represents the mean of at least four responses in two tissues.

Experimental Section

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are corrected. Infrared spectra were recorded on a Beckman IR-5A spectrophotometer. NMR spectra were determined with Varian A-60 and T-60 MHz spectrometers using tetramethylsilane (Me_4Si) as internal standard except in those spectra taken in D_2O where sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) was used. The following notations are used in the NMR descriptions: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, and m = multiplet. Microanalyses were performed by Dr. F. B. Strauss, Oxford, England. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of theoretical values.

4-Trimethylammonio-2-butynyl *N*-(4-Chlorophenyl)-carbamate Iodide (2). To a stirred solution of 6.80 g (0.08 mol) of 2-butyne-1,4-diol (11) in 25 ml of anhydrous THF was added dropwise a solution of 6.60 g (0.043 mol) of 4-chlorophenyl isocyanate (Eastman Organic) in 10 ml of THF. The reaction was stirred overnight at room temperature. The reaction solution was diluted with 50 ml of H_2O and extracted with EtOAc (6 × 25 ml); the combined EtOAc extracts were washed with H_2O and dried (Na_2SO_4). The EtOAc was removed by rotary evaporation and the residue crystallized from benzene to yield 8.1 g (79%) of 13 as white granular crystals: mp 118.5–120°.

To a stirred, water–ice bath cooled solution of 2.40 g (0.01 mol) of alcohol 13 in 50 ml of anhydrous Et_2O was added dropwise a solution of 3.00 g (0.011 mol) of PBr_3 in 25 ml of Et_2O and the mixture allowed to stand overnight at room temperature. The reaction mixture was then poured over 150 ml of ice water, the Et_2O phase separated, and the aqueous phase extracted with Et_2O (3 × 40 ml). The combined Et_2O extracts were washed with H_2O,

aqueous saturated $NaHCO_3$, and H_2O. Et_2O solution was dried (Na_2SO_4), the Et_2O removed by rotary evaporaton, and the residue crystallized from an *n*-hexane–benzene mixture giving 1.60 g (53%) of **15** as tan needles: mp 114–116°.

To a stirred, water–ice bath cooled solution of 2.10 g (47 mmol) of anhydrous $(CH_3)_2NH$ in 50 ml of benzene was added dropwise a solution of 1.50 g (5 mmol) of halide **15** in 40 ml of benzene. The reaction was stirred cold for 1 hr and then refluxed for 4 hr. After cooling the reaction mixture was filtered to remove the precipitate of $(CH_3)_2{}^+NH_2Br^-$. The benzene solvent and excess $(CH_3)_2NH$ were removed by rotary evaporation and the residue was crystallized from an *n*-hexane–benzene mixture to yield 1.30 g (97%) of **17** as white, granular crystals: mp 90–91°.

To a solution of 1.20 g (4.5 mmol) of amine **17** in 40 ml of benzene was added with stirring 9.20 g (65 mmol) of CH_3I. The reaction was stirred at room temperature overnight. The precipitate was collected by suction filtration and crystallized from a MeOH–Et_2O mixture to afford 1.50 g (82%) of white granular crystals: mp 183–184° dec; infrared (KBr) 2.98, 3.31, 3.40, 5.79 μ; NMR (Me_2SO-d_6) δ 10.0 (s, broad, 1, NH, $W_{1/2}$ = 4 Hz), 7.60 and 7.37 (two d, 4, ArH, J = 9 Hz), 5.00 (m, 2, $2H_1$, $W_{1/2}$ = 5 Hz), 4.56 (m, 2, $2H_4$, $W_{1/2}$ = 5 Hz), 3.24 [s, 9, $-N^+(CH_3)_3$]. Anal. ($C_{14}H_{18}ClIN_2O_2$) C, H, N.

***cis*-4-Trimethylammonio-2-butenyl *N*-(4-Chlorophenyl)carbamate Iodide (5).** A mixture of 1.00 g (2.5 mmol) of alkyne **2**, 98 mg of 5% Pd-on-$BaSO_4$ catalyst, 100 ml of MeOH, and 4 drops of synthetic quinoline was hydrogenated on a low-pressure Parr apparatus at an initial H_2 pressure of 3.2 kg/cm^2 for 8 hr. The mixture was filtered through a Celite pad and the MeOH was removed by rotary evaporation. The crude oil residue was crystallized twice from a MeOH–Et_2O mixture to yield 0.75 g (75%) of **5** as white, flake-like crystals: mp 178–181° dec; infrared (KBr) 3.08, 3.22 (w), 3.30, 3.40 (w), 5.82 μ (s); NMR (Me_2SO-d_6) δ 9.94 (s, 1, NH), 7.58 and 7.33 (2 d, 4, ArH, J = 9 Hz), 5.70–6.40 (m, 2, H_2 and H_3, overlapping signals), 4.95 (d, 2, $2H_1$, $J_{1,2}$ = 6 Hz), 4.20 (d, 2, $2H_4$, $J_{4,3}$ = 7 Hz), 3.17 [s, 9, $-^+N(CH_3)_3$]. Anal. ($C_{14}H_{20}ClIN_2O_2$) C, H, N.

***trans*-4-Trimethylammonio-2-butenyl *N*-(4-Chlorophenyl)carbamate Iodide (6).** To a stirred solution of 3.00 g (34 mmol) of *trans*-2-butene-1,4-diol (**12**)[11] in 25 ml of anhydrous THF was added dropwise a solution of 3.00 g (20 mmol) of 4-chlorophenyl isocyanate in 10 ml of THF. The reaction was stirred at room temperature overnight. The reaction solution was then diluted with 100 ml of H_2O and extracted with EtOAc (3 × 75 ml). The combined EtOAc extracts were washed with H_2O and dried (Na_2SO_4), and the EtOAc was removed by rotary evaporation. The residue was crystallized from benzene to give 3.50 g (73%) of crude **14** as white granular crystals: mp 90–118°.

To a stirred, water–ice bath cooled solution of 2.40 g (10 mmol) of alcohol **14** in 50 ml of anhydrous Et_2O was added dropwise a solution of 3.00 g (11 mmol) of PBr_3 in 25 ml of Et_2O. The solution was stirred at 0° for 1 hr and then the reaction was allowed to stand overnight at room temperature. The reaction solution was poured into 150 ml of ice water, the Et_2O phase separated, and then the aqueous phase extracted with Et_2O (3 × 40 ml). The combined Et_2O extracts were washed with H_2O, saturated aqueous Na_2CO_3, and H_2O and then dried (Na_2SO_4). The Et_2O was removed by rotary evaporation and the residue crystallized from an *n*-hexane–benzene mixture to yield 2.00 g (67%) of **16** as tan crystals: mp 84–86°.

To a stirred, water–ice bath cooled solution of 2.10 g (47 mmol) of anhydrous $(CH_3)_2NH$ in 50 ml of benzene was added dropwise a solution of 1.00 g (3.3 mmol) of halide **16** in 30 ml of benzene. The reaction mixture was refluxed for 5 hr and after cooling was filtered to remove the precipitated $(CH_3)_2{}^+NH_2Br^-$. The benzene and excess $(CH_3)_2NH$ were removed by rotary evaporation. The residue was crystallized from an *n*-hexane–benzene mixture to afford 0.80 g (91%) of **18** as white needles: mp 106–107°.

A solution of 0.74 g (2.8 mmol) of amine **18**, 25 ml of benzene, and 7.00 g (49 mmol) of CH_3I was stirred overnight at room temperature. The precipitate was collected by suction filtration and the solid crystallized from MeOH–Et_2O to give 0.80 g (73%) of white, flake-like crystals: mp 186–188° dec; infrared (KBr) 3.00, 3.31, 3.40 (w), 5.78 μ (s); NMR (Me_2SO-d_6) δ 9.86 (s, 1, NH), 7.50 and 7.32 (two d, 4, ArH, J = 9 Hz), 6.16 (m, 2, H_2 and H_3, overlapping signals), 4.73 (d, 2, $2H_1$, $J_{1,2}$ = 4.5 Hz), 4.12 (d, 2, $2H_4$, $J_{4,3}$ = 6 Hz), 3.12 [s, 9, $-^+N(CH_3)_3$]. Anal. ($C_{14}H_{20}ClIN_2O_2$) C, H, N.

***cis*-4-Trimethylammonio-2,3-epoxybutyl *N*-(4-Chlorophenyl)carbamate Iodide (7).** To a cold (4°) solution of 1.00 g (11 mmol) of *cis*-2-butene-1,4-diol (**19**) in 30 ml of CH_3CN was added 2.50 g (12 mmol) of 85% 3-chloroperbenzoic acid (Aldrich). The reaction was allowed to stand for 72 hr in the refrigerator (4°). The precipitate of 3-chlorobenzoic acid was removed by suction filtration and the filtrate diluted with 75 ml of cold H_2O. This aqueous solution was then washed with $CHCl_3$ (twice) to remove any residual peracid or benzoic acid. The water was removed by lyophilization to yield 1.10 g (92%) of white, "fluffy" solid: mp 44–47°.

To a stirred solution of 1.00 g (9.6 mmol) of epoxide diol **20** in 20 ml of anhydrous THF was added dropwise a solution of 1.60 g (10 mmol) of 4-chlorophenyl isocyanate in 30 ml of THF. The reaction was allowed to stand overnight at room temperature. The reaction solution was then diluted with 150 ml of H_2O and the aqueous solution extracted with Et_2O (4 × 35 ml). The combined Et_2O extracts were washed with H_2O and dried (Na_2SO_4), and the Et_2O was removed by rotary evaporation. The residue was fractionally crystallized from an Et_2O–petroleum ether (bp 30–60°) mixture to first remove the *N*,*N*′-di(4-chlorophenyl)urea (identified by NMR, mp 305–307° dec) and then to yield 0.60 g (25%) of carbamate **22** as white, fibrous crystals: mp 108–109°.

To a cold (4°) solution of 100 mg (0.4 mmol) of alcohol **22** in 3 ml of anhydrous pyridine was added 120 mg (0.6 mmol) of TsCl. The reaction was allowed to stand in the refrigerator (4°) for 72 hr. The reaction solution was then poured into 30 ml of ice water and the aqueous solution extracted with Et_2O (4 × 25 ml). The combined Et_2O extracts were washed with H_2O and dried (Na_2SO_4), and the Et_2O was removed by rotary evaporation. The residue was crystallized from an Et_2O–petroleum ether (bp 30–60°) mixture to give 90 mg (57%) of **24** as white granular crystals: mp 114–115°.

To a cold solution of 100 mg (0.24 mmol) of **24** in 15 ml of Et_2O was added 70 mg (1.6 mmol) of anhydrous $(CH_3)_2NH$. The reaction was stirred at room temperature and its progress followed on TLC (silica gel) using a $CHCl_3$–MeOH (10:1) mixture as eluent (**24**, R_f 0.62; **26**, R_f 0.13). After 7 days very little starting tosylate **24** remained. The reaction mixture was then washed with H_2O (twice), the Et_2O phase separated and dried ($MgSO_4$), and the Et_2O removed with a stream of N_2 at room temperature to yield 70 mg (99%) of crude **26** as a colorless oil which was used without further purification.

To a solution of 400 mg (1.4 mmol) of **26** in 40 ml of benzene was added 2.30 g (16 mmol) of CH_3I. The reaction was stirred and then allowed to stand overnight at room temperature. The benzene was decanted from the viscous oil which formed and this oil was crystallized and recrystallized from a MeOH–Et_2O mixture to give 500 mg (84%) of **7** as white, granular crystals: mp 141–144° dec; infrared (KBr) 2.96, 3.08, 3.32, 5.79 μ (s); NMR (Me_2SO-d_6) δ 10.0 (s, broad, 1, NH, $W_{1/2}$ = 5 Hz), 7.56 and 7.34 (2 d, 4, ArH, J = 9 Hz), 4.54 (dd, 1, H_1, J_{gem} = 12 Hz, $J_{1,2}$ = 4 Hz), 4.14 (dd, 1, H_1, J_{gem} = 12 Hz, $J_{1,2}$ = 7 Hz), 3.5–4.0 (m, 2, H_2 and H_3, overlapping signals), 3.0–3.5 (m, 2, $2H_4$), 3.26 [s, 9, $-^+N(CH_3)_3$]. Anal. ($C_{14}H_{20}ClIN_2O_3$) C, H, N.

***trans*-4-Trimethylammonio-2,3-epoxybutyl *N*-(4-Chlorophenyl)carbamate Iodide (8).** To a cold (4°) solution of 3.00 g (34 mmol) of **12** in 75 ml of CH_3CN was added 9.00 g (44 mmol) of 85% 3-chloroperbenzoic acid. The reaction was allowed to stand 4 days in the refrigerator (4°). The precipitate of 3-chlorobenzoic acid was removed by suction filtration and the filtrate diluted with 100 ml of H_2O. This aqueous solution was then washed with $CHCl_3$ (3 × 25 ml) to remove any residual peracid and/or benzoic acid. The H_2O was removed by lyophilization to yield 2.90 g (82%) of white, "fluffy" solid: mp 62–65° (lit.[12] 73.5–74.5°).

To a stirred solution of 2.90 g (28 mmol) of **21** in 100 ml of anhydrous THF was added dropwise a solution of 4.40 g (29 mmol) of 4-chlorophenyl isocyanate in 25 ml of THF. The reaction was stirred at room temperature for 24 hr and then refluxed for 6 hr. After cooling, the reaction solution was diluted with 200 ml of H_2O and then extracted with Et_2O (4 × 50 ml). The combined Et_2O extracts were washed with H_2O (twice) and dried ($MgSO_4$), and the Et_2O was removed by rotary evaporation. The residue was fractionally crystallized from an Et_2O–petroleum ether (bp

30–60°) mixture to first remove the *N,N'*-di(4-chlorophenyl)urea and then yielded 2.45 g (34%) of **23** as white crystals: mp 161–163°.

To a cold (4°) solution of 2.00 g (7.8 mmol) of **23** in 10 ml of anhydrous pyridine was added 2.00 g (10 mmol) of TsCl. The reaction was allowed to stand in the refrigerator (4°) for 4 days. The reaction solution was then poured into 150 ml of ice water and the aqueous solution extracted with Et_2O (4 × 35 ml). The combined Et_2O extracts were washed with a portion of aqueous 1 *N* HCl and a portion of H_2O and dried ($MgSO_4$), and the Et_2O was removed by rotary evaporation. The residue was crystallized and recrystallized from an Et_2O–petroleum ether (bp 30–60°) mixture to give 1.20 g (38%) of **25** as white crystals: mp 127–128°.

To a cold (0°) solution of 0.65 g (1.6 mmol) of **25** in 150 ml of Et_2O was added 0.68 g (15 mmol) of anhydrous $(CH_3)_2NH$. The reaction was stirred at room temperature and its progress monitored by TLC (silica gel) using a $CHCl_3$–MeOH (10:1) mixture as eluent (**25**, R_f 0.62; **27**, R_f 0.13). After 7 days the reaction mixture was suction filtered to remove the precipitated salt and the filtrate rotary evaporated to remove the Et_2O and excess $(CH_3)_2NH$ to afford 0.40 g (90%) of crude **27** as a colorless oil which was used without further purification.

To a solution of 0.40 g (1.4 mmol) of **27** in 40 ml of benzene was added 2.30 g (16 mmol) of CH_3I. The reaction was allowed to stand overnight at room tempeature. The benzene was decanted from the viscous oil which formed and this oil was crystallized and recrystallized from a MeOH–Et_2O mixture to yield 0.40 g (67%) of white, granular crystals: mp 160–162° dec; infrared (KBr) 3.04, 3.31, 5.80 μ (s); NMR (Me_2SO-d_6) δ 10.0 (s, broad, 1, NH, $W_{1/2}$ = 4 Hz), 7.57 and 7.37 (2 d, 4, ArH, J = 9 Hz), 4.60 (dd, 1, H_1, J_{gem} = 12 Hz, $J_{1,2}$ = 3 Hz), 3.97 (dd, 1, H_1, J_{gem} = 12 Hz, $J_{1,2}$ = 6 Hz), 3.5–4.0 (m, 2, H_2 and H_3, overlapping signals), 3.2–3.5 (m, 2, $2H_4$), 3.27 [s, 9, $-{}^+N(CH_3)_3$]. Anal. ($C_{14}H_{20}ClIN_2O_3$) C, H, N.

***cis*-1-Trimethylammoniomethyl-2-[*N*-(4-chlorophenyl)-carbamoyloxymethyl]cyclopropane Iodide (9).** To a stirred solution of 0.40 g (3 mmol) of **28** prepared by the method of Cannon,[10] in 3 ml of anhydrous THF, was added dropwise a solution of 0.45 g (3 mmol) of 4-chlorophenyl isocyanate in 3 ml of THF. The reaction was allowed to stand at room temperature overnight. The THF was then removed by rotary evaporation and the residue dissolved in warm benzene. The insoluble solid [*N,N'*-di(4-chlorophenyl)urea] was removed by suction filtration and the product crystallized from a benzene–hexane mixture providing 0.80 g (90%) of white crystals: mp 125–126°.

To a solution of 0.40 g (1.4 mmol) of the amine in 10 ml of benzene was added 1.20 g (8.5 mmol) of CH_3I. The reaction was stirred and allowed to stand overnight at room temperature. The quaternary salt was collected by suction filtration and crystallized from a MeOH–Et_2O mixture to afford 0.40 g (67%) of **9** as white crystals: mp 178–180° dec; infrared (KBr) 2.90, 3.09, 3.21 (w), 3.30, 5.80 μ (s); NMR (Me_2SO-d_6) δ 9.90 (s, 1, NH), 7.54 and 7.30 (2 d, 4, ArH, J = 9 Hz), 4.0–4.6 (m, 2, OCH_2, overlapping signals), 3.3–4.0 (m, 2, $^+NCH_2$, overlapping signals), 3.20 [s, 9, $^+N(CH_3)_3$], 0.4–1.8 (m, 4, H_1, H_2, and $2H_3$). Anal. ($C_{15}H_{22}ClIN_2O_2$) C, H, N.

***trans*-1-Trimethylammoniomethyl-2-[*N*-(4-chlorophenyl)carbamoyloxymethyl]cyclopropane Iodide (10).** To a stirred solution of 0.40 g (3.0 mmol) of **29** prepared by the method of Cannon,[10] in 10 ml of anhydrous THF, was added dropwise a solution of 0.50 g (3.3 mmol) of 4-chlorophenyl isocyanate in 5 ml of THF. The reaction was stirred at room temperature for 8 hr. The THF was then removed by rotary evaporation; the residue was dissolved in Et_2O and extracted with aqueous 1 *N* HCl (3 × 15 ml). The combined aqueous HCl extracts were made alkaline with 10 *N* NaOH and extracted with $CHCl_3$ (3 × 25 ml). The combined $CHCl_3$ extracts were washed with H_2O, dried (Na_2SO_4), and rotary evaporated affording 0.30 g (34%) of a light brown oil.

To a solution of 0.25 g (1 mmol) of the crude amine in 20 ml of benzene was added 1.20 g (8.5 mmol) of CH_3I. The reaction was stirred and allowed to stand overnight at room temperature. The quaternary salt was removed by suction filtration and crystallized from a MeOH–Et_2O mixture to yield 0.25 g (67%) of large, white, granular crystals: mp 190–191° dec; infrared (KBr) 3.05, 3.30, 3.36 (w), 5.82 μ (s); NMR (Me_2SO-d_6) δ 9.90 (s, 1, NH), 7.57 and 7.35 (2 d, 4, ArH, J = 9 Hz), 4.08 (d, 2, OCH_2, J = 6 Hz), 3.2–3.7 (m, 2, $^+NCH_2$, overlapping signals), 3.20 [s, 9, $^+N(CH_3)_3$], 0.5–1.6 (m, 4, H_1, H_2, and $2H_3$). Anal. ($C_{15}H_{22}ClIN_2O_2$) C, H, N.

Pharmacology. Cats weighing approximately 3–4 kg were anesthetized with pentobarbital (38 mg/kg ip). Tracheal, venous, and arterial cannulae were inserted and both vagi were cut. Cats were prepared for recording of ECG, heart rate, and direct arterial blood pressure by standard methods. Systolic pressure changes are reported. All drugs were applied intravenously in normal saline.

The isolated terminal ileum of the rabbit was prepared for measurement of isotonic contraction of longitudinal smooth muscle in a 5-ml chamber maintained at 37°. The nutrient solution was the same as described previously.[13] Quantification of contractions was based on electronic integration of the area under the contraction curve, taking the response to 10^{-4} *M* ACh as the 100% response in each preparation.

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