18, 120710-38-5; **19**, 120667-28-9; **20**, 120667-29-0; **21** ($n$ = 0), 108-86-1; **21** ($n$ = 2), 103-63-9; **21** ($n$ = 3), 637-59-2; **22**, 109125-34-0; **23**, 120667-30-3; **24**, 120667-31-4; **25**, 120667-32-5; **26**, 120667-33-6; **27**, 120667-34-7; **28**, 120667-35-8; **29**, 120667-36-9; **30**, 120667-37-0; **31**, 120667-38-1; **32**, 120667-39-2; **33**, 120667-40-5; **34**, 120667-41-6; **35**, 626-15-3; **36**, 120667-42-7; **37**, 120667-43-8; **38**, 120667-44-9; **38** (de-$N$-acetyl derivative), 120667-59-6; **39**, 3433-80-5; **40**, 823-78-9; **41**, 589-15-1; **42**, 120667-45-0; **43**, 15017-44-4; **44**, 71078-92-7; **45**, 117571-56-9; **46**, 120667-46-1; **47**, 120667-47-2; **48**, 120667-48-3; **49**, 120667-49-4; **51**, 120667-50-7; **52**, 110762-21-5; **53**, 626-16-4; **54**, 623-25-6; **55**, 120667-51-8; **56**, 114791-26-3; **57**, 89-95-2; **58**, 120667-52-9; **59**, 120667-53-0; **60**, 120667-54-1; **61**, 120667-55-2; **62**, 120667-56-3; **63**, 120667-57-4; NMDA, 6384-92-5; 3-$BrC_6H_4CHO$, 3132-99-8; $H_2C{=}CHP(O)(OEt)_2$, 682-30-4; (±)-$H_2NCH(3\text{-}BrC_6H_4)CN$, 120667-58-5; $EtOCOCH(NHAc)COOEt$, 1068-90-2; $EtOCOC(NHAc)(3\text{-}ClCH_2C_6H_4CH_2)COOEt$, 120667-60-9; $EtOCOC(NHAc)(4\text{-}ClCH_2C_6H_4CH_2)COOEt$, 114791-24-1; $BrCH_2CH(OMe)_2$, 7252-83-7; $2\text{-}(HOCH_2)C_6H_4CH_2CH_2CH(OMe)_2$, 120667-62-1; 2-(2-bromoethyl)-1,3-dioxolane, 18742-02-4; 2-[3-(1,3-dioxolan-2-yl)propyl]benzenemethanol, 120667-61-0.

# Dimethylsulfonium Analogues of the Muscarinic Agent McN-A-343: [4-[[*N*-(3- or 4-Halophenyl)carbamoyl]oxy]-2-butynyl]dimethylsulfonium Perchlorates

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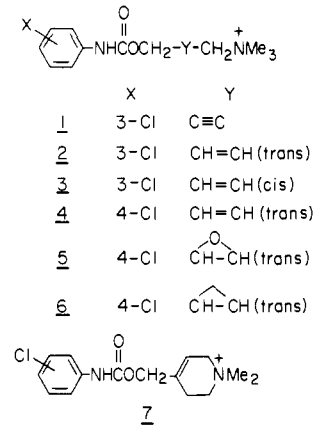
Some 3- and 4-bromophenyl and dimethylsulfonium analogues of the muscarinic agent [4-[[*N*-(3-chlorophenyl)-carbamoyl]oxy]-2-butynyl]trimethylammonium chloride (McN-A-343) (1) were synthesized. The new compounds were assayed for effects on arterial blood pressure in the pithed rat (ganglionic muscarinic activity). The dimethylsulfonium salts (**13a–d**) appeared to be partial agonists in relation to 1. The 4-bromophenyl-substituted trimethylammonium iodide **10d** exceeded 1 in potency by 3-fold. The compounds retained the selectivity for ganglionic muscarinic receptors shown by 1 since they had only weak effects on the guinea pig ileum in vitro.

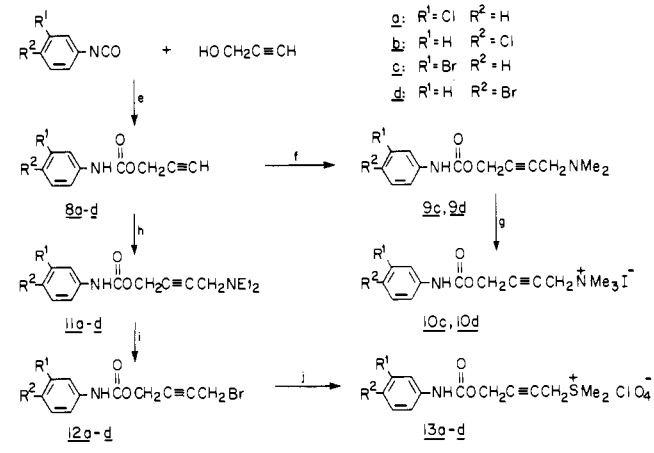
McN-A-343 (1; see Chart I) is potent in stimulating muscarinic receptors in sympathetic ganglia but has only weak direct actions on the heart and on smooth muscles.[1] The selective actions of 1 have been claimed[2,3] to be mediated by a subtype of muscarinic receptors (M1 receptors). The selectivity, however, has also been explained by a combination of low intrinsic efficacy and tissue differences in receptor reserve.[4]

The structural requirements for McN-A-343-like activity appear to be quite specific. Thus N-demethylation of 1 abolished activity whereas replacement of the trimethylammonium group by a triethylammonium group yielded an antagonist. A shift of the chlorine atom of the phenyl ring from the 3- to the 4-position produced a 3-fold enhancement of ganglionic stimulant activity. The corresponding 2-chloro derivative had only one-tenth of the potency of 1.[5] The trans olefinic derivative **2** had about half the potency of 1 as a ganglionic stimulant in the anesthetized cat whereas the cis olefin **3** was much less active. Both **2** and **3** were weak partial muscarinic agonists on the rabbit ileum. The 4-chlorophenyl analogue **4** was more potent than **2** but was less selective.[6] The trans epoxide **5** approached 1 in potency at the ganglion and was very selective since it showed little or no muscarinic activity on smooth muscle. Its cis isomer as well as the cyclopropane derivative **6** was inactive.[7] Some quaternary isoarecolinol derivatives (**7**) of **2** and **4** in which the conformational flexibility of the cationic head is reduced were about one-fifth as potent muscarinic ganglionic stimulants as 1. The corresponding tertiary amines were virtually inactive.[8] Collectively, the structure–activity studies on analogues of 1 showed that a quaternary nitrogen, unsaturation at C-2 of the amino alcohol moiety, and a distance of about 57 nm between the ether oxygen and the ammonium group are necessary for high muscarinic ganglion-stimulating activity.[7,8]

**Chart I**




**Scheme I**[a]




[a] Reagents: (e) neat; (f) bis(dimethylamino)methane, HOAc, $CuCl_2$, dioxane; (g) MeI, acetone; (h) $HNEt_2$, $CH_2O$, $CuCl_2$, dioxane; (i) BrCN, $CH_2Cl_2$; (j) $SMe_2$, $AgClO_4$, acetonitrile.

We have shown that substitution of a sulfonium group for the ammonium group in analogues of oxotremorine,

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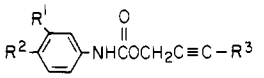
**Table I.** Physical Data of the Compounds Studied



| compd | $R^1$ | $R^2$ | $R^3$ | preparation method[a] | yield, % | mp, °C (solv)[b] | lit. data or formula[c] |
|---|---|---|---|---|---|---|---|
| **8a** | Cl | H | H | I | 93 | 39–40 (A) | 40[d] |
| **8b** | H | Cl | H | I | 90 | 126–127[e] (A) | $C_{10}H_8NO_2Cl$ |
| **8c** | Br | H | H | I | 92 | 55–57 (A) | 58–59[f] |
| **8d** | H | Br | H | I | 92 | 143–144 (A) | 144–145[f] |
| **9c** | Br | H | $CH_2NMe_2$ | II | 58 | 143–144 (B) | $C_{13}H_{15}N_2O_2Br(COOH)_2$ |
| **9d** | H | Br | $CH_2NMe_2$ | II | 64 | 179–181 (B) | $C_{13}H_{15}N_2O_2Br(COOH)_2$ |
| **10c** | Br | H | $CH_2NMe_3I$ | III | 74 | 132–134 (B) | $C_{14}H_{18}N_2O_2BrI$ |
| **10d** | H | Br | $CH_2NMe_3I$ | III | 82 | 198–199 (B) | $C_{14}H_{18}N_2O_2BrI$ |
| **11a** | Cl | H | $CH_2NEt_2$ | IV | 74 | 77–78 (A) | 77–78[g] |
| **11b** | H | Cl | $CH_2NEt_2$ | IV | 80 | 63–64 (A) | $C_{15}H_{19}N_2O_2Cl$ |
| **11c** | Br | H | $CH_2NEt_2$ | IV | 86 | 120–122 (B) | $C_{15}H_{19}N_2O_2Br(COOH)_2$ |
| **11d** | H | Br | $CH_2NEt_2$ | IV | 81 | 134–135 (B) | $C_{15}H_{19}N_2O_2Br(COOH)_2$ |
| **12a** | Cl | H | $CH_2Br$ | V | 59 | 80–81 (A) | 81–82[h] |
| **12b** | H | Cl | $CH_2Br$ | V | 58 | 115–117 (A) | 114–116[i] |
| **12c** | Br | H | $CH_2Br$ | V | 78 | 84–86 (A) | $C_{11}H_9NO_2Br_2$[j] |
| **12d** | H | Br | $CH_2Br$ | V | 82 | 119–121 (A) | $C_{11}H_9NO_2Br_2$ |
| **13a** | Cl | H | $CH_2S^+Me_2$ | VI | 46 | 150–151 (C) | $C_{13}H_{15}NO_2SClClO_4$ |
| **13b** | H | Cl | $CH_2S^+Me_2$ | VI | 58 | 157–158 (C) | $C_{13}H_{15}NO_2SClClO_4$ |
| **13c** | Br | H | $CH_2S^+Me_2$ | VI | 69 | 137–138 (C) | $C_{13}H_{15}NO_2SBrClO_4$ |
| **13d** | H | Br | $CH_2S^+Me_2$ | VI | 62 | 156–158 (C) | $C_{13}H_{15}NO_2SBrClO_4$ |

[a] See Experimental Section. [b] Recrystallization solvents: A, $CHCl_3$/hexane; B, EtOH/ether; C, $CH_3CN$/ether. [c] Unless otherwise indicated, C, H, and N analyses were within ±0.4% of the theoretical values. [d] Reference 10. [e] A mp of 49 °C is reported in ref 13. [f] Reference 13. [g] Reference 14. [h] Reference 15. [i] Reference 7. [j] C: calcd, 38.07; found, 38.55.

*N*-(4-pyrrolidinyl-2-butynyl)-2-pyrrolidone, retains muscarinic potency.[9] In view of the structural resemblance of **1** to oxotremorine analogues, we have synthesized some dimethylsulfonium derivatives (**13a–d**) of **1**. We also describe some new trimethylammonium (**10c** and **10d**) and dimethylamino analogues (**9c** and **9d**) of **1** (Scheme I). The new compounds were assayed for effects on arterial blood pressure in the pithed rat (ganglionic muscarinic activity), for muscarinic activity on the isolated guinea pig ileum, and for nicotinic activity on the frog rectus abdominis muscle.

## Chemistry

The syntheses of the compounds are outlined in Scheme I. The carbamates **8a–d** and the bromides **12a–d** were prepared by methods described previously.[10,11] A condensation between **8c** or **8d** and bis(dimethylamino)methane[12] afforded the dimethylamines **9c** and **9d**. Alkylation of dimethyl sulfide by **12a–d** in the presence of silver perchlorate as described previously[9] gave the sulfonium compounds **13a–d** as perchlorate salts. Some physical data on the compounds synthesized are summarized in Table I.

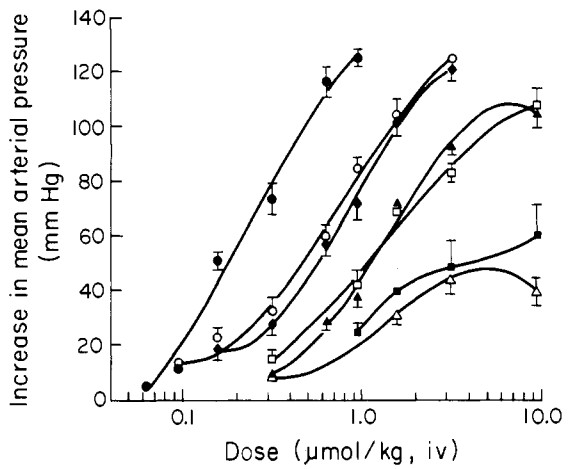



**Figure 1.** Dose–response curves of **10d** (●), **1** (○), **10c** (♦), **13b** (□), **13d** (▲), **13a** (■), and **13c** (△) obtained from blood pressure measurements in the pithed rat. Data points are mean values, and vertical bars show standard errors. Four to six rats were used for each compound.

## Pharmacology

**Ganglionic Muscarinic Activity.** Changes in mean arterial blood pressure of the pithed rat which had been treated with pentolinium (to block nicotinic receptors) were used as a measure of ganglionic muscarinic activity. The initial blood pressure of this preparation averaged 63 ± 4 mmHg ($N$ = 17). With the exception of the tertiary amines **9c** and **9d**, which were inactive when assayed over a dose range of 1–10 μmol/kg, the new compounds pro-

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Table II. Intravenous Doses of 1 and Its Analogues Required To Produce a Half-Maximal Pressor Response in the Pithed Rat

| compd | $ED_{50}$, μmol/kg (mean ± SE) | compd | $ED_{50}$, μmol/kg (mean ± SE) |
|---|---|---|---|
| 1 | 0.59 ± 0.04 | **13b** | 1.52 ± 0.16[a] |
| **10c** | 0.70 ± 0.02 | **13c** | 1.47 ± 0.11[a] |
| **10d** | 0.22 ± 0.02 | **13d** | 1.56 ± 0.11[a] |
| **13a** | 1.49 ± 0.06[a] | | |

[a] These compounds produced submaximal pressor effects.

duced dose-dependent increases in mean arterial pressure (Figure 1). This predominant pressor response was preceded by a small, transient fall in blood pressure at each dose tested. These effects were qualitatively similar to those elicited by 1. Since the hypertensive effects of 1 and its analogues were abolished by pretreatment with *N*-methylatropine (1.3 μmol/kg), they most likely were mediated by activation of muscarinic receptors.

Substitution of a bromine atom for the chlorine atom in the phenyl ring of 1 had no apparent effect on potency. Thus the dose–response curve of the *N*-(3-bromophenyl)carbamate **10c** was virtually identical with that displayed by 1 (Figure 1). A shift of the bromine atom of **10c** to the 4-position of the phenyl ring (to give **10d**) was accompanied by a 3-fold increase in potency.

In addition to ring modifications, we examined four analogues that contained a dimethylsulfonium group in place of the trimethylammonium moiety. Replacement of the trimethylammonium group of the *N*-(3-halophenyl)carbamates 1 and **10c** by a dimethylsulfonium group yielded compounds (**13a** and **13c**) that, by eliciting a submaximal response, behaved like partial agonists. However, in terms of potency ($ED_{50}$ values), they differed less than 2.5-fold from the parent compounds, 1 and **10c** (Table II). The *N*-(4-halophenyl) analogues (**13b** and **13d**) of the dimethylsulfonium salts **13a** and **13c** were nearly full agonists with respect to the pressor response. Their potencies, however, were similar to those of **13a** and **13c**.

**Guinea Pig Ileum.** Compounds **10c** and **10d** behaved similarly to 1 by being weak partial agonists on the ileum. Over the concentration range of $1 \times 10^{-6}$ to $1 \times 10^{-4}$ M, 1, **10c**, and **10d** produced dose-dependent contraction. The maximal response varied between 17 and 40% of that obtained with carbachol. In contrast, the four dimethylsulfonium analogues (**13a–d**) were completely inactive when assayed as muscarinic agonists on the ileum. The compounds appeared to be weak antagonists of carbachol on this preparation, but this antagonism was not examined further.

**Frog Rectus Abdominis.** The trimethylammonium (**10c** and **10d**) and dimethylsulfonium (**13a–d**) derivatives were tested for nicotinic activity on the frog rectus abdominis preparation. Only compounds **10c** and **10d** displayed contractile activity via the stimulation of nicotinic receptors. **10c** and **10d** had equipotent molar ratios relative to carbachol of 4.0 ± 0.7 ($N$ = 8) and 3.7 ± 0.6 ($N$ = 4), respectively. The corresponding value for 1 was 3.8 ± 0.4 ($N$ = 8), which agrees with its previously reported potency.[16] The $EC_{50}$ value for carbachol was 5.8 ± 0.6 μM on the frog rectus.

## Discussion

In contrast to the tertiary amines **9c** and **9d**, all of the trimethylammonium and dimethylsulfonium derivatives induced pressor responses in the pithed rat by activation of muscarinic receptors in the ganglia. These actions on the ganglia appeared to be selective since the compounds had little or no effect on the smooth muscle of the guinea pig ileum.

Our results show that a bromine atom may replace the chlorine atom in the phenyl ring of 1 without any change in potency. The increased potency caused by the presence of a bromine atom at the 4-position of the phenyl ring (**10d**) is reminiscent of similar increases in potency caused by 4-chloro substitution in 1[5] or in its olefinic derivative (4 vs **2**).[6,17]

Previous structural modifications of the trimethylammonium group of 1 have yielded compounds with reduced potency.[5,8] The dimethylsulfonium derivatives reported here also were less potent than 1. Their behavior as partial agonists suggests that replacement of the trimethylammonium group in 1 and in its analogues by a dimethylsulfonium group decreases efficacy at ganglionic muscarinic receptors. The effect of such replacement on affinity appears to be less dramatic. Similar observations were made recently with sulfonium analogues of oxotremorine.[9] Comparison of the relative maximal responses of **13a** and **13c** with those of **13b** and **13d** (Figure 1) indicates that a shift of the halogen atom from the 3- to the 4-position is accompanied by an increase in efficacy. Because of the absence of a receptor reserve for partial agonists, their $ED_{50}$ values generally agree with their dissociation constants.[18,19] Consequently, the similar $ED_{50}$ values of **13a–d** imply that they have similar affinity for ganglionic muscarinic receptors. Collectively, these results suggest that variations in potency observed among the new compounds may be ascribed to variations in agonist efficacy rather than to differences in affinity for the receptor.

## Experimental Section

**Chemistry. General Comments.** Melting points (uncorrected) were determined in open glass capillaries on a Thomas-Hoover apparatus. Routine $^1$H NMR spectra were recorded on a JEOL FX 90Q or a Bruker AM360/Wb spectrometer and were referenced to internal tetramethylsilane. IR spectra (recorded on a Perkin-Elmer 157-G spectrometer) and mass spectra (recorded at 70 eV on a Hewlett-Packard 5981A mass spectrometer) were all in accordance with the assigned structures. The elemental analyses (C, H, and N), which were performed by Galbraith Laboratories, Knoxville, TN, were within ±0.4% of the theoretical values unless otherwise indicated. Thin-layer chromatography was carried out on Merck silica gel 60 $F_{254}$ analytical plates. Chromatographic spots were visualized by UV and/or $I_2$.

**Synthesis.** Below are given representative examples of the chemical reactions referred to in Table I and Scheme I.

**2-Propynyl *N*-(3-Bromophenyl)carbamate (8c). Method I.** A mixture of 3-bromophenyl isocyanate (5.0 g, 25 mmol) and propargyl alcohol (1.6 g, 28 mmol) was stirred and cooled on an ice bath. A few drops of triethylamine was added to start the exothermic reaction. The ice bath was removed, and the stirring was continued for 1 h. The semisolid reaction mixture was recrystallized directly to yield 5.9 g (92%) of pure **8c**: $^1$H NMR ($CDCl_3$) δ 7.40–7.09 (m, 4 H), 6.90 (br s, NH), 4.78 (d, $J$ = 2.4 Hz, $OCH_2$), 2.52 (t, $J$ = 2.4 Hz, CH); MS, $m/e$ (relative intensity) 255 [$M^+$ + 2 (46)], 253 [$M^+$ (41)], 91 (100).

**4-(Dimethylamino)-2-butynyl *N*-(4-Bromophenyl)carbamate (9d). Method II.** A mixture of **8d** (0.80 g, 3.15 mmol), bis(dimethylamino)methane (0.35 g, 3.5 mmol), acetic acid (0.21 g, 3.46 mmol), and $CuCl_2$ (0.1 g) in dioxane (10 mL) was stirred at room temperature for 2 days. The volatiles were evaporated, and the residue was partitioned between aqueous 1 N HCl and ether. The aqueous layer was made alkaline (pH 10) with $K_2CO_3$ and $NH_4OH$ and extracted with $CH_2Cl_2$. The organic layer was

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dried ($K_2CO_3$) and concentrated. The residue was converted to the oxalate salt and recrystallized to give 0.81 g (64%) of **9d** $(COOH)_2$: $^1H$ NMR ($CD_3OD$) $\delta$ 7.40 (s, 4 H), 4.85 (t, $J$ = 1.8 Hz, $OCH_2$), 4.07 (t, $J$ = 1.8 Hz, $CH_2N$), 2.90 (s, Me's); MS, $m/e$ (relative intensity) 312 [$M^+$ + 2 (5.9)], 310 [$M^+$ (5.6)], 95 (100).

**4-(Dimethylamino)-2-butynyl *N*-(3-Bromophenyl)carbamate Methiodide (10c). Method III.** Compound **10c** was prepared by adding an excess of $CH_3I$ to a solution of **9c** (0.30 g, 0.96 mmol) in acetone (10 mL). Concentration and recrystallization yielded 0.32 g (74%) of pure **10c**: $^1H$ NMR ($CD_3OD$) $\delta$ 7.75 (s, 1 H), 7.36–7.34 (m, 1 H), 7.20–7.18 (m, 2 H), 4.90 (t, $J$ = 1.8 Hz, $OCH_2$), 4.42 (t, $J$ = 1.8 Hz, $CH_2N$), 3.30 (s, Me's); MS, $m/e$ (relative intensity) 268 [$M^+$ + 2 − $N(Me)_2$ (7.8)], 266 [$M^+$ − $N(Me)_2$ (9.8)], 142 (100).

**4-(Diethylamino)-2-butynyl *N*-(4-Chlorophenyl)carbamate (11b). Method IV.** A mixture of **8b** (30 g, 143 mmol), paraformaldehyde (4.2 g, 143 mmol), diethylamine (10.5 g, 143 mmol), and $CuCl_2$ (0.5 g) in dioxane (250 mL) was stirred at room temperature for 2 days. The volatiles were evaporated, and the residue was extracted as described for compound **9d**. The base was recrystallized to yield 33.7 g (80%) of **11b**: $^1H$ NMR ($CDCl_3$) $\delta$ 7.43–7.18 (m, 4 H), 7.00 (br s, NH), 4.80 (t, $J$ = 1.8 Hz, $OCH_2$), 3.50 (t, $J$ = 1.8 Hz, $CH_2N$), 2.60 (q, $J$ = 7.2 Hz, 4H), 1.09 (t, $J$ = 7.2 Hz, 6H); MS, $m/e$ (relative intensity) 296 [$M^+$ + 2 (1.3)], 294 [$M^+$ (2.8)], 69 (100).

**4-Bromo-2-butynyl *N*-(4-Bromophenyl)carbamate (12d). Method V.** A solution of **11d** (7.9 g, 23.4 mmol) in $CH_2Cl_2$ (50 mL) was added dropwise to a solution of BrCN (2.7 g, 25.8 mmol) in $CH_2Cl_2$ (50 mL). The mixture was stirred at room temperature overnight and then washed with aqueous 0.5 N HCl. The organic layer was dried ($MgSO_4$) and concentrated. A liquid fraction was removed by vacuum distillation (bp 40 °C/0.1 mmHg), and the solid residue was recrystallized to give 6.6 g (82%) of pure **12d**: $^1H$ NMR ($CDCl_3$) $\delta$ 7.50–7.20 (m, 4 H), 6.80 (br s, NH), 4.83 (t, $J$ = 2.0 Hz, $OCH_2$), 3.93 (t, $J$ = 2.0 Hz, $CH_2Br$); MS, $m/e$ (relative intensity) 347 [$M^+$ + 2 (4.4)], 199 (58), 197 (57), 51 (100).

**[4-[[*N*-(3-Chlorophenyl)carbamoyl]oxy]-2-butyn-1-yl]dimethylsulfonium Perchlorate (13a). Method VI.** To a solution of anhydrous $AgClO_4$ (0.68 g, 3.30 mmol) and dimethyl sulfide (0.17 mL, 3.64 mmol) in $CH_3CN$ (30 mL) was added **12a** (1.0 g, 2.88 mmol) in portions. The mixture was stirred at room temperature for 5 days, after which precipitated AgBr was removed by filtration. The solution was concentrated and if necessary purified on a silica gel column with $MeOH/CH_2Cl_2$ (3:17) as eluant. Recrystallization gave 0.58 g (46%) of pure **13a**: $^1H$ NMR ($CD_3CN$) $\delta$ 8.00 (br s, NH) 7.60–7.55 (m, 1 H), 7.35–7.25 (m, 2 H), 7.12–7.08 (m, 1 H), 4.86 (t, $J$ = 2.0 Hz, $OCH_2$), 4.17 (t, $J$ = 2.0 Hz, $CH_2S$), 2.82 (s, Me's); MS $m/e$ (relative intensity) 224 [$M^+$ + 2 − $S(Me)_2$ (12)], 222 [$M^+$ − $S(Me)_2$ (38)], 153 (100).

**Blood Pressure Recording in the Pithed Rat.** Experiments were conducted in male Sprague-Dawley rats weighing between 250 and 325 g. Animals were anesthetized with sodium amytal (100 mg/kg, ip) and then intubated with a tracheal tube. Animals were subsequently pithed with a steel rod inserted through the ocular orbit and respirated with room air (1 mL/100 g of body weight, 75 strokes/min). Blood pressure changes were detected from the femoral artery via a PE 50 cannula coupled to a Deseret transducer. A femoral vein was cannulated for intravenous infusion of drugs. All drugs were dissolved in 0.9% saline and injected in a volume of 0.1 mL/100 g of body weight. Body temperature was measured with a rectal thermistor probe and maintained at 37 °C with a heating pad. Nicotinic receptors were blocked by administering pentolinium tartrate (18.5 μmol/kg, iv) 20–25 min prior to agonist infusion. In some experiments, *N*-methylatropine bromide (1.3 μmol/kg, iv) was administered 10 min before agonists were tested. Dose–response curves for two or three compounds were recorded in the same animal.

**Guinea Pig Ileum.** A standard guinea pig ileum preparation was set up in Tyrode solution (pH 7.4) at 37 °C as described previously.[19] The Tyrode solution contained hexamethonium (0.3 mM). Contractions were recorded isotonically at 1 g of tension with an electromechanical displacement transducer and a potentiometric recorder. Concentration–response curves were constructed by the cumulative dose–response technique by increasing stepwise the concentration of agonist by a factor of 2.15.

**Frog Rectus Abdominis.** A standard frog rectus abdominis preparation was set up at 22 °C in aerated Clark–Ringer solution (pH 7.4) as described previously.[16] Contractions were recorded as described above for the ileum. The preparation was exposed to each drug concentration for 5 min. Equipotent molar ratios relative to carbachol were determined in three-point assays.[20]

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(20) Edinburgh Pharmacology Department Staff. *Pharmacological Experiments on Isolated Preparations*; Livingstone: Edinburgh, 1968; pp 13 and 28.