sition-state mimics for aspartic acid proteases, the hydroxyethylene, dihydroxyethylene, and hydroxyethylamine isosteres appear to provide the greatest intrinsic affinity for the enzyme. A number of inhibitors from these structural classes show high specificity for HIV protease in comparison to other aspartic acid proteases.

A variety of highly potent and specific inhibitors of the viral protease are therefore available. Moreover, several of these molecules strongly inhibit viral replication in cell culture at nanomolar concentrations. The chief remaining challenge in transforming such molecules into effective therapeutic agents lies in overcoming deficiencies in a metabolism, distribution, and oral bioavailability. The fact that the more potent inhibitors are largely peptide in character presents a significant obstacle to this goal.[121]

One of the intriguing circumstances in this area has been the relatively early availability of high resolution structural information. The possibility of leapfrogging classical inhibitor design and the resulting peptoid class of inhibitors is appealing. Some efforts are already apparent. Although still peptide in nature, the symmetrical inhibitors reported by Kempf et al. were based on analysis of the enzyme's unique architecture. The discovery that haloperidol weakly inhibits HIV protease resulted directly from computer-assisted analysis of potential protein–ligand interactions. Strong efforts have been mounted in several laboratories to exploit this rare opportunity to test current strategies for de novo drug design and to develop novel classes of inhibitors.

Acknowledgment. The valuable assistance of Beverly Schaefer in the preparation of this manuscript is gratefully acknowledged, as is the provision of artwork by Paula M. D. Fitzgerald.

Registry No. Aspartic proteinase, 78169-47-8.

(121) Plattner, J. J.; Norbeck, D. W. *Drug Discovery Tech.*; Clark, C. R., Moos, W. H. Eds.; Ellis Horwood: Chichester, England, 1990; pp 92–126.
(122) Britcher, S. F. Unpublished results.

Articles

Cholinergic Activity of Acetylenic Imidazoles and Related Compounds

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A series of acetylenic imidazoles related to oxotremorine (**1a**) were prepared and evaluated as cholinergic agents with in vitro binding assays and in vivo pharmacological tests in mice. 1-[4-(1*H*-Imidazol-1-yl)-2-butynyl]-2-pyrrolidinone (**1b**) was a cholinergic agonist with one-half the potency of oxotremorine. Analogues of **1b** with a 5- or 2-methyl substituent in the imidazole ring (compounds **1c** and **1g**) were cholinergic partial agonists. Analogues of **1b** with a methyl substituent at the 5-position in the pyrrolidinone ring (**7b**) or at the α-position in the acetylenic chain (**8b**) were antagonists. Various analogues of these imidazole acetylenes where the pyrrolidinone ring was replaced by an amide, carbamate, or urea residue were prepared. Several compounds which contained 5-methylimidazole as the amine substituent were partial agonists. The activities of the imidazole compounds are compared with those of the related pyrrolidine and dimethylamine analogues. Agonist and antagonist conformations for these compounds at muscarinic receptors are proposed.

Introduction

There has been considerable interest recently in the development of cholinergic agonists and partial agonists for the treatment of Alzheimer's disease or as cognition activators.[1] As part of a program in this area we have prepared a series of compounds related to oxotremorine (**1a**). Our major interest in this work was the preparation of cholinergic partial agonists in the belief that such a compound would selectively ameliorate the cholinergic deficits characteristic of Alzheimer's disease without producing excessive cholinergic side effects such as tremor, salivation, or lachrimation which may be associated with a full cholinergic agonist. In this paper we describe the synthesis of various acetylenic amines and their evaluation as cholinergic agents in binding assays and in in vivo pharmacological tests in mice.

Oxotremorine is a potent, centrally active, cholinergic agonist. Since its discovery in 1961,[2] many related acetylenic amines have been described. It has been shown

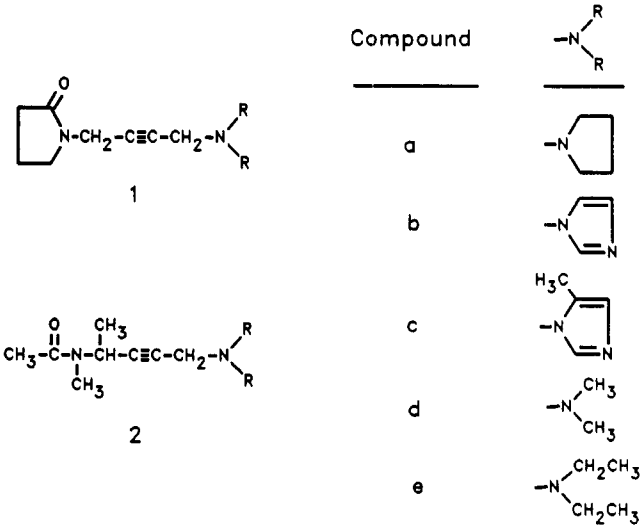

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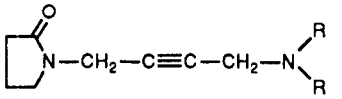
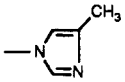
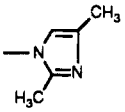
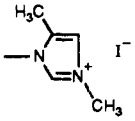
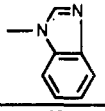
Table I. Structures and Activities for Various Substituted 4-Amino-2-butynyl-2-pyrrolidinones



compound no.	—NRR	receptor binding data[a] K_i Oxo-M, nM	K_i QNB, nM	K_i ratio (QNB/Oxo-M)	ED_{50}, mg/kg cholinergic agonist data[b] tremor	saliv	lacrim	oxotremorine antagonism[b] tremor	saliv	lacrim
1a		0.50	193	386	0.11	0.22	0.28			
1b		1.30	600	460	0.45	0.45	0.45	>100	>100	>100
1c		3.20	64.0	20	2.50	>100	>100	>100	>100	0.80
1d		1.10	2600	2364	–	–	–	–	–	–
1f		10.3	377	37	>100	>100	>100	>100	37.0	14.2
1g		0.30	3.80	13	0.25	0.37	>100	>100	>100	0.45
1h		29.1	56.9	2	>100	>100	>100	9.7	2.5	0.54
1j		68.0	160	2.4	>100	>100	>100	54	14.2	8.0
1k		53.0	303	5.7	30	>100	>100	>100	25	9.7
1m		I	I	–	>100	>100	>100	>100	>100	>100
1n		I	I	–	>100	>100	>100	>100	>100	>100
1p		I	I	–	>100	>100	>100	>100	>100	80

[a] I indicates K_i > 10000 nM. For K_i determination, each drug was investigated at five concentrations and each observation was the mean of three experiments; standard error was <5%. [b] Salivation and lacrimation abbreviated saliv and lacrim; 95% confidence intervals were between 0.4 and 2.0 times the ED_{50}.

that minor modifications in structure profoundly affect activity in this series of compounds. Introduction of a single methyl group at the various sites in the oxotremorine molecule greatly reduces potency or gives compounds with cholinergic antagonist properties.[3] A related compound, BM-5 (**2a**), a cholinergic partial agonist, has also been described[4] and proposed as a compound for improving mental performance without the side effects of oxotremorine.[5,6] We have prepared analogues of oxotremorine and BM-5 in a search for new cholinergic partial agonists which may be useful in the treatment of cognitive disorders. In this report, we describe the synthesis and activities

(1) For recent reviews, see: Moos, W. H.; Davis, R. E.; Schwarz, R. D.; Gamzu, E. R. Cognition Activators. *Med. Res. Rev.* **1988**, *8*, 353–393. Baker, R.; Saunders, J. Central Muscarinic Ligands and Receptors. *Ann. Rep. Med. Chem.* **1989**, *24*, 31–40.

(2) Cho, A. K.; Haslett, W. L.; Jenden, D. J. The Identification of an Active Metabolite of Tremorine. *Biochem. Biophys. Res. Commun.* **1961**, *5*, 276–279.

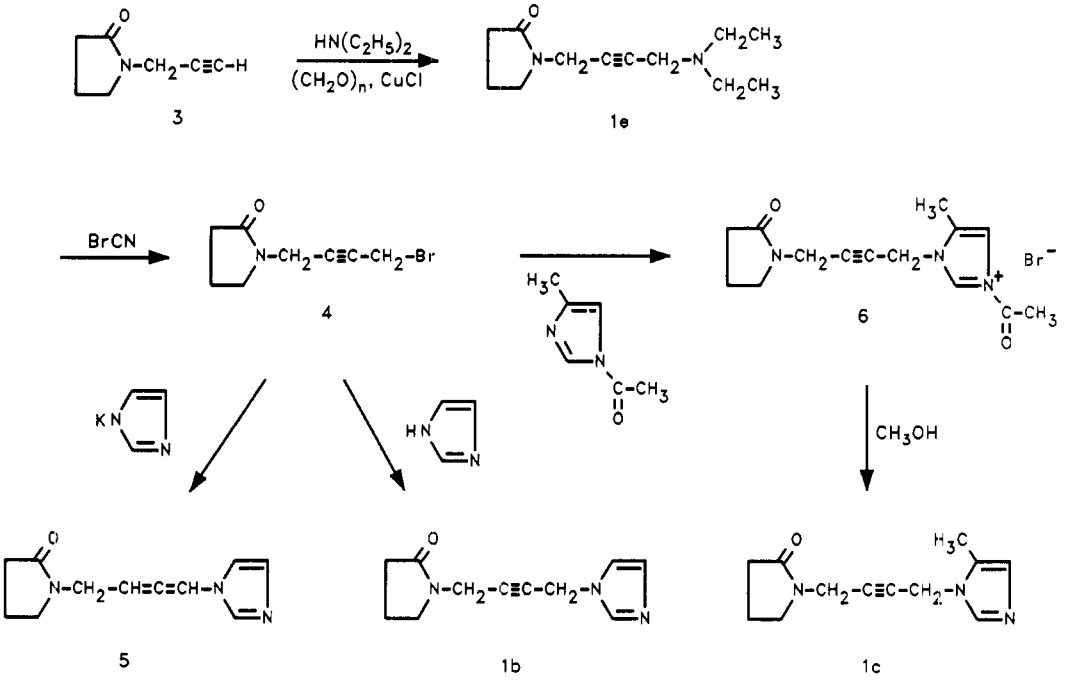
(3) Ringdahl, B.; Jenden, D. J. Affinity, Efficacy and Stereoselectivity of Oxotremorine Analogues for Muscarinic Receptors in the Isolated Guinea Pig Ileum. *Mol. Pharmacol.* **1983**, *23*, 17–25.

(4) Resul, B.; Dahlbom, R.; Ringdahl, B.; Jenden, D. J. *N*-Alkyl-*N*-(4-*tert*-amino-1-methyl-2-butynyl)carboxamides, a New Class of Potent Oxotremorine Antagonists. *Eur. J. Med. Chem.—Chim. Ther.* **1982**, *17*, 317–322.

(5) Engström, C.; Undén, A.; Ladinsky, H.; Consolo, S.; Bartfai, T. BM-5, a Centrally Active Partial Muscarinic Agonist with Low Tremorogenic Activity: in Vivo and in Vitro Studies. *Psychopharmacology* (Berlin) **1987**, *91*, 161–167.

(6) Brown, F.; Clark, M.; Graves, D.; Hadley, M.; Hatcher, J.; McArthur, R.; Riley, G.; Semple, J. Variation of Muscarinic Activities of Oxotremorine Analogues. *Drug Dev. Res.* **1988**, *14*, 343–347.

Scheme I



of oxotremorine analogues where the pyrrolidine ring is replaced by other heterocyclic rings (see Table I). One of these compounds, **1c**, having 5-methylimidazole as the amine substituent was found to be a cholinergic partial agonist. We also report a series of analogues of **1c** where the pyrrolidinone ring is replaced by an amide (**2c**, **9c**, **10c**), a carbamate (**11c–16c**), or urea (**17c–21c**) residue (Table II). The activities of these compounds are compared with those of the corresponding imidazole (**7b–21b**), pyrrolidine (**7a–21a**), and dimethylamine analogues (**7d–21d**). The compounds prepared include potent cholinergic agonists and antagonists and several compounds which were active as partial agonists.

We have used molecular modeling studies to understand agonist, partial agonist, and antagonist activities in terms of likely conformational differences caused by changes in structure. The three-dimensional structures of **1c** and **2a** were determined by X-ray crystallography to aid in these studies.

Chemical Methods

1-(2-propynyl)-2-pyrrolidinone (**3**) was prepared from propargyl bromide and the potassium salt of pyrrolidinone.[7] Oxotremorine (**1a**) was prepared by literature procedures by reacting **3** with paraformaldehyde and pyrrolidine using cuprous chloride as catalyst.[7] The dimethylamine (**1d**)[8] and diethylamine (**1e**)[9] (Scheme I) analogues were prepared similarly. The remaining compounds of Table I were prepared from 1-[4-(diethylamino)-2-butynyl]-2-pyrrolidinone (**1e**) as outlined in Scheme I for the preparation of **1b** and **1c**. Compound **1e** was reacted with cyanogen bromide to give 1-(4-bromo-2-propynyl)-2-pyrrolidinone (**4**).[10,11] This was reacted with excess imidazole to give 1-[4-(1*H*-imidazol-1-yl)-2-butynyl]-2-pyrrolidinone (**1b**). It was essential to avoid use of strong bases in this reaction, as compound **4** reacted with the potassium salt of imidazole to give allene **5** as the major product.[12] Reaction of **4** with 4-methylimidazole gave a 2:3 mixture of **1c** and its 4-methyl isomer **1f** as determined by GC or by NMR spectroscopy. The mixture could not be separated by chromatography, but could be separated with difficulty by fractional crystallization of the oxalate salts. Compound **1c** was more conveniently prepared from 1-acetyl-4-methylimidazole[13] by using a method first described by Godefroi and Mentjens[14] for the preparation of 1,5-disubstituted imidazoles. Compound **4** was refluxed

(7) Bebbington, A.; Shakeshaft, D. An Improved Synthesis for Oxotremorine. *J. Med. Chem.* **1965**, *8*, 274–275.

(8) Dickinson, W. B. *N*-(4-Tertiary amino-2-butynyl)-*N*-alkylcarboxamides. US Patent 3,354,178, Nov 21, 1967 (*Chem. Abstr.* **1968**, *68*, 114430z).

(9) Levy, J.; Estera, M-B. Comparison in Mice of Central and Peripheral Cholinergic or Anticholinergic Properties of Some Structural Analogs of 1-(2-Oxo-1-pyrrolidinyl)-4-(1-pyrrolidinyl)-2-butyne (Oxotremorine). *C. R. Acad. Sci., Paris, Ser. D.* **1967**, *264*, 2250.

(10) Resul, B.; Ringdahl, B.; Dahlbom, R. Acetylenic Compounds of Potential Pharmacological Value. XXX. Synthesis and Pharmacological Properties of *N*-(4-Pyrrolidino-2-pentynyl) Substituted 2-Pyrrolidones and Succinimides. *Acta Pharm. Suec.* **1979**, *16*, 161–165. We have observed the formation of *N*-ethyl-*N*-[4-(2-oxo-1-pyrrolidinyl)-2-butynyl]cyanamide as a byproduct (ca. 7%) in the reaction of **1e** with cyanogen bromide.

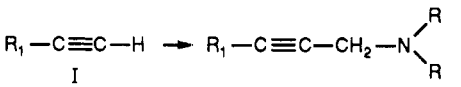
(11) Resul, B.; Lewander, T.; Zetterström, T.; Ringdahl, B.; Muhi-Eldeen, Z.; Dahlbom, R. Synthesis and Pharmacological Properties of *N*-[(1-Azetidinyl)-2-butynyl]-2-pyrrolidone, a Highly Potent Oxotremorine-Like Agent. *J. Pharm. Pharmacol.* **1980**, *32*, 439–440.

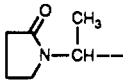
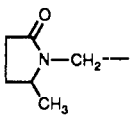
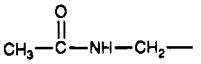
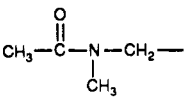
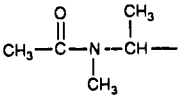
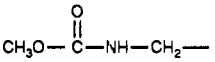
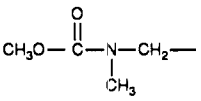
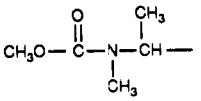
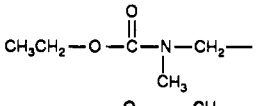
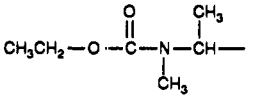
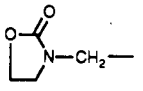
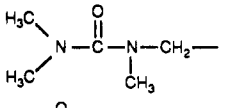
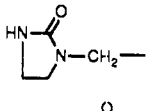
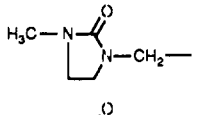
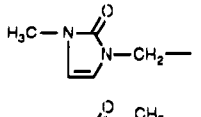
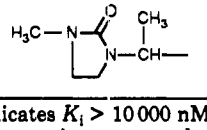
(12) While no 1,4-diamino-1,2-butadiene analogues of oxotremorine or BM-5 have been reported, related rearrangements have been noted in the synthesis of intermediate *N*-propargyl heterocycles; see: e.g., Dickinson, W. B.; Lang, P. C. Synthesis and Rearrangement of an Allenamide. *Tetrahedron Lett.* **1967**, *32*, 3035–3040. Nilsson, B. M.; Hacksell, U. Base-Catalyzed Cyclization of *N*-Propargylamides to Oxazoles. *J. Heterocycl. Chem.* **1989**, *26*, 269–275. Allene **5** shows weak cholinergic agonist activity (K_i Oxo-M 67 nM, K_i QNB > 10000 nM, tremor 17.3, salivation 14.2, and lachrimation 30.8 mg/kg). Rearrangement to allenes was not a problem in the synthesis of compounds **1m–p**.

(13) Jezo, I.; Markovic, O. Preparation of *N*-Acetylimidazole. *Chem. Zvesti* **1978**, *32*, 128–130.

(14) Godefroi, E. F.; Mentjens, J. H. F. M. A Regiospecific N-Substitution of Asymmetrically Alkylated Imidazoles. The Preparation of 1,5-Dialkyl- and 1,2,5-Trialkylimidazoles. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 56–58.

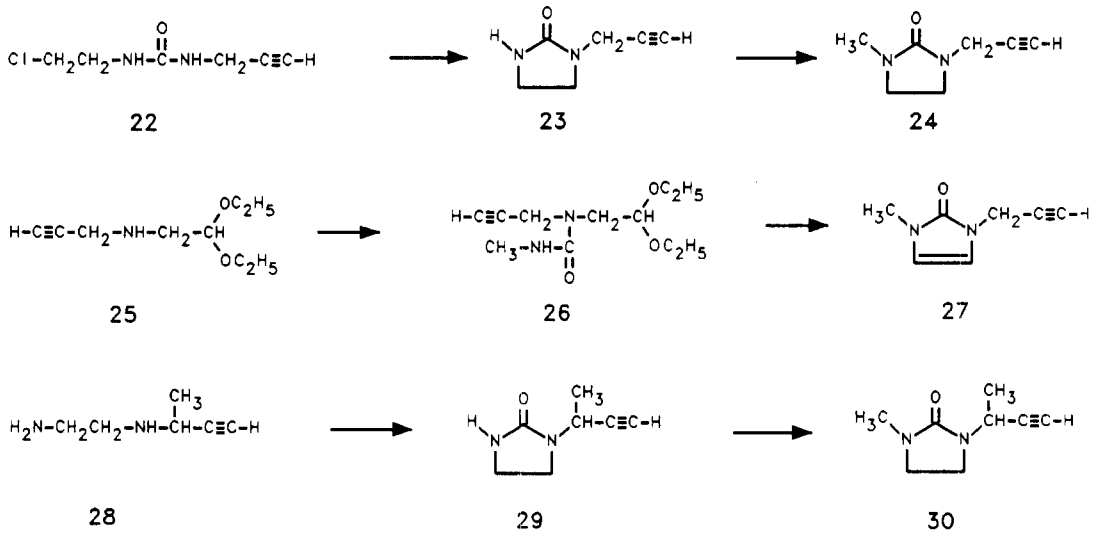
Table II. Structures and Activities for Various Acetylenic Amines



compound			receptor binding data[a]			ED_{50}, mg/kg					
	structure[c]					cholinergic agonist data[b]			oxotremorine antagonism[b]		
no.	R_1	$-N(R)(R)$	K_i Oxo-M, nM	K_i QNB, nM	K_i ratio QNB/Oxo-M	tremor	saliv	lacrim	tremor	saliv	lacrim
7a		pyrrolidine	1.10	14.0	13	>30	>30	>30	3.0	0.55	0.55
7b		imidazole	33.5	566	17	>100	>100	>100	45.0	3.7	2.0
7c		5-Me-Im[c]	5.22	16.8	3.2	>100	>100	>100	25.4	2.5	0.45
7d		NMe_2	26.4	1702	65	100	6.6	6.6	>100	>100	>100
8a		pyrrolidine	1.5	14.0	9.4	>30	>30	>30	1.7	2.0	0.55
8b		imidazole	23.0	171	7.4	>100	>100	>100	20.9	1.1	0.54
8c		5-Me-Im	1.68	11.6	6.9	>100	>100	>100	14.2	1.4	0.80
8d		NMe_2	7.10	690	97	1.7	3.0	3.7	>100	>100	>100
9b		imidazole	187	I		>100	>100	>100	>100	>100	>100
9c		5-Me-Im	213	I		>100	>100	66	>100	66	66
10a		pyrrolidine	0.92	260	283	0.30	0.55	0.55	>10	>10	>10
10b		imidazole	1.92	I		0.97	1.40	1.40	>100	>100	>100
10c		5-Me-Im	3.61	172	48	5.4	45	>100	>100	>100	6.6
10d		NMe_2	4.20	I		0.97	1.73	1.73	>10	>10	>10
2a		pyrrolidine	0.86	23.4	27	>10	0.55	0.66	3.7	>10	>10
2b		imidazole	12.0	1500	125	2.0	3.0	3.0	>100	>100	>100
2c		5-Me-Im	10.0	184	18	>100	>100	>100	80	3.7	1.10
2g		2-Me-Im	1.60	19.0	12	>100	>100	>100	11.8	0.20	0.05
11c		5-Me-Im	191	6825	36	>100	>100	>100	>100	80	66
12a		pyrrolidine	2.60	550	211	1.4	5.5	3.0	>10	>10	>10
12b		imidazole	10.2	I		2.0	4.5	4.5	>100	>100	>100
12c		5-Me-Im	36.0	1001	28	4.5	>100	>100	>100	5.4	3.0
12d		NMe_2	19.0	I		17.3	14.3	9.7	>30	>30	>30
13a		pyrrolidine	1.50	64.0	43	9.7	14.2	20.9	>100	>100	>100
13b		imidazole	13.0	1355	104	6.6	8.0	8.0	>100	>100	>100
13c		5-Me-Im	9.5	97.0	10	97	>100	>100	>100	6.6	3.7
13d		NMe_2	16.0	I		11.8	17.3	17.3	>100	>100	>100
14a		pyrrolidine	65.0	4219	65	66	>100	>100	>100	>100	>100
14b		imidazole	206	I		>100	>100	>100	>100	97	97
14c		5-Me-Im	156	568	3.6	97	>100	>100	30	66	66
15a		pyrrolidine	22	110	5.0	>100	>100	>100	>100	>100	97
15b		imidazole	273	I		>100	>100	>100	>100	66	54
15c		5-Me-Im	156	568	3.6	>100	>100	>100	30	17.3	9.7
16a		pyrrolidine	8.9	1362	153	3.7	5.4	>10	>10	>10	>10
16b		imidazole	5.7	929	164	3.0	2.0	3.0	>100	>100	>100
16c		5-Me-Im	18.0	151	8.4	30	>100	>100	>100	80	37
17a		pyrrolidine	3.6	140	39	1.2	>10	>10	>10	>10	6.6
17b		imidazole	14.6	I		11.8	25.4	>100	>100	>100	11.8
17c		5-Me-Im	82.0	I		45.2	>100	>100	>100	11.8	9.7
17d		NMe_2	16.0	I		2.0	8.0	6.6	>100	>100	>100
18a		pyrrolidine	13.0	800	62	>3.0	>3.0	>3.0	>3.0	>3.0	>3.0
18b		imidazole	62.0	I		>100	17.3	30	>100	>100	>100
18c		5-Me-Im	138	I		>100	>100	>100	>100	66	21
18d		NMe_2	43.0	I		9.7	9.7	9.7	>100	>100	>100
19a		pyrrolidine	2.7	180	67	0.14	0.21	0.30	>3.0	>3.0	>3.0
19b		imidazole	2.1	1868	890	0.97	1.40	1.40	>100	>100	>100
19c		5-Me-Im	8.6	381	44	2.50	14.0	>100	>100	>100	14.0
19d		NMe_2	4.5	180	40	0.37	0.54	0.54	>10	>10	>10
20a		pyrrolidine	7.10	510	72	3.7	6.6	6.6	>10	>10	>10
20b		imidazole	35.0	I		4.5	3.7	4.4	>100	>100	>100
20c		5-Me-Im	39.0	614	16	100	>100	>100	>100	22	8.0
20d		NMe_2	37.0	I		5.4	8.0	8.0	>100	>100	>100
21a		pyrrolidine	13.0	130	10	>30	>30	>30	37	25	4.5
21b		imidazole	120	4009	33	97	>100	>100	>100	21	21

[a] I indicates K_i > 10 000 nM. For K_i determination, each drug was investigated at five concentrations and each observation was the mean of three experiments; standard error was <5%. [b] Salivation and lacrimation abbreviated saliv and lacrim. >100 indicates no lethality or cholinergic activity at 100 mg/kg. >30, >10, and >3 indicates mice dead at doses above 30, 10, and 3 mg/kg, respectively; 95% confidence intervals were between 0.4 and 2.0 times the ED_{50}. [c] 5-Me-Im indicates 5-methylimidazole.

Scheme II



in acetonitrile for 1 h with 1-acetyl-4-methylimidazole to give imidazolium salt **6** as the major product. Methanol was added to hydrolyze imidazolium intermediates, and the crude product was chromatographed to give a 9:1 mixture of **1c** and **1f**. Compound **1c** was readily obtained pure from the mixture as the hydrobromide salt. Other analogues (Table I) were prepared by reacting **4** with 2-methylimidazole, 2-ethylimidazole, or 2,4-dimethylimidazole (compounds **1g–j**), the sodium salts of pyrazole and triazole (compounds **1m** and **1n**), or benzimidazole (compound **1p**). Alkylation of **1c** with methyl iodide afforded the quaternary iodide **1k**.

With the procedure of Scheme I, but substituting a variety of propynylamides, propynylcarbamates, and propynylureas of structure I (see Table II for structure) for 1-(2-propynyl)-2-pyrrolidinone, the various acetylenic amines of Table II were prepared. The propynyl intermediates required for the synthesis of compounds **7**, **8**, and **16** were prepared by reacting 1-bromo-2-propyne or 3-chloro-1-butyne[15] with the sodium salt of the appropriate amide or urea.[16] The intermediates for compounds **2** and **9–15** were prepared by reacting 1-amino-2-propyne or *N*-methyl-3-butyne-2-amine[17] with an acyl chloride or alkyl chloroformate.[18] Several of these intermediates are literature compounds.[16,18,19] Imidazolidinone intermediates of structure I required for the synthesis of compounds **18–21** were prepared as outlined in Scheme II. Reaction of propargylamine with chloroethyl isocyanate gave **22**, which was cyclized to **23** with sodium hydride. Alkylation of **23** with methyl iodide/sodium hydride afforded **24**.

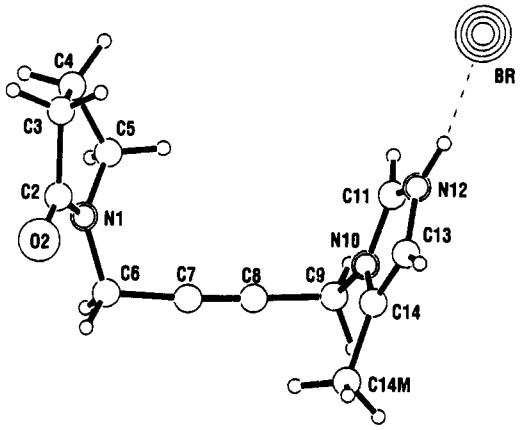


Figure 1. Conformation and numbering in the crystal structure of **1c**. The angle between N(1) and N(10), when viewed in projection down the acetylenic rod, is 56°. The torsion angle C(2)–N(1)–C(6)–C(7) is −104.3°. The torsion angle C(14)–N(10)–C(9)–C(8) is 77.8°.

Propargylamine was reacted with bromoacetaldehyde diethyl acetal to give **25**. Addition of methyl isocyanate gave **26**, which cyclized on hydrolysis to give **27**. Ethylenediamine was reacted with 3-chloro-1-butyne to give **28**, which was reacted with carbonyldiimidazole to give **29**. Alkylation of **29** with methyl iodide/sodium hydride gave **30**.

The intermediates of structure I are for the most part liquids which were purified by chromatography on silica gel; purity was conveniently determined by gas chromatographic analysis. Mannich reaction of these intermediates with paraformaldehyde and pyrrolidine or dimethylamine gave the **a** and **d** series of compounds listed in Table II. With the exception of compounds **2a**, **7a**,[20] **7d**,[21] **8a**,[9] **8d**,[22] **10a**,[9] **10d**,[9] **16a**,[9] and **17a**,[23] which are in-

(15) Hennion, G. F.; Campbell, J. M. Acetylenic 1,4-Aminoalcohols. *J. Org. Chem.* **1956**, *21*, 791–794.

(16) For related alkylations of propargyl halides, see: (a) ref 9. (b) Avetisyan, A. A.; Boyadzhyan, Zh. G.; Melikyan, O. V.; Dangyan, M. T.; Sidel'kovskaya, F. P. Synthesis of N-Substituted Unsaturated Derivatives of Pyrrolidinones and Their Isomeric Transformations. *Arm. Khim. Zh.* **1970**, *23*, 1044 (*Chem. Abstr.* **1971**, *75*, 88417*y*).

(17) Schlecht, H.; Albers, H. Production of Methylmonoisobutynylamine. Ger. Patent 1,200,287 1965. (*Chem Abstr.* **1965**, *63*, 16213*g*).

(18) For related acylations of propargylamines, see: (a) ref 4. (b) Tam, T. F.; Everton, E.; Krantz, A. Synthesis of 5-Alkylidine-oxazolidin-2-ones. *Tetrahedron Lett.* **1987**, *28*, 1127–1130.

(19) Svennson, U.; Hacksell, U.; Dahlbom, R. Acetylenic Compounds of Potential Pharmacological Value. XXV. *N*-(4-Pyrrolidino-2-butynyl)-*N*-alkylcarboxamides. *Acta Pharm. Suec.* **1978**, *15*, 67–70.

(20) Dahlbom, J. R.; Karlen, B. L.; Lindgren, S. G. Oxotremorin Antagonists. Ger. Offen. 1,807,218, 1967.

(21) Svennson, U.; Dahlbom, R.; Blair, M. R. Acetylenic Compounds of Potential Pharmacological Value. XIX. *N*-(Dialkylaminoalkynyl)-Substituted Succinimides and 2-Pyrrolidones as Partial Cholinergic Agonists. *Acta Pharm. Suec.* **1975**, *12*, 209–214.

(22) Ringdahl, B.; Muhi-Eldeen, Z.; Ljunggren, C.; Karlen, B.; Resul, B.; Dahlbom, R. Acetylenic Compounds of Potential Pharmacological Value. XXVIII. Oxotremorine Analogs Substituted with a Methyl Group in the Lactam Ring. *Acta Pharm. Suec.* **1979**, *16*, 89–94.

Table III. Chemical Data for Acetylenic Amines of Tables I and II

no.	formula[a]	mp, °C[b]	no.	formula[a]	mp, °C[b]
1b	$C_{11}H_{13}N_3O \cdot C_2H_2O_4$	115–118	**13d**	$C_{10}H_{18}N_2O_2 \cdot C_2H_2O_4$	114–117
1c[c]	$C_{12}H_{15}N_3O \cdot HBr$	178–181	**14a**	$C_{12}H_{20}N_2O_2 \cdot C_2H_2O_4$	82–85
1f[d]	$C_{12}H_{15}N_3O \cdot 0.5C_2H_2O_4$	134–137	**14b**	$C_{11}H_{15}N_3O_2 \cdot C_2H_2O_4$	124–127
1g	$C_{12}H_{15}N_3O \cdot C_2H_2O_4$	81–85	**14c**	$C_{12}H_{17}N_3O_2 \cdot C_2H_2O_4$	115–119
1h	$C_{13}H_{17}N_3O$		**15a**	$C_{13}H_{22}N_2O_2 \cdot C_2H_2O_4$	112–115
1j	$C_{13}H_{17}N_3O$		**15b**	$C_{12}H_{17}N_3O_2 \cdot C_2H_2O_4$	123–125
1k	$C_{13}H_{18}IN_3O$	140–143	**15c**	$C_{13}H_{19}N_3O_2 \cdot C_2H_2O_4$	108–111
1m	$C_{11}H_{13}N_3O \cdot C_7H_8O_3S$	121–123	**16b**	$C_{10}H_{11}N_3O_2$	85–88
1n	$C_{10}H_{12}N_4O \cdot HCl$	155–157	**16c**	$C_{11}H_{13}N_3O_2$	112–114
1p	$C_{15}H_{15}N_3O \cdot C_7H_8O_3S$	187–189	**17b**	$C_{11}H_{16}N_4O \cdot C_2H_2O_4$	130–132
2a[e]	$C_{12}H_{20}N_2O \cdot HCl$	143–146	**17c**[f]	$C_{12}H_{18}N_4O$	
2b	$C_{11}H_{15}N_3O$		**17d**	$C_{10}H_{19}N_3O \cdot C_2H_2O_4$	88–90
2c[f]	$C_{12}H_{17}N_3O$		**18a**	$C_{11}H_{17}N_3O$	71–75
2g	$C_{12}H_{17}N_3O$		**18b**	$C_{10}H_{12}N_4O$	97–101
5	$C_{11}H_{13}N_3O \cdot C_2H_2O_4$	141–144	**18c**	$C_{11}H_{14}N_4O$	163–167
7b	$C_{12}H_{15}N_3O \cdot 1.5C_2H_2O_4$	114–116	**18d**	$C_9H_{15}N_3O$	83–87
7c	$C_{13}H_{17}N_3O \cdot HBr$	171–174	**19a**	$C_{12}H_{19}N_3O \cdot C_2H_2O_4$	94–96
8b	$C_{12}H_{15}N_3O \cdot C_2H_2O_4$	108–110	**19b**	$C_{11}H_{14}N_4O \cdot C_2H_2O_4$	132–134
8c	$C_{13}H_{17}N_3O \cdot C_2H_2O_4$	124–126	**19c**	$C_{12}H_{16}N_4O \cdot C_2H_2O_4$	112–115
9b	$C_9H_{11}N_3O$	93–95	**19d**	$C_{10}H_{17}N_3O \cdot C_2H_2O_4$	122–125
9c	$C_{10}H_{13}N_3O$	111–115	**20a**	$C_{12}H_{17}N_3O \cdot 0.5C_4H_4O_4$	125–128
10b	$C_{10}H_{13}N_3O \cdot 1.5C_2H_2O_4$	113–115	**20b**	$C_{11}H_{12}N_2O \cdot C_2H_2O_4$	128–131
10c	$C_{11}H_{15}N_3O \cdot 0.5C_2H_2O_4$	170–173	**20c**	$C_{12}H_{14}N_4O \cdot CH_4O_3S$	149–153
11c	$C_{10}H_{13}N_3O_2$	106–108	**20d**	$C_{10}H_{15}N_3O \cdot C_2H_2O_4$	102–114
12a	$C_{11}H_{18}N_2O_2 \cdot C_2H_2O_4$	63–65	**21a**	$C_{13}H_{21}N_3O \cdot C_2H_2O_4$	98–101
12b	$C_{10}H_{13}N_3O_2 \cdot C_2H_2O_4$	113–115	**21b**	$C_{12}H_{16}N_4O$	89–92
12c	$C_{11}H_{15}N_3O_2 \cdot C_2H_2O_4$	119–121	**23**	$C_6H_8N_2O$	123–125
12d	$C_9H_{16}N_2O_2 \cdot C_2H_2O_4$	93–96	**24**	$C_7H_{10}N_2O$	57–59
13a	$C_{12}H_{20}N_2O_2 \cdot C_2H_2O_4$	89–92	**27**	$C_7H_8N_2O$	69–72
13b	$C_{11}H_{15}N_3O_2 \cdot C_2H_2O_4$	147–149	**29**	$C_7H_{10}N_2O$	90–92
13c	$C_{12}H_{17}N_3O_2 \cdot C_2H_2O_4$	108–110			

[a] $C_2H_2O_4$ indicates oxalate salt; $C_7H_8O_3S$, *p*-toluenesulfonate salt; $C_4H_4O_4$, fumarate salt; CH_4O_3S, methanesulfonate salt. Satisfactory elemental analyses (±0.4%) were obtained for all elements (C, H, N; S and halogen where present) for all compounds except the following liquid products [compound, element, calcd (found value)]: **1h**, C, 67.50 (66.81); **1j**, C, 67.50 (66.40) and N, 18.17 (17.50); **2b**, C, 64.36, (63.75); **2c**, C, 65.72 (65.00) and N, 19.16 (18.38). All liquids were pure by TLC, GC, NMR, and showed the correct molecular ion in the mass spectrum. GC retention times (see General Procedures for conditions) for liquids were as follows [compound, retention time in min on column A (retention time on column B)]: **1a**, 3.45 (6.22); **1h**, 9.72 (7.72); **1j**, 9.40 (7.65); **2b**, 4.22 (6.51); **2c**, 5.69 (6.56); **2g**, 4.58 (6.65); **17c**, (7.42). [b] No melting point indicates a liquid product. [c] Compound **1c** has also been obtained as the hemioxalate salt, mp 194–197 °C. [d] Contains 10% of **1c** by GC and NMR analysis. [e] Previously reported as the oxalate salt (see ref 4). [f] Contains 10% of the 4-methyl isomer by GC and NMR analysis.

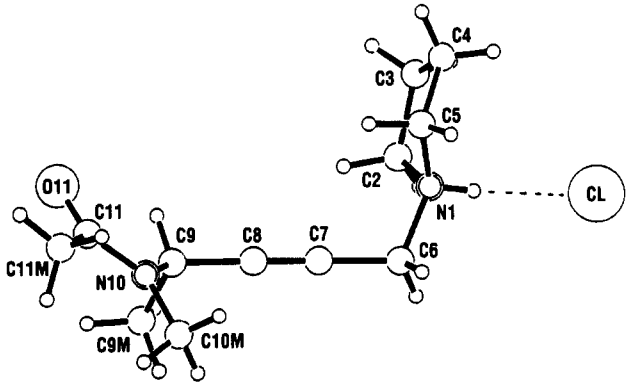


Figure 2. Conformation and numbering in the crystal structure of **2a**, (BM-5). The angle between N(1) and N(10), when viewed in projection down the acetylenic rod, is 117°. The torsion angle C(8)–C(9)–N(10)–C(11) is 137.2°. The torsion angles C(7)–C(6)–N(1)–C(2)/C(5) are −55.4°/67.0°.

Table IV. Fractional Coordinates (×10⁴) and Equivalent Isotropic Thermal Parameters for **1c**[a]

atom	*x*	*y*	*z*	B_{eq},[b] Å²
N(1)	9154 (2)	39 (4)	1468 (4)	1.47 (15)
C(2)	9077 (3)	−1126 (5)	508 (5)	1.33 (16)
O(2)	9296 (2)	−2297 (4)	888 (4)	2.05 (14)
C(3)	8655 (3)	−616 (6)	−1065 (6)	2.27 (21)
C(4)	8699 (3)	936 (5)	−1019 (6)	1.77 (19)
C(5)	8785 (3)	1334 (6)	751 (5)	1.75 (19)
C(6)	9342 (3)	−72 (5)	3176 (5)	1.45 (17)
C(7)	8586 (3)	190 (5)	4034 (5)	1.56 (17)
C(8)	7956 (3)	427 (5)	4632 (5)	1.46 (17)
C(9)	7175 (3)	762 (6)	5358 (6)	2.16 (21)
N(10)	6484 (2)	−137 (4)	4727 (4)	1.47 (15)
C(11)	5888 (3)	282 (5)	3649 (6)	1.68 (18)
N(12)	5370 (2)	−804 (4)	3383 (5)	1.68 (16)
C(13)	5639 (3)	−1936 (6)	4309 (6)	1.96 (19)
C(14)	6344 (3)	−1535 (5)	5146 (5)	1.41 (16)
C(14M)	6925 (3)	−2307 (5)	6301 (6)	1.85 (19)
Br	6198 (1)	4153 (1)	4211 (1)	1.74 (2)

[a] Standard deviations are in parentheses. [b] $B_{eq} = {}^4/_3(a^2B_{11} + b^2B_{22} + c^2B_{33} + ab\cos\gamma B_{12} + ac\cos\beta B_{13} + bc\cos\alpha B_{23})$.

cluded for comparison purposes, all of the remaining compounds are hitherto unreported. Intermediates of structure I were converted in three steps by using the general procedure described in Scheme I (reaction with paraformaldehyde/diethylamine, followed by cyanogen bromide and imidazole or 5-methylimidazole) to the **b** and **c** series of compounds presented in Table II.

The acetylenic amines, mostly liquids, were converted to crystalline salts for biological testing. Compounds were tested as liquids when the hydrochloride, fumarate, methanesulfonate, maleate, oxalate, and *p*-toluenesulfonate salts of the purified free bases failed to crystallize; chemical and analytical data for all new compounds are provided in Table III.

(23) Bebbington, A.; Brimblecombe, R. W.; Shakeshaft, D. The Central and Peripheral Activity of Acetylenic Amines Related to Oxotremorine. *Br. J. Pharmacol. Chemother.* **1966**, *26*, 56–67.

Table V. Fractional Coordinates (×10⁴) and Equivalent Isotropic Thermal Parameters for 2a (BM-5)[a]

atom	x	y	z	B_{eq},[b] Å²
Cl	4468 (1)	-1306 (1)	8996 (1)	1.84 (1)
N(1)	5491 (1)	2481 (1)	8849 (1)	1.38 (5)
C(2)	4420 (2)	3751 (2)	9078 (1)	1.74 (6)
C(3)	3332 (2)	3720 (2)	8416 (1)	2.21 (7)
C(4)	3970 (2)	2731 (2)	7765 (1)	2.08 (7)
C(5)	5477 (2)	2653 (2)	8004 (1)	1.80 (6)
C(6)	6860 (2)	2684 (2)	9271 (1)	1.70 (6)
C(7)	7389 (1)	4495 (2)	9217 (1)	1.67 (6)
C(8)	7807 (1)	5964 (2)	9185 (1)	1.64 (6)
C(9)	8292 (2)	7818 (2)	9178 (1)	1.58 (6)
C(9M)	8474 (2)	8582 (2)	9982 (1)	2.19 (7)
N(10)	9543 (1)	7952 (1)	8772 (1)	1.60 (5)
C(10M)	10632 (2)	6677 (2)	8964 (1)	2.40 (7)
C(11)	9670 (2)	9321 (2)	8282 (1)	1.71 (6)
O(11)	8759 (1)	10430 (1)	8169 (1)	2.41 (5)
C(11M)	10964 (2)	9415 (2)	7876 (1)	2.25 (7)

[a] Standard deviations are shown in parentheses. [b] $B_{eq} = {}^4/_3(a^2B_{11} + b^2B_{22} + c^2B_{33} + ab\cos\gamma B_{12} + ac\cos\beta B_{13} + bc\cos\alpha B_{23})$.

X-ray Crystallography and Molecular Mechanics

The crystal and molecular structures of 1c as the hydrobromide salt and of 2a (BM-5) as the hydrochloride salt were determined; details of the structure determination are in the Experimental Section. Figures 1 and 2 show the conformations and the numbering schemes; fractional crystal coordinates for 1c and 2a are given in Tables IV and V. Coordinates for oxotremorine (1a) as the sesquioxalate salt[24] and (*R*)-QNB[25] were available via the Cambridge Crystallographic Database. The other molecules in the molecular mechanics study were built from these four molecules with standard geometry. The molecular mechanics program CONFOS[26] was used to calculate relative energies among different conformations of the same molecule and to calculate barriers for rotations about torsion angles. With CONFOS, barriers are calculated using extra potentials to force the torsion angles to take on incremental values with complete energy minimization carried out at each step.[27] Proceeding from a low-energy conformation, calculations were done at 15° steps for 390°, a little more than one complete revolution. Each calculation was then repeated stepping in the opposite direction around the bond, and energy barriers were taken to be the lower of the two values in the neighborhood of the barrier.

Biological Methods

Inhibition constants were determined with the antagonist ligand [^{3}H]QNB ([^{3}H]3-quinuclidine benzilate) and the agonist ligand [^{3}H]Oxo-M ([^{3}H]oxotremorine M, [*methyl*-^{3}H]-*N*,*N*,*N*-trimethyl-*N*-[4-(2-oxo-1-pyrrolidinyl)-2-butyn-1-yl]ammonium acetate). Compounds were also evaluated for cholinergic agonist and antagonist activities in mice. The procedures are described in the Experimental Section and results are presented in Tables I and II.

Results and Discussion

Various chemical moieties are active at muscarinic cholinergic receptors and may show agonist, antagonist, or partial agonist activities. All of these compounds bind to muscarinic receptors, but have varying binding affinities and intrinsic activities. Agonists such as carbachol and oxotremorine show full intrinsic activity for most biological effects in mice (e.g., producing salivation, lacrimation, and contraction of smooth muscle), whereas antagonists such as atropine and QNB have no intrinsic activity and block the biological effects of cholinergic agonists. Partial agonists have less intrinsic activity and may show both agonist and antagonist effects in mice. We have used both in vitro binding data and in vivo pharmacological effects to define the biological activity of our compounds. We have determined the inhibition constants using the antagonist ligand [^{3}H]QNB and the agonist ligand [^{3}H]-Oxo-M and have used the ratio of these constants (K_i QNB/K_i Oxo-M) to characterize the compounds as agonists, antagonists, and partial agonists, a procedure previously reported by Brown et al.[6] In our hands, agonists have a K_i ratio > 50, partial agonists a K_i ratio of 15–50, while acetylenic amine antagonists have K_i ratios of 15 or less.[6,28] In vivo activities in mice (Tables I and II) were used to confirm these assignments; this information was particularly useful to verify assignment of compounds which had K_i ratios close to 15 as partial agonists or antagonists.

Among the acetylenic amines already described in the literature there are examples of agonists, antagonists, and partial agonists at muscarinic receptors. Oxotremorine and its dimethylamine analogue (compounds 1a and 1d, Table I) are examples of full agonists. In binding assays, they readily displace [^{3}H]Oxo-M (K_i = 0.50 and 1.10 nM) but are less effective in displacing the antagonist ligand [^{3}H]QNB (K_i = 193 and 2600 nM), showing a ratio (K_i QNB/K_i Oxo-M) characteristic of agonists (386 and 2364). They show cholinergic agonist effects, including tremor, salivation, and lacrimation in mice (Table I). Compounds 7a[20] and 8a[8] of Table II are examples of acetylenic amines which are potent cholinergic antagonists. They displace both tritiated agonist and antagonist ligands (K_i ratios of 13 and 9.4) from cholinergic receptors. These compounds show no agonist effects in mice, but are able to block the effects of oxotremorine at low doses. Compound 2a (BM-5) is an acetylenic amine showing partial agonist activity.[4-6] It shows a K_i ratio of 27, intermediate between those found for agonists and antagonists, and a combination of cholinergic agonist (salivation and lacrimation) and antagonist (tremor) activities in mice (Table II). The newly synthesized compounds listed in Tables I and II include agonists, antagonists, and partial agonists.

Biological activities of oxotremorine and a series of analogues of structure 1, where the pyrrolidine ring has been replaced by an unsaturated heterocyclic ring, are

(24) Clarke, P. J.; Pauling, P. J.; Petcher, T. J. Crystal Structure of Oxotremorine Sesquioxalate, 1-[4-(2-Oxopyrrolidin-1-yl)-but-2-ynyl]pyrrolidinium Sesquioxalate. *J. Chem. Soc. Perkin 2*, **1975**, 774–778.

(25) Meyerhöffer, A.; Carlström, D. The Crystal and Molecular Structure of Quinuclidine Benzilate Hydrobromide. *Acta Crystallogr.* **1969**, *B25*, 1119–1126.

(26) The molecular mechanics program CONFOS was written by D. J. Duchamp, The Upjohn Co., Kalamazoo, MI 49001. The development and parameterization of the force-field used in CONFOS is described in Duchamp, D. J.; Pschigoda, L. M.; Chidester, C. G. Molecular Mechanics, Crystallography, and Drug Research. In *Molecular Structure, Chemical Reactivity and Biological Activity*; Stezowski, J. J., Ed.; Oxford University Press: New York, 1988; pp 34–39.

(27) A more complete description of the method for calculating torsion angle rotation barriers is given: Duchamp, D. J. Crystallography and Molecular Mechanics in Designing Drugs with Unknown Receptor Structure. In *Crystallographic and Modeling Methods in Molecular Design*; Bugg, C. E., Ealick, S. E., Eds.; Springer-Verlag: New York, 1990; pp 161–174.

(28) A similar approach has been used by Freedman et al., using the *N*-methylscopolamine/oxotremorine-M ratio; see: Freedman, S. B.; Harley, E. A.; Iverson, L. L. Relative Affinities of Drugs Acting at Cholinoceptors in Displacing Agonist and Antagonist Radioligands: the NMS/Oxo-M Ratio as an Index of Efficacy at Cortical Muscarinic Receptors. *Br. J. Pharmacol.* **1988**, *93*, 437–445.

shown in Table I. The unsubstituted imidazole **1b** is an agonist with about half the potency of oxotremorine. Compounds with a single methyl group in the imidazole ring (**1c,f,g**) are partial agonists, with the 2-methyl analogue being extremely potent in both the in vitro and in vivo tests. Further increasing the size or number of the substituents in the imidazole ring reduced binding affinities at least 10-fold; the 2-ethyl and 2,4-dimethyl analogues (**1h** and **1j**) were weak antagonists, while the imidazolium compound (**1k**) derived from **1c** was a weak partial agonist. Pyrazole and triazole analogues (**1m** and **1n**) were inactive, suggesting that molecular size alone is not sufficient for activity and that a basic amine component is also required for activity. Pyrazole and triazole are weak bases (pK_a's $\approx$ 2.5) compared to imidazole (pK_a = 7.5) and pyrrolidine (pK_a = 11.1);[29] compounds **1m** and **1n** would not be ionized at physiological pH. The benzimidazole analogue **1p** was also inactive.

The most potent compounds in Table I are oxotremorine, imidazoles **1b**, **1c**, and **1g**, and dimethylamine analogue **1d**. In our further work we have emphasized the preparation of analogues of these compounds. Table II shows activity of a series of analogues where the portion of the molecule to the left of the acetylenic bond has been modified while the substituents at the right were held as pyrrolidine (**a** series), imidazole (**b** series), 5-methylimidazole (**c** series), or dimethylamine (**d** series). Compounds prepared include pyrrolidinones **7** and **8**, amides **2**, **9**, and **10**, carbamates **11–16**, ureas **17**, and cyclic ureas (imidazolidinones and imidazolones) **18–21**.

Introduction of a methyl group at the α-position[30] in the acetylene chain of oxotremorine gives the potent antagonist **7a**[20] (Table II). Imidazole analogues **7b** and **7c** were less potent antagonists, with the 5-methyl analogue **7c** being the more potent of the two imidazole compounds (the reverse of the potency order found for **1b** and **1c**). Dimethylamine analogue **7d** was a weak agonist, both in the binding assays and in mice. A similar activity order was found for the 5-methyl substituted compounds **8a–d** [**8a** = **8c** > **8b** (all antagonists) > **8d** (agonist)]; compound **8c** is one of the most potent antagonists among the acetylenic imidazoles we have prepared, comparing favorably with **8a** both in the binding assays and in in vivo effects.

A series of acetamide analogues, compounds lacking the pyrrolidinone ring, were prepared (compounds **9**, **10**, and **2**). Acetamides **9b** and **9c**, which lack both *N*- and α-methyl substituents, showed low activity, while the *N*-methyl analogues **10b** and **10c** were 100 times more potent. Compound **10b** was an agonist with one-third the potency of its pyrrolidine analogue **10a**, while **10c** was a partial agonist. Further addition of an α-methyl group to **10a** gave the cholinergic partial agonist **2a** (BM-5).[4-6] Imidazole analogues of **2a** did not show partial agonist activity; compound **2b** was an agonist, while methyl-substituted imidazoles **2c** and **2g** were antagonists.

The activities of the series of compounds **2**, **9**, and **10** further illustrate the profound effect addition of a single methyl group can have on potency or agonist/antagonist activity of acetylenic amines, an observation already reported for compounds related to **2a**, **10a**, and **10d**.[4,19] This is further illustrated when the data for carbamates **11–16** is examined. The carbamate lacking *N*- and α-methyl substituents (**11c**) showed low activity, while *N*-methylation significantly improved the potency (**12c**) and afforded a partial agonist; the related products **12a**, **12b**, and **12d** were all agonists. Compounds with an α-methyl substituent (**13a–d**) also had good activity. Noteworthy, **13a**, while showing comparable binding affinities to the related acetamide **2a**, was considerably less active in mice and showed only agonist activity. Ethyl carbamates **14** and **15** were considerably less active than the corresponding methyl carbamate analogues **12** and **13**, showing that a small carbamate residue is important for high in vitro and in vivo potency. Cyclic carbamates also showed good activity; compounds **16a** and **16b** were agonists, while **16c** was a partial agonist. Imidazole **16b** was as active as the related pyrrolidine **16a** in all assays but was significantly less toxic in mice, showing no lethality at 100 mg/kg.

Bebbington et al. have reported that urea **17a** is a cholinergic partial agonist when tested on the guinea pig ileum.[23] We have confirmed that **17a** is a partial agonist with our testing procedures and find that the related imidazoles **17b** and **17c** are also partial agonists, while dimethylamine **17d** shows only agonist activity. In view of the partial agonist properties of **17a–c**, we prepared a variety of cyclic analogues (**18–21**) in an attempt to improve on this activity. The unsubstituted imidazolidinones **18a–d** were less potent than their *N*-methyl analogues **19a–d**. This improved activity for the *N*-methyl compounds was surprising, as methylation of oxotremorine at the equivalent position affords a much less active analogue [3-methyl-1-(4-pyrrolidinyl-2-butynyl)-2-pyrrolidinone].[3] Most of these imidazolidinone analogues showed agonist activity, but compound **19c** was a partial agonist. Unsaturated analogues **20a–d** were less active than the corresponding saturated analogues **19a–d**. Introduction of an α-methyl group did not improve activity; compound **21a** was an antagonist, while **21b** was a weak partial agonist.

Models for Agonist and Antagonist Binding

In order to understand the profound differences in activity associated with slight modifications in structure, we have made some assumptions about the manner in which these molecules bind at the receptor site. We have already indicated that molecular size is an important factor in determining potency and agonist or antagonist activity. In addition, we believe that hydrogen bonding is important for a molecule to bind either as an agonist or antagonist, as has been already reported for various cholinergic agonists by other groups.[23,31,32] We assume that the formation of hydrogen bonds from the carbonyl oxygen and the protonated nitrogen in these ligands to donor and acceptor atoms in the receptor cause modification of receptor conformation that is associated with agonist activity. We also assume that when structurally very similar antagonists bind, although these ligands have the same atoms taking part in hydrogen bonding as agonists, at least one of the hydrogen bonds must be to a different receptor site so that agonist-mediated changes in the receptor do not take place. These assumptions are consistent with a model for quinuclidine-type agonist and antagonist binding at muscarinic receptors in the cerebral cortex which was recently proposed by Saunders et al.[31] In their study, the

(29) Albert, A.; Sergeant, A. P. In *The Determination of Ionization Constants*, 3rd ed.; Chapman and Hall: New York, 1984; pp 151–155.

(30) We have denoted the 1-position of the acetylenic chain as the α-position to avoid confusion with the ring positions.

(31) Saunders, J.; Cassidy, M.; Freedman, S. B.; Harley, E. A.; Iversen, L. L.; Kneen, C.; MacLeod, A. M.; Merchant, K. J.; Snow, R. J.; Baker, R. Novel Quinuclidine-Based Ligands for the Muscarinic Cholinergic Receptor. *J. Med. Chem.* **1990**, *33*, 1128–1138.

(32) Schulman, J. M.; Sabio, M. L.; Disch, R. L. Recognition of Cholinergic Agonists by the Muscarinic Receptor. 1. Acetylcholine and Other Agonists with the NCCOCC Backbone. *J. Med. Chem.* **1983**, *26*, 817–823.

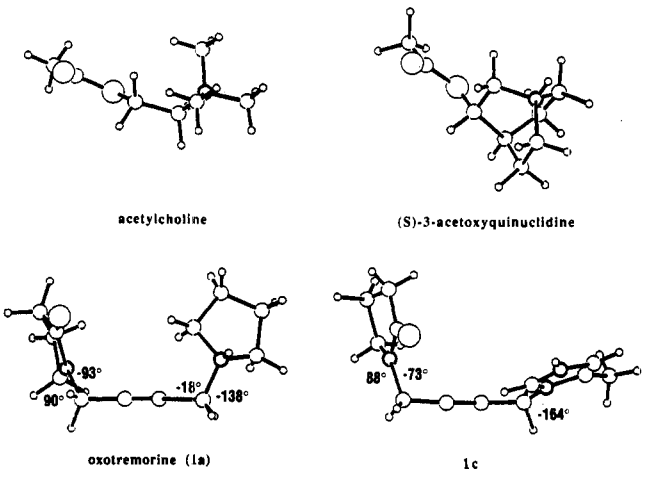


Figure 3. Agonist conformations. The carbonyl oxygen to nitrogen distance in acetylcholine is 4.9 Å; the carbonyl to protonated nitrogen is 4.4 Å in 3-acetoxyquinuclidine, 5.7 Å in **1a**, and 5.3 Å in **1c**. The angle between the nitrogens linked by the acetylenic rod, when viewed in projection down this rod, is 40° for **1a** and 78° for **1c**. Torsion angles at each end of the acetylenic rod are shown in the figure.

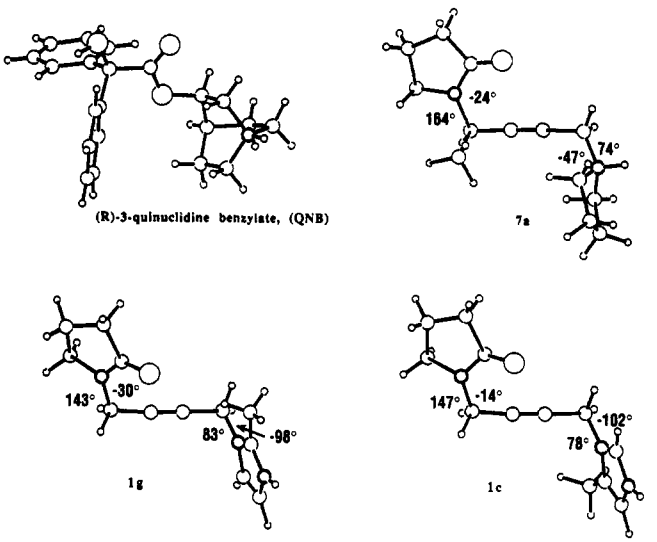


Figure 4. Antagonist conformations. The carbonyl oxygen to protonated nitrogen distance is 4.4 Å in QNB, 5.2 Å in **7a**, 5.7 Å in **1g**, and 6.1 Å in **1c**. The angle between the nitrogens linked by the acetylenic rod, when viewed in projection down this rod, is 155° for **7a**, 117° for **1g**, and 132° for **1c**. Torsion angles at each end of the acetylenic rod are shown in the figure.

authors propose that agonists are able to interact with two different aspartate residues in the receptor, one buried more deeply than the other, and that antagonists are able to interact only with the more accessible aspartate group. The authors do not, however, propose structural models for agonists and antagonists.

We have developed tentative structural models for the agonist and antagonist conformations for the acetylenic amines. Several structural constraints were considered: (1) The four central carbons are linear and act as a rigid pole, the "acetylenic rod", separating left and right ends of the molecules. Except in the case of 2- or 5-alkyl-substituted imidazoles, left and right ends are too far apart to affect each other, so rotation about either end is essentially free. Because it has been suggested that the acetylenic linkage itself may be important in binding,[23,33] the acetylenic rod was always placed similarly in the models, although we have not considered this as an additional binding site in our modeling studies. (2) The configuration at the α-carbon and at position 5 in the pyrrolidinone ring when these are optical centers (e.g., compounds **7a** and **8a**, Table II) is known to be *R*; *S* enantiomers have much less affinity for the receptor.[34] (3) In the imidazole analogues, it is the N(3) of the imidazole ring that is involved with hydrogen bonding. The crystal structure of **1c** (Figure 1) shows that this is the protonated nitrogen; the nitrogen at the 1-position is planar and does not protonate.

For most molecules, the two main torsion angles varied in the modeling study were about the bonds from the carbons at the ends of the acetylenic rod to the nitrogens. Often, when the structure of a molecule is altered, barriers for torsion angle rotation change, and the molecule may then prefer different conformations. The models were developed by studying the structural modifications and conformational preferences along with the activities until we were able to choose models for agonist and antagonist conformations that enabled us to rationalize these activities. Molecular mechanics calculations were used to ensure that the conformations chosen were among the low-energy conformations available to the molecules.

Figure 3 shows proposed agonist conformations for three cholinergic agonists and the imidazole partial agonist **1c**. Acetylcholine is in the conformation proposed by Schulman et al.;[32] the semirigid agonist (*S*)-3-acetoxyquinuclidine,[35] oxotremorine, and compound **1c** are drawn with carbonyl oxygens and protonated nitrogens oriented similarly; pertinent O–N distances and torsion angles are noted in the figure.

Because displacement of bound QNB is relevant to the agonist/antagonist classification of these ligands, Figure 4 shows QNB along with three ligands in this study which displace QNB efficiently. The QNB molecule is in the conformation found in the crystal structure.[25] Note that the absolute configuration of QNB is opposite to that of the related agonist analogue (*S*)-3-acetoxyquinuclidine in Figure 3.[35-37] The oxotremorine analogues have conformations such that they can be overlaid with QNB so that hydrogen bonds to carbonyls and protonated nitrogens would have similar directions. The major agonist/antagonist difference is in the orientation of these putative hydrogen-bonding groups relative to the acetylenic bond. In the agonist conformation of oxotremorine and its analogues in Figure 3, left and right moieties are essentially cis, whereas in the antagonist conformations in Figure 4, they are more nearly trans. Bebbington and coworkers

(33) Trybulski, E. J.; Kramss, R. H.; Mangano, R. M.; Rusinko, A. III. Chemical and Biochemical Studies of 2-Propynylpyrrolidine Derivatives. Restricted Rotation Analogues of *N*-Methyl-*N*-(1-methyl-4-pyrrolidino-2-butynyl)acetamide (BM-5). *J. Med. Chem.* **1990**, *33*, 3190.

(34) Dahlbom, R.; Jenden, D. J.; Resul, B.; Ringdahl, B. Stereochemical Requirements for Central and Peripheral Muscarinic and Antimuscarinic Activity of Some Acetylenic Compounds Related to Oxotremorine. *Br. J. Pharmacol.* **1982**, *76*, 299–304.

(35) Saunders, J.; Showell, G. A.; Baker, R.; Freedman, S. B.; Hill, D.; McKnight, A.; Newberry, N.; Salamone, J. B.; Hirshfield, J.; Springer, J. P. Synthesis and Characterization of All Four Isomers of the Muscarinic Agonist 2′-Methylspiro[1-azabicyclo[2.2.2]octane-3,4′-[1,3]dioxolane]. *J. Med. Chem.* **1987**, *30*, 969–975.

(36) Ringdahl, B.; Ehler, F. J.; Jenden, D. J. Muscarinic Activity and Receptor Binding of the Enantiomers of Aceclidine and Its Methiodide. *Mol Pharmacol.* **1982**, *21*, 594–599.

(37) Rehavi, M.; Maayani, S.; Sokolovsky, M. Enzymatic Resolution and Cholinergic Properties of (±)-3-Quinuclidinol Derivatives. *Life Sci.* **1977**, *21*, 1293–1302.

observed that oxotremorine can exist in "two planar forms, cisoid and transoid" and suggested that the "distance between active centers in the molecule in the transoid form (5 Å) corresponds with those in muscarone and in the dioxolanes".[23] In our models, which are not planar, the O–N distances are similar for both agonist and antagonist conformations.

Dimethylamine Analogues (d Structures). The K_i's for both QNB and Oxo-M displacement are higher than for the corresponding pyrrolidine analogues, but the effect on QNB displacement is greater, so the ratio K_i QNB/K_i Oxo-M is higher and there is a shift in activity toward agonist. The decreased bulk of the dimethylamine group compared to pyrrolidine tends to decrease binding ability because the surface area available for hydrophobic contacts is decreased. A more specific effect occurs because rotation about the C–N bond is more hindered for dimethylamine than for pyrrolidines or imidazoles. There are two barriers to rotation about this C–N bond of ca. 4 kcal, corresponding to nonbonded contacts when either methyl group is cis to the acetylenic rod. According to the models in Figures 3 and 4, the resulting tendency for methyl groups to point away from the acetylenic rod would position the N–H favorably for the agonist-type hydrogen bond. The antagonist conformation is less likely because the methyl groups would be closer to the acetylenic rod. This explains the shift toward agonist observed with *N,N*-dimethyl substitution.

Imidazole Analogues (b Structures). The K_i's for both QNB and Oxo-M displacement are almost always higher for the imidazole than for the corresponding pyrrolidine analogue; the only exceptions are compounds **16b** and **19b**, which have similar Oxo-M K_i's to **16a** and **19a**, respectively. The weaker binding affinity for the imidazole structures is not surprising, for two reasons. The pyrrolidines have a more bulky hydrophobic surface, and generally, as long as the maximum capacity of the hydrophobic pocket in the receptor is not exceeded, binding is enhanced as the hydrophobic bulk is increased. K_i's for the less bulky imidazoles would therefore be expected to be higher. The protonated nitrogen in the imidazoles, because it is at the 3-position instead of at the alkylation site as for the pyrrolidines, is affected by rotation about the C–N bond, and in the unsubstituted imidazole ring there are only weak barriers to this rotation. This added uncertainty in the nitrogen position decreases the likelihood of hydrogen-bond formation and tends to increase the K_i's.

5-Methylimidazole Analogues (c Structures). The K_i QNB/K_i Oxo-M ratio is lower for these compounds when compared to the pyrrolidine analogues, so that activity is shifted toward antagonist. The K_i's for QNB displacement are both increased and decreased, but the K_i's for Oxo-M displacement are increased significantly. Agonist and antagonist conformations for **1c** are shown in Figures 3 and 4, respectively. In the agonist conformation, the pyrrolidinone and imidazole substituents are nearly cis; in the antagonist conformation they are more nearly trans. Imidazoles with a 5- or 2-methyl substituent are more likely to be in the trans, antagonist conformation because in the agonist conformation free rotation about the C–N bonds on the left and right ends is not possible due to contacts between the carbonyl oxygen on the left and the methyl substituent on the right.

2-Methylimidazole Analogues (1g and 2g). These two compounds exhibit exceptionally good binding as antagonists. As with the 5-methylimidazoles just described, the 2-methyl substituent would increase the likelihood of the antagonist conformation. An additional consideration is that the barrier for rotation about the C–N bond is 2.3 kcal and occurs when the methyl group is cis to the acetylenic rod. It may be that even this 2 kcal difference is enough to aid in positioning the proton on N(3) for antagonist-type hydrogen bonding. The 5-methylimidazole in Figure 4 has its methyl group pointing slightly toward the acetylenic rod; this conformation is actually less likely for this molecule than for **1g**, also in Figure 4, which has a methyl on the opposite side of the ring pointed slightly away from the acetylenic rod.

Effect of α-Methyl Substitution on the Left. The K_i QNB/K_i Oxo-M ratio is always lower than for compounds lacking this substituent (compare series **7** to **1**, **2** to **10**, **13** to **12**, and **15** to **14**). As with 5-methylimidazole substitution on the right, activity is shifted toward antagonist. The shift is more pronounced for structures with pyrrolidine at the right, and for these structures is accomplished more because the QNB K_i's are decreased than because Oxo-M K_i's are increased. The imidazole structures appear at first to behave differently, because the antagonist shift is achieved sometimes from an increase in Oxo-M K_i's and sometimes from decreasing QNB K_i's. This apparent difference can be understood by recalling that the effect of imidazole substitution, already discussed, is to increase both K_i's, whereas α-methyl substitution tends to increase K_i Oxo-M and decrease K_i QNB. The net effect is still to shift the activity toward antagonist, but for the imidazoles, the amount of shift is less predictable.

In order to understand the effect of α-methyl substitution in terms of the conformational preferences of these molecules, consider **7a**, α-methyl oxotremorine, in the antagonist conformation in Figure 4. This is a low-energy conformation for this molecule; however, if the C–N bond on the left were to be rotated to the agonist conformation, as in Figure 3, a barrier of about 5.3 kcal caused by repulsions between the carbonyl and the α-methyl groups would be encountered. In the case of **7a** and related compounds with a cyclic amide at the left, the α-methyl group effectively prevents the agonist-type hydrogen-bond formation. However, for the ring-opened amides such as **2a**, two conformations are possible due to restricted rotation about the amide bond.[38] In the crystal structure of **2a** (Figure 2), the trans form of the amide is found (methyl group of acetyl group and acetylenic chain attached to N trans about the C–N bond). In this conformation, which is similar to that of the cyclic amides, interaction between the carbonyl oxygen and the α-methyl group would again prevent agonist-type hydrogen bonding, but because **2a** can also adopt cis geometry about the amide bond, it can form the hydrogen bonds characteristic of agonists. Because this molecule is likely to be bound in both conformations, it will sometimes bind without making the correct hydrogen bonds for agonist activity and is only a partial agonist.

5-Methyl Substitution on the Left (Structures 8a–d). The calculation of energy barriers for rotation about the same C–N torsion angle is almost identical with the one obtained for α-methyl oxotremorine, because the high-energy contacts between the 5-methyl and the acetylenic rod occur in almost the same torsion angle range as the bad contacts between the α-methyl and the carbonyl in structures **7a–d**. A shift in activity toward antagonist

(38) We have observed the presence of cis and trans forms of the amides in the NMR spectra of **2a** and related acetamides, an observation already reported by other groups (see refs 19 and 41).

similar to that observed with the α-methyl substitution would therefore be expected.

Conclusions

We have synthesized a series of acetylenic imidazoles which includes the potent cholinergic agonist **1b** and antagonists **7c** and **8c**. Several of the new compounds were partial agonists, showing the expected K_i ratio and a mixture of agonist and antagonist properties in mice (compounds **1c**, **1g**, **10c**, **12c**, **16c**, **17b**, **17c**, and **19c**). None of the partial agonists has a substituent at the α-position in the acetylenic chain. A structural feature common to six of these compounds is the 5-methylimidazole substituent, while some variation is possible (ring or open chain) at the left of the molecule. Unlike BM-5, all of these compounds produce tremors in mice and antagonize salivation and lacrimation produced by oxotremorine, suggesting that these compounds would show central cholinergic agonist effects with minimal peripheral side effects. One of these compounds, **1c** (U-80816) has been selected for further evaluation; the detailed pharmacology of this compound will be presented in the near future.[39]

There have been several recent reports of the preparation of analogues of the promising partial agonist BM-5 (**2a**). Analogues with an additional carbon atom in the molecule[40] and cyclic analogues[33,40,41] show only antagonist properties. Several of the compounds we prepared (**2**, **13**, **15**, **21**) have the α-methyl substituent found in BM-5; these were prepared in an attempt to find compounds with a similar pharmacological profile to BM-5. While these compounds showed cholinergic activity, none were partial agonists.

Experimental Section

General Procedures. ^{1}H NMR spectra were recorded on a Bruker AM 300 spectrometer; chemical shifts are recorded in δ units using tetramethylsilane as the internal standard (in NMR description s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet). GC data were obtained on a Hewlett-Packard Model 5890A capillary gas chromatograph using a helium carrier gas (flow rate 100 mL/min) and a hydrogen flame ionization detector. Column A was a J&W Scientific Inc DB-5 5% phenylmethylpolysiloxane column (15 m × 0.53 mm × 1.5 μm film thickness); samples were injected at 200 °C and run isothermally. Column B was a Hewlett-Packard HP-1 methyl silicone column (5 m × 0.53 mm × 2.65 μm film thickness); samples were injected at 100 °C and after 1 min the column temperature was raised 20 °C/min to a final temperature of 250 °C.

General Procedure for Preparation of Acetylenic Amines Containing Pyrrolidine, Dimethylamine, and Diethylamine (Series a, d, and e). A mixture of the appropriate propargyl intermediate (structure I of Table II, 0.1 mol), the amine (pyrrolidine, dimethylamine, or diethylamine, 0.11 mol), powdered paraformaldehyde (0.12 mol), and cuprous chloride (0.05 g) in dioxane (100 mL) was stirred at 70 °C for 3 h. The reaction was cooled to room temperature, the solvent was removed under reduced pressure, and the crude product was purified by chromatography on silica gel using chloroform as the initial eluant. Elution with 1–5% methanol/chloroform gave the pure acetylenic amine.

General Procedure for Conversion of Diethylamines (Series e) to Propargyl Bromides Using Cyanogen Bromide. Cyanogen bromide (5.2 g, 0.05 mol) was added to a stirred solution of the acetylenic diethylamine (0.047 mol) in dioxane (100 mL). After stirring at room temperature for 10 min, the solvent was removed under reduced pressure and the crude product was purified by chromatography on silica gel using chloroform as the initial eluant to give the propargyl bromide as an oil.

General Procedure for Preparation of Acetylenic Imidazoles (Series b, c, and g). The method used to prepare compound **1b** was used to prepare all of the unsubstituted 1*H*-imidazole and 2-methyl-1*H*-imidazole compounds of Table II (series **b** and **g**). The procedure used to prepare **1c** from 1-acetyl-4-methylimidazole was used in the synthesis of all compounds of series **c**.

1-[4-(1*H*-Imidazol-1-yl)-2-butynyl]-2-pyrrolidinone (1b). 1*H*-Imidazole (3.4 g, 0.05 mol) was added to a stirred solution of 1-(4-bromo-2-butynyl)-2-pyrrolidinone (**4**; 3.3 g, 0.015 mol) in THF (300 mL). After 3 days at room temperature, the THF was removed under reduced pressure and the product was partitioned between ethyl acetate and 4 N NaOH solution (5 mL). The ethyl acetate was removed and the residual oil was chromatographed on silica gel using chloroform as the initial eluant. Elution of the column with 2.5% methanol/chloroform gave 2.2 g of product as a liquid. The product was dissolved in methanol, anhydrous oxalic acid (1.1 g) was added, and the solution was diluted with ether to give 2.4 g of **1b** as the oxalate salt, mp 109–115 °C. Recrystallization from methanol/ether gave 2.2 g: mp 115–118 °C; GC t_R column A, 7.61 min (100%), column B, 7.38 min; NMR (CD_3OD) δ 2.07 (m, 2 H), 2.37 (t, 2 H), 3.53 (t, 2 H), 4.19 (t, J = 1.0 Hz, 2 H), 5.17 (t, J = 1.0 Hz, 2 H), 7.53 (s, 1 H), 7.46 (s, 1 H), and 8.91 (s, 1 H). Anal. ($C_{11}H_{13}N_3O \cdot C_2H_2O_4$) C, H, N.

1-[4-(1*H*-Imidazol-1-yl)-2,3-butandienyl]-2-pyrrolidinone (5). A suspension of potassium hydride (2.0 g of 35% by wt dispersion in mineral oil, washed with ether to remove oil, 0.017 mol) in dry THF was added dropwise, with cooling, to a stirred solution of imidazole (1 g, 0.015 mol) in dry THF (50 mL). After warming to room temperature and stirring for 20 min, the reaction was cooled and *N*-(4-bromo-2-butynyl)-2-pyrrolidinone (**4**; 3.0 g, 0.014 mol) was added dropwise. The reaction was allowed to slowly warm to room temperature and stirred for 1 h. The reaction was quenched with methanol and solvent was removed under reduced pressure. The crude product was partitioned between ethyl acetate and water, the ethyl acetate phase was evaporated and the residual oil was chromatographed on silica gel using chloroform/methanol as eluant to give 2.4 g of product (a mixture of **1b** and **5**). This was dissolved in methanol and anhydrous oxalic acid (0.9 g) was added. Diethyl ether was added until the solution became cloudy and the solution was cooled to −10 °C for 4 h. The precipitate was filtered off, washed with methanol/ether, and air-dried to give the oxalate salt of **5** (0.7 g), mp 138–142 °C. This was recrystallized from methanol/ether to give 0.58 g of product: mp 141–144 °C; GC t_R column A, 6.38 min (100%), column B, 7.11 min; NMR (CD_3OD) δ 2.05 (m, 2 H), 2.34 (m, 2 H), 3.51 (m, 2 H), 4.01 and 4.19 (d of d of d, J = 17, 4.5, and 3 Hz, each 1 H, NCH_2CH), 6.25 (q, J = 4.5 Hz, 1 H, NCH_2CH), 7.48 (m, 1 H, C*H*-imidazole), 7.50 (s, 1 H), 7.60 (s, 1 H) and 8.75 (s, 1 H). Anal. ($C_{11}H_{13}N_3O \cdot C_2H_2O_4$) C, H, N.

1-Acetyl-4-methyl-1*H*-imidazole. A mixture of 4-methyl-1*H*-imidazole (82.1 g, 1.0 mol) and acetic anhydride (190 mL, 2.0 mol) was refluxed for 15 min after which time 150 mL of solvent was removed by distillation at atmospheric pressure (head temperature 125 °C) over a 1-h period. The remaining acetic anhydride was removed at 50 °C (0.5 mm) and the residual liquid[42] was crystallized from ether (150 mL) at −20 °C to give 85.5 g of product: mp 42–45 °C; GC t_R column B (75°C initial temperature) 2.50 min (100%). Anal. ($C_6H_8N_2O$) C, H, N. Evaporation of the

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(42) GC of the product at this stage (column B, 75 °C initial temperature) shows two peaks at 2.50 min (95%) and 2.64 min (5%, 5-methyl isomer); the residual liquid may be purified by distillation to remove colored impurities, but the product tends to crystallize in the condenser.

mother liquors gave 33 g of less pure product.

1-[4-(5-methyl-1*H*-imidazol-1-yl)-2-butynyl]-2-pyrrolidinone (1c). A mixture of 1-(4-bromo-2-butynyl)-2-pyrrolidinone (4; 10.8 g, 0.05 mol) and 1-acetyl-4-methylimidazole (12.4 g, 0.10 mol) in acetonitrile (20 mL) was heated at 85 °C for 1 h.[43] The acetonitrile was evaporated and methanol (20 mL) was added to hydrolyze imidazolium salts. After 1 h, the solvent was removed and the residual oil was partitioned between ethyl acetate and sodium hydroxide solution. The ethyl acetate phase was washed with water, evaporated, and the residual oil was chromatographed on silica gel to give 10.5 g of crude product (a 9:1 mixture of **1c** and **1f** by GC and NMR analysis). This was dissolved in methanol (30 mL); 48% hydrobromic acid (8.1 g) was added followed by ether (30 mL). The precipitate was filtered off and washed with methanol/ether (1:10) to give 7.85 g of hydrobromide salt of **1c**, mp 175–177 °C. A sample was recrystallized from methanol/ether for analysis: mp 178–182 °C; NMR (CD_3OD) δ 2.06 (m, 2 H), 2.36 (s, 3 H), 2.35 (t, 2 H), 3.53 (t, 2 H), 4.18 (t, J = 0.2 Hz, 2 H), 5.12 (t, J = 0.2 Hz, 2 H), 7.35 (s, 1 H), and 8.96 (s, 1 H). Anal. ($C_{12}H_{15}N_3O$·HBr) C, H, Br, N.

A portion of the salt (2.80 g) was dissolved in water (2 mL) and partitioned between ethyl acetate (100 mL) and 4 N sodium hydroxide solution (3.8 mL). Evaporation of the ethyl acetate gave a solid which was crystallized from ethyl acetate/hexane (15 mL of 1:1) to give 1.62 g of **1c**: mp 79–82 °C; GC t_R column A, 10.6 min (100%), column B, 7.96 min; NMR ($CDCl_3$) δ 2.04 (m, 2 H), 2.22 (s, 3 H), 2.40 (t, 2 H), 3.45 (t, 2 H), 4.14 (t, J = 0.2 Hz, 2 H), 4.66 (t, J = 0.2 Hz, 2 H), 6.79 (s, 1 H), and 7.50 (s, 1 H). Anal. ($C_{12}H_{15}N_3O$) C, H, N.

1-[4-(4-Methyl-1*H*-imidazol-1-yl)-2-butynyl]-2-pyrrolidinone (1f). A mixture of 4-methylimidazole (17.4 g, 0.21 mol) and 1-(4-bromo-2-butynyl)-2-pyrrolidinone (4; 11.4 g, 0.053 mol) in dioxane (250 mL) was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the product was partitioned between ethyl acetate and 4 N NaOH solution (5 mL). The ethyl acetate was removed and the residual oil was chromatographed on silica gel using chloroform as the initial eluant. Elution of the column with 2.5% methanol/chloroform gave 7.9 g of material, a 2:3 mixture of **1c** and **1f** by gas chromatography. Oxalic acid (1.65 g, 0.5 equiv) in methanol (30 mL) was added and the solution was cooled to −10 °C overnight. The precipitate was filtered off to give 2.98 g of the hemioxalate salt of **1c** (84% pure by GC). Recrystallization from methanol/ether gave 2.43 g of 98% pure product, mp 194–197 °C. Anal. ($C_{12}H_{15}N_3O$·0.5$C_2H_2O_4$) C, H, N.

A second crop of crystals (5.05 g) was obtained from the initial mother liquors, and these were recrystallized from methanol/ether to give 3.29 g of the hemioxalate salt of **1f**: mp 134–137 °C (90% isomeric purity by GC); NMR (CD_3OD) δ 2.06 (m, 2 H), 2.25 (s, 3 H), 2.37 (t, 2 H), 3.52 (t, 2 H), 4.16 (m, 2 H), 4.96 (t, 2 H), 7.15 (s, 1 H), and 8.25 (s, 1 H). Anal. ($C_{12}H_{15}N_3O$·0.5$C_2H_2O_4$) C, H, N.

The product was partitioned between ethyl acetate and sodium hydroxide solution to give the free base: GC t_R column A, 9.3 min (90%) and 10.6 min (10%), column B, 7.53 min (90%) and 7.86 min (10%); NMR ($CDCl_3$) δ 2.04 (m, 2 H), 2.22 (s, 3 H), 2.40 (t, 2 H), 3.45 (t, 2 H), 4.14 (m, 2 H), 4.66 (t, 2 H), 6.71 (s, 1 H), and 7.43 (s, 1 H).

1,4-Dimethyl-3-[4-(2-oxo-1-pyrrolidinyl)-2-butynyl]-1*H*-imidazolium Iodide (1k). Methyl iodide (1 mL) was added to a stirred solution of 1-[4-(5-methyl-1*H*-imidazol-1-yl)-2-butynyl]-2-pyrrolidinone (**1c**; 350 mg) in THF/ether (5 mL, 1:1). After 4 h the precipitate was filtered off and recrystallized from methanol/ether to give 210 mg of **1k**, mp 140–143 °C. Anal. ($C_{13}H_{18}IN_3O$) C, H, N, I.

1-[4-(1*H*-Pyrazol-1-yl)-2-butynyl]-2-pyrrolidinone (1m). Sodium methoxide in methanol (8.3 mL of 4.25 M, 35.2 mmol) was added to a solution of pyrazole (2.00 g, 29.4 mmol) in methanol (5 mL). 1-(4-Bromo-2-butynyl)-2-pyrrolidinone (**4**; 7.62 g, 35.2 mmol) was then added. Following the initial exothermic reaction, the solvent was removed under reduced pressure and the product was partitioned between ethyl acetate and water. The ethyl acetate was removed and the residual oil was chromatographed on silica gel using chloroform as the initial eluant to give 2.0 g of **1m** which was converted to the *p*-toluenesulfonate salt, mp 121–123 °C from methanol/ether. Anal. ($C_{10}H_{12}N_4O$·$C_7H_8O_3S$) C, H, N, S.

1-[4-(1*H*-1,2,4-Triazol-1-yl)-2-butynyl]-2-pyrrolidinone (1n). Sodium methoxide in methanol (8.7 mL of 4.25 M, 37.4 mmol) was added to a solution of 1,2,4-triazole (2.1 g, 30.5 mmol) in methanol (5 mL). 1-(4-Bromo-2-butynyl)-2-pyrrolidinone (**4**; 7.88 g, 36.5 mmol) was added and the solution was stirred at room temperature for 4 h. The solvent was removed under reduced pressure and the product was partitioned between ethyl acetate and 4 N NaOH solution (5 mL). The ethyl acetate was removed and the residual oil was chromatographed on silica gel using chloroform as the initial eluant. The first product eluted from the column was (4-methoxy-2-butynyl)-2-pyrrolidinone (0.43 g). Continued elution of the column gave 4.3 g of **1n**, which was converted to the hydrochloride salt, mp 155–157 °C dec (from methanol/ether). Anal. ($C_{10}H_{12}N_4O$·HCl) C, H, N, Cl.

1-[4-(1*H*-benzimidazol-1-yl)-2-butynyl]-2-pyrrolidinone *p*-Toluenesulfonate (1p). A mixture of benzimidazole (2.73 g, 23 mmol) and 1-(4-bromo-2-butynyl)-2-pyrrolidinone (**4**, 2.5 g, 11.5 mmol) in methanol (100 mL) was stirred under reflux for 18 h. The solvent was removed under reduced pressure and the product was partitioned between ethyl acetate and 4 N NaOH solution (5 mL). The ethyl acetate was removed and the residual oil was chromatographed on silica gel using chloroform as the initial eluant to give 1.7 g of **1p**. This was dissolved in methanol and treated with *p*-toluenesulfonic acid (1.34 g). Ether was added to precipitate **1p** as the *p*-toluenesulfonate salt, mp 187–189 °C. Anal. ($C_{15}H_{15}N_3O$·$C_7H_8O_3S$) C, H, N, S.

1-(2-Propynyl)-2-imidazolidinone (23). Chloroethyl isocyanate (12.2 g, 0.11 mol) was added at 0 °C to a stirred solution of propargylamine (6.6 g, 0.12 mol) in THF (200 mL). The solution was allowed to warm to room temperature and sodium hydride (5.5 g of 50% in oil, 0.115 mol) was added. The reaction was quenched with acetic acid (6.0 mL), the THF was removed under reduced pressure, and the residue was partitioned between ethyl acetate and water. The ethyl acetate was evaporated and the residual solid was crystallized from ethyl acetate/hexane to give 11.1 g of **23**, mp 123–125 °C. Anal. ($C_6H_8N_2O$) C, H, N.

1-Methyl-3-(2-propynyl)-2-imidazolidinone (24). Sodium hydride (21.3 g of 50% in oil) was added at 0 °C to a stirred solution of 1-(2-propynyl)-2-imidazolidinone (**23**; 50.0 g) in dry THF (1.0 L). After 15 min, methyl iodide (62.8 g) was added and the solution was allowed to warm to room temperature and was then stirred for an additional 1 h. Acetic acid (23 mL) was added and the solvent was removed under reduced pressure and the residual oil was partitioned between ethyl acetate and sodium hydroxide (10 mL of 2 N). The ethyl acetate was removed and the crude product was chromatographed on silica gel using chloroform as the initial eluant to give 31.7 g of **24** as an oil (purity > 95%). A portion of the product (4.8 g) was crystallized twice from ether to give 3.4 g of **24**, mp 57–59 °C. Anal. ($C_7H_{10}N_2O$) C, H, N.

1,3-Dihydro-1-methyl-3-(2-propynyl)-2-imidazol-2-one (27). Propargyl bromide (14.7 g of 80% solution in toluene, 0.1 mol) was added to a stirred solution of aminoacetaldehyde diethyl acetal (13.3 g, 0.1 mol) in THF (200 mL). After 2 h the THF was removed and the residual oil was partitioned between ether and sodium hydroxide solution. Evaporation of the ether gave an oil which was chromatographed on silica gel using chloroform as the initial eluant to give, in order of elution from the column, 4.7 g of 2,2-diethoxy-*N*,*N*-bis-(2-propynyl)ethylamine and 8.1 g of 2,2-diethoxy-*N*-(2-propynyl)ethylamine (**25**). Methyl isocyanate (1.3 g, 0.02 mol) was added to a stirred solution of **25** (3.4 g, 0.02 mol) in ether (50 mL). After 30 min, the ether was evaporated and the residue of **26** was dissolved in water (50 mL), oxalic acid (1.7 g) was added, and the solution was heated at 50 °C for 30 min. The solution was then concentrated to 10 mL, neutralized

(43) While some imidazolium salts have been isolated (see ref 14), isolation of **6** in pure state was not possible, probably due to instability of this intermediate. Cooling the reaction solution at this point afforded a precipitate which appeared to be a mixture of **1c** and **6**, free of isomeric 4-methylimidazole products and unreacted imidazole. Hydrolysis of this mixture with methanol afforded an alternative synthesis of the hydrobromide salt of **1c** in somewhat lower overall yield, but without the need for chromatography.

with 4 N NaOH solution, and extracted with ethyl acetate (4 × 50 mL). The ethyl acetate was evaporated and the residue was chromatographed on silica gel to give 2.1 g of **27** which was recrystallized from ethyl acetate/hexane, mp 69–72 °C. Anal. ($C_7H_8N_2O$) C, H, N.

1-(1-Methyl-2-propynyl)-2-imidazolidinone (29). A mixture of ethylenediamine (100 mL) and 3-chloro-1-butyne (19.0 g) was stirred for 18 h, at which time the excess ethylenediamine was removed by distillation under reduced pressure. Sodium hydroxide (50 mL of 50% aqueous) was added to the residual oil and the product was extracted with ether (4 × 150 mL). The ether was washed with saturated sodium chloride solution (2 × 10 mL) and was then evaporated to give 13.5 g of *N*-(1-methyl-2-propynyl)ethylenediamine (**28**) which was used without further purification. The bulk of this product (12.5 g) was dissolved in DMF (100 mL) and carbonyldiimidazole (25 g) was added over a period of 10 min. The solution was stirred for 30 min and was then evaporated and the residue was chromatographed on silica gel using chloroform/methanol as the eluant to give 7.8 g of product. Crystallization from ethyl acetate/hexane gave 6.3 g of **29**, mp 90–92 °C. Anal. ($C_7H_{10}N_2O$) C, H, N.

X-ray Crystallography. Intensity data for both structures were collected on Siemens diffractometers (Model $P2_1$ for **1c**, and Model $P\bar{1}$ for **2a**), with graphite monochromators, controlled by a Harris computer. Cu Kα radiation was used with $2\theta_{max} = 138°$; 2°/min $\theta/2\theta$ step scans were taken for **1c**; for **2a**, 4°/min step scans were taken in two quadrants, and intensities for equivalent reflections were averaged; all scan widths were >3.4°. Ten reflections periodically monitored showed no trend toward deterioration; $\sigma^2(I)$ was approximated by $\sigma^2(I)$ from counting statistics + dI^2, where the coefficient of I was calculated from the variations in intensities of the monitored reflections and was 0.009 for **1c** and 0.016 for **2a**. Cell parameters were measured by least squares fit of $K\alpha_1$ 2θ values ($\lambda K\alpha_1 = 1.5402$) for 25 high 2θ reflections.[44] Lorentz and polarization corrections appropriate for monochromators with 50% perfect character were made. The structure was solved by direct methods, using DIREC.[45] Hydrogens were found in difference maps close to generated positions; generated positions were used except for the 10 methyl group in **2a**, which was rotated −30° to match found hydrogen positions. Least-squares refinement included all coordinates, and anisotropic thermal parameters for non-hydrogen atoms. Isotropic thermal parameters for hydrogens were 0.5 unit higher than attached atoms. The function minimized in the refinement was $\Sigma w (F_o^2 - F_c^2)^2$, where weights w were $1/\sigma^2(F_o^2)$. Atomic form factors were from Doyle and Turner[46] and, for hydrogen, from Stewart et al.[47] The CRYM system of computer programs was used.[45]

Data for 1c: $C_{12}H_{16}N_3OBr$, $M_r = 298.2$, monoclinic, $P2_1/c$, $a = 16.059$ (2) Å, $b = 9.479$ (1) Å, $c = 8.448$ (5) Å, $\beta = 93.78$ (2)°, $V = 1283.3$ (19) Å^3, $Z = 4$, $D_c = 1.54$ g cm^{-3}, λ(Cu Kα) = 1.5418 Å, $\mu = 4.0$ mm^{-1}, $T = 123$ (2) K, $R = 0.041$ for 2290 unique reflections.

Data for 2a, BM-5: $C_{12}H_{21}N_2OCl$, $M_r = 244.8$, monoclinic, $P2_1/c$, $a = 9.836$ (2) Å, $b = 7.553$ (1) Å, $c = 17.577$ (5) Å, $\beta = 94.25$ (2)°, $V = 1302.2$ (11) Å^3, $Z = 4$, $D_c = 1.25$ g cm^{-3}, λ(Cu Kα) = 1.5418 Å, $\mu = 2.3$ mm^{-1}, $F_{(000)} = 528$, $T = 123$ (2) K, $R = 0.037$ for 2213 unique reflections.

Drug–Receptor Binding Assays. Rats were decapitated, the brain was quickly removed, and bilateral cerebral cortex was dissected out. The tissue was homogenized in 25.0 mL of cold (0 °C) 10 mM Na^+/K^+ phosphate buffer, pH 7.4, using a Brinkman Polytron PCU-110 homogenizer at setting #6 for 30 s. The homogenate was centrifuged at 1000*g* for 10 min, and the supernatant was centrifuged at 30000*g* for 20 min. The resulting pellet was resuspended in 25.0 mL of buffer with the polytron as described before. The suspension was then centrifuged at 30000*g* for 10 min. The final pellet was suspended in 500 volumes (w/v) of the buffer.

Binding of [^{3}H]QNB to muscarinic receptors was carried out by incubating 1.0-mL aliquots of membrane suspension with 0.1 mL [^{3}H]QNB (0.08 nM), 0.1 mL of distilled water or drug solution as indicated, and 0.8 mL of 10 mM Na^+/K^+ phosphate buffer to give a final volume of 2.0 mL. The mixture was incubated for 60 min at 25 °C. The binding reaction was terminated by filtering the mixture under vacuum through a Whatman GF/B filter. The incubation tube was rinsed with ice-cold buffer, and this rinse was filtered through the same filter. The filter was then washed three times with 5.0-mL aliquots of buffer each time. Finally, the filter paper was placed in a scintillation vial to which 15 mL of Amersham Searle ACS cocktail was added. The vials were shaken for 30 min on a mechanical shaker (Eberbach) and then the radioactivity was counted by liquid scintillation spectrometry. For K_i determination, each drug was investigated at five concentrations and each observation was the mean of three experiments; standard error was <5%.

The method for [^{3}H]Oxo-M binding to muscarinic receptors was similar to that described for the [^{3}H]QNB binding assay, with the exception that the final pellet was suspended in 50 volumes (w/v) of buffer, and the filter disks were soaked in ice-cold 0.1% polyethylenimine (w/v) for 30–60 min before use for the termination of incubation by vacuum filtration. The concentration of [^{3}H]Oxo-M was 0.2 nM. Atropine (1 μM) was used for determination of nonspecific binding.

Cholinergic Agonist/Oxotremorine Antagonist Assay. Groups of six CF1 mice weighing 18–22 g each were dosed intraperitoneally with the test compound prepared in 0.25% methylcellulose and were placed in individual cages. Twenty minutes later the mice were scored for the presence of body tremor, salivation, or lacrimation. Body tremor was evaluated while the mice were positioned on the edge of the test cage. After scoring the cholinergic effects the mice were injected subcutaneously with 0.5 mg/kg of oxotremorine dissolved in saline. Ten minutes later the mice were again scored on the three cholinomimetic end points. Doses of the compound under study began at 100 mg/kg and were decreased at a 0.5 log interval until no responders were obtained. The procedure described by Spearman and Karber[48] was used to calculate the ED_{50} and confidence intervals; 95% confidence intervals were between 0.4 and 2.0 times the ED_{50}.

Registry No. **1a**, 70-22-4; **1b**, 129056-95-7; **1b** oxalate, 129056-96-8; **1c**, 129057-00-7; **1c** hemioxalate, 134594-85-7; **1c** hydrobromide, 129057-55-2; **1d**, 3854-02-2; **1f**, 129057-14-3; **1f** hemioxalate, 129057-15-4; **1g**, 129056-97-9; **1g** oxalate, 129056-98-0; **1h**, 129057-12-1; **1j**, 129057-05-2; **1k**, 134594-86-8; **1m**, 134594-87-9; **1m** toluenesulfonate, 134594-88-0; **1n**, 134594-89-1; **1n** hydrochloride, 134594-90-4; **1p**, 134594-91-5; **1p** toluenesulfonate, 134594-92-6; **2a**, 82890-18-4; **2a** hydrochloride, 134594-93-7; **2b**, 134594-94-8; **2c**, 134594-95-9; **2g**, 134594-96-0; **4**, 85733-62-6; **5**, 134594-97-1; **5** oxalate, 134594-98-2; **6**, 129056-99-1; **7a**, 54164-70-4; **7b**, 134594-99-3; **7b** sesquioxalate, 134595-00-9; **7c**, 134595-01-0; **7c** hydrobromide, 134595-02-1; **7d**, 134595-03-2; **8a**, 72314-33-1; **8b**, 134595-04-3; **8b** oxalate, 134595-05-4; **8c**, 134595-06-5; **8c** oxalate, 134595-07-6; **8d**, 98673-90-6; **9b**, 129057-32-5; **9c**, 129057-34-7; **10a**, 3854-05-5; **10b**, 129057-27-8; **10b** sesquioxalate, 129057-28-9; **10c**, 134595-08-7; **10c** hemioxalate, 134595-09-8; **10d**, 18327-42-9; **11c**, 134595-10-1; **12a**, 134103-53-0; **12a** oxalate, 134103-54-1; **12b**, 129057-39-2; **12b** oxalate, 129057-40-5; **12c**, 129057-41-6; **12c** oxalate, 129057-42-7; **12d**, 134103-73-4; **12d** oxalate, 134103-74-5; **13a**, 134595-11-2; **13a** oxalate, 134595-12-3; **13b**, 134595-13-4; **13b** oxalate, 134595-14-5; **13c**, 134595-15-6; **13c** oxalate, 134595-16-7; **13d**, 134595-17-8; **13d** oxalate, 134595-18-9; **14a**, 134103-60-9; **14a** oxalate, 134103-61-0; **14b**, 134595-19-0; **14b** oxalate, 134595-20-3; **14c**, 134595-21-4; **14c** oxalate, 134595-22-5; **15a**, 134595-23-6; **15a** oxalate, 134595-24-7; **15b**, 134595-25-8; **15b** oxalate, 134595-26-9; **15c**, 134595-27-0; **15c** oxalate, 134595-28-1; **16a**, 134595-29-2; **16b**, 134595-30-5; **16c**, 134595-31-6; **17a**, 46746-43-4; **17b**, 129057-36-9; **17b** oxalate, 129057-37-0; **17c**,

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