Novel Quinuclidine-Based Ligands for the Muscarinic Cholinergic Receptor

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Recent clinical studies on Alzheimer's patients have implied that only agents displaying high efficacy at the cortical muscarinic receptor have yielded encouraging results. This paper describes the design, synthesis, and biochemical characterization of novel quinuclidine-based muscarinic agonists which can readily penetrate into the central nervous system and which are capable of displaying high efficacy at cortical sites. With use of a biochemical assay capable of measuring receptor affinity and predicting cortical efficacy, it has been discovered that an oxadiazole ring and related heterocycles can function as bioisosteric replacements for the ester moiety found in several known muscarinic ligands. Within this series there exist compounds which span the efficacy range from high-efficacy agonist through partial agonists to antagonists with affinity comparable or superior to that of classical quaternary ammonium ligands. Consistent with recent molecular biology studies, structure–activity trends are interpreted in terms of separate binding sites for agonists and antagonists with H-bonding interactions characterizing agonist behavior and lipophilic binding characterizing antagonist behavior. Thus the aminooxadiazole moiety has structural features which are optimized for an agonist profile.

There has been much recent interest[1,2] in agents which enhance cortical cholinergic transmission as potential therapies in the treatment of Alzheimer's disease (AD) or senile dementia of the Alzheimer type. The so-called "cholinergic hypothesis" for AD is based on a wide body of clinical and neurochemical evidence[3,4] which indicates that the marked deficits in cognitive function which accompany AD can be most consistently related to selective degeneration of cholinergic neurones projecting from the nucleus basalis of Meynert into cortical and hippocampal regions. Two clear-cut strategies to accentuate cholinergic transmission have been evaluated extensively in the clinic:[5,6] inhibition of acetylcholinesterase (ACHE) to potentiate the effects of endogenous neurotransmitter (acetylcholine) and directly acting agonists at postsynaptic muscarinic receptors in the cortex. It is important to understand information gathered from both these approaches in order to appreciate the tactics employed in this paper.

Several clinical studies with ACHE inhibitors such as physostigmine and more recently with tacrine[7] have revealed modest, albeit statistically significant, improvements in cognitive function in AD patients. Variable oral activity, short duration of action, and side effects (possibly related to simultaneous activation of nicotinic sites) have continued to restrict the acceptance of these agents. On the other hand, experience with directly acting agonists[5] such as arecoline (1), RS-86 (2), and pilocarpine (3) have yielded either disappointing or equivocal results. Only 1 showed a significant improvement in a rather limited patient population, but its extremely short duration of action renders its clinical use impractical.

We suggest that these results can be interpreted in terms of the low efficacy of those agonists described above at cortical muscarinic receptors. Although molecular biological studies[8,9] have revealed the presence of at least five genetic products which code for distinct muscarinic receptors in human brain, it is still believed that the pirenzepine-sensitive M-1 site,[10] whose signal-transduction mechanism is linked to the stimulation of phosphatidylinositol (PI) hydrolysis,[11,12] is that which is most clearly associated with cognitive deficits. For this reason, efficacy of a given ligand at this site is related to its ability to stimulate the hydrolysis of PI. The tertiary amines described above behave as weak partial agonists at these receptors[13,14] and are incapable of eliciting a PI response of the same magnitude as that observed for classical quaternary ammonium agonists. In contrast to these directly acting agonists, ACHE inhibitors augment the availability of high-efficacy agonist, that is acetylcholine itself, in the synaptic cleft and this may account for their more robust activity.

In order to study in detail the role of cholinergic mechanisms in memory and cognition, we sought to develop nonquaternary muscarinic agonists capable both of displaying high efficacy at cortical receptors and readily penetrating the blood–brain barrier. Incompatible with this goal was the long-held view that the quaternary ammonium cationic head group present in classical agonists was an obligatory feature necessary to induce activation of those muscarinic receptors located in cerebral cortex where there is limited receptor reserve. This paper describes the design, synthesis, and biochemical characterization of a group of quinuclidine-based derivatives which assist in mapping the muscarinic receptor(s) in cerebral cortex. Within this series there exist compounds which span the efficacy range from highly efficacious agonist, through partial agonists, to antagonists with affinity comparable or superior to that of classical quaternary ammonium ligands. In addition, information from published molecular biological data on related receptors is interpreted in line with the current findings which corroborate the proposal that the high- and low-affinity states of the receptor may constitute two distinct loci on the protein with

† Department of Chemistry.
‡ Department of Biochemistry.

(1) Perry, E. K. *Br. Med. Bull.* **1986**, *42*, 63.
(2) Moos, W. H.; Davis, R. E.; Schwarz, R. D.; Gamzu, E. R. *Med. Res. Rev.* **1988**, *8*, 353.
(3) Iversen, S. *Chem. Br.* **1988**, 338.
(4) Growdon, J. H. *Med. Res. Rev.* **1983**, *3*, 237.
(5) Hollander, E.; Mohs, R. C.; Davis, K. L. *Br. Med. Bull.* **1986**, *42*, 97.
(6) Hershenson, F. M.; Moos, W. H. *J. Med. Chem.* **1986**, *29*, 1125.
(7) Summers, W. K.; Majovski, L. V.; Marsh, G. M.; Tachiki, K.; Kling, A. *N. Eng. J. Med.* **1986**, *315*, 1241.
(8) Bonner, T. L.; Buckley, N. J.; Young, A. C.; Brann, M. R. *Science* **1987**, *237*, 527.
(9) Peralta, E. G.; Ashkenazi, A.; Winslow, J. W.; Smith, D. H.; Ramachandran, J.; Capon, D. J. *Embo J.* **1987**, *6*, 3923.
(10) Hammer, R.; Berrie, C. P.; Birdsall, N. J. M.; Burgen, A. S. V.; Hulme, E. C. *Nature (London)* **1980**, *238*, 90.
(11) Brown, E.; Kendall, D. A.; Nahorski, S. R. *J. Neurochem.* **1984**, *42*, 1379.
(12) Fisher, S. K.; Bartus, R. T. *J. Neurochem.* **1985**, *45*, 1085.
(13) Saunders, J.; Showell, G. A.; Snow, R. J.; Baker, R.; Harley, E. A.; Freedman, S. B. *J. Med. Chem.* **1988**, *31*, 486.
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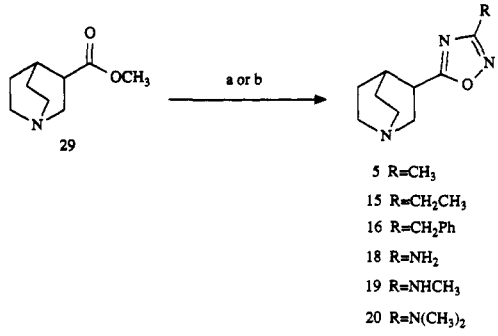
Scheme I[a]

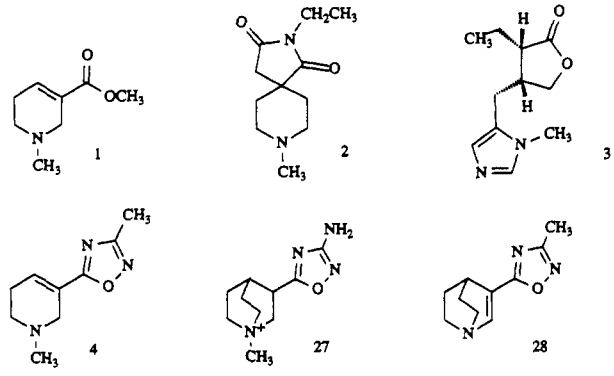


[a] Reagents: (a) Na, EtOH, powdered molecular sieves, RC(=NOH)NH_2, reflux; (b) NaH, THF, RC(=NOH)NH_2, reflux.

independent sets of interactions.

Synthetic Chemistry

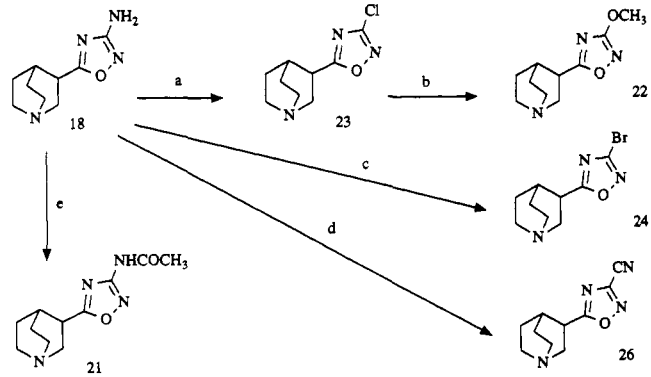
As a starting point in the design process a hydrolytically stable bioisostere of the ester functionality in tetrahydropyridine **1**[15] was sought. Methyloxadiazole **4** was



chosen because it had been previously shown[16] that such tactics in the benzodiazepine-receptor field achieved this objective without compromising affinity for the receptor. However, molecular orbital calculations showed that the charge distribution of the protonated form of quinuclidine rather than piperidine more closely resembled that of the quaternary ammonium entity in acetylcholine. Accordingly, our attention was directed to the range of quinuclidine-based derivatives **5–28**, all analogues of the known agonist methyl quinuclidine-3-carboxylate (**29**),[17] listed in Tables I and II.

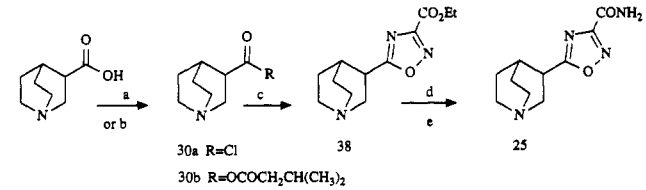
The key building block for many of the compounds was **29**, which was readily available on the 100-g scale from quinuclidin-3-one using the method of Grob.[18] Thus oxadiazoles **5**, **15**, **16**, and **18–20** were made in one step from **29** by reaction with the appropriate amide oxime or hydroxyguanidine in refluxing THF or ethanol (Scheme I). Aminooxadiazole **18**, in addition to providing a key compound in the structure–activity study, also proved to be a valuable intermediate toward other derivatives (Scheme II). Diazotization of **18** under aqueous acidic conditions afforded a route to the halooxadiazoles **23** and **24**. While replacement of the chlorine substituent in **23** by methoxide

Scheme II[a]



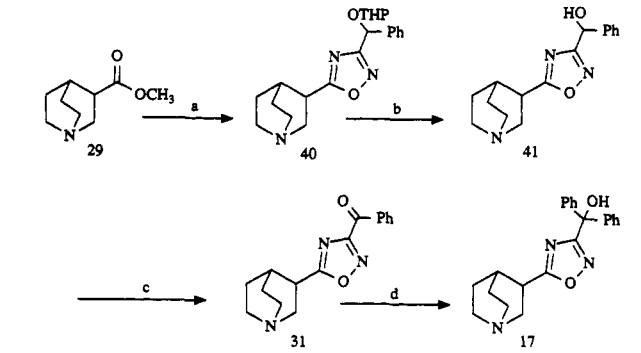
[a] Reagents: (a) $NaNO_2$, HCl, H_2O; (b) NaOMe, MeOH; (c) $NaNO_2$, HBr, H_2O; (d) amyl nitrite, HCl, DMF, then Bu_4NCN; (e) Ac_2O, AcOH, heat.

Scheme III[a]



[a] Reagents: (a) $SOCl_2$; (b) $(CH_3)_2CHCH_2OCOCl$, Et_3N, THF; (c) $H_2NC(=NOH)CO_2Et$, THF, then dioxane, reflux; (d) NaOH, H_2O then evaporate; (e) EtOCOCl then NH_3.

Scheme IV[a]



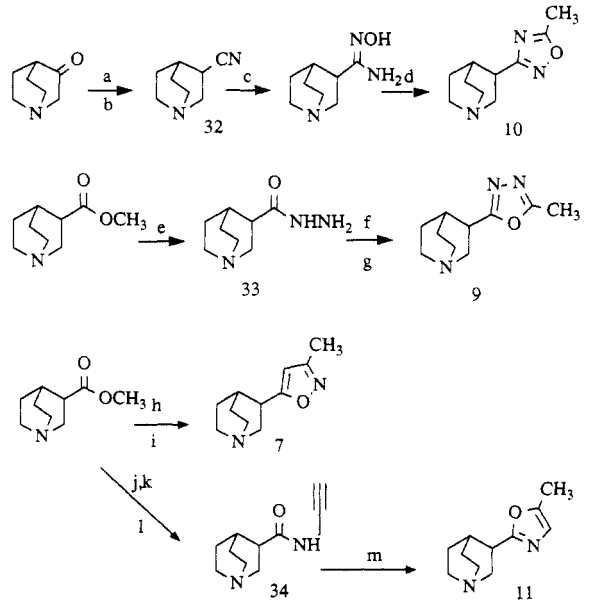
[a] Reagents: (a) NaH, THF, PhCH(OTHP)C(=NOH)NH_2, (**39**); (b) dilute HCl; (c) MnO_2; (d) PhMgBr, Et_2O.

was readily achieved, **23** was unreactive toward cyanide. Instead, **26** was prepared directly from **18** by diazotization under nonaqueous conditons in the presence of tetra-*n*-butylammonium cyanide. Since **26** could not be hydrolyzed to amide **25** without disruption of the oxadiazole ring, the amide was made by a circuitous route starting from acid chloride **30a** or, subsequently, from mixed anhydride **30b** (Scheme III). After initial acylation at low temperature, ring closure was effected by refluxing in anhydrous dioxane. This alternative procedure offered an efficient and general method of oxadiazole ring formation for molecules with base-sensitive functionality. For synthesis of oxadiazoles with more bulky substituents, benzoyloxadiazole **31** was a key substrate for a variety of nucleophiles yielding, for example, the quinuclidine benzilate (QNB) analogue **17** upon treatment with phenylmagnesium bromide (Scheme IV).

Compounds with heterocyclic replacements for oxadiazole were obtained by two general approaches involving (a) construction of the ring to incorporate the one-carbon unit formerly from quinuclidine-3-carboxylic acid (Scheme

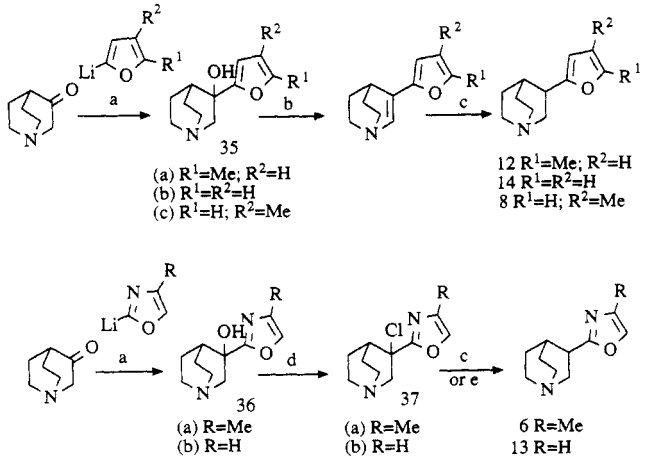
(15) Saunders, J.; MacLeod, A. M.; Merchant, K.; Showell, G. A.; Snow, R. J.; Street, L. J.; Baker, R. *J. Chem. Soc., Chem. Commun.* **1988**, 1618.
(16) Watjen, F.; Baker, R.; Engelstoff, M.; Herbert, R.; MacLeod, A.; Knight, A.; Merchant, K.; Moseley, J.; Saunders, J.; Swain, C. J.; Wong, E.; Springer, J. P. *J. Med. Chem.* **1989**, *32*, 2282.
(17) Lambrecht, G.; Mutschler, E. *Arzneim. Forsch.* **1974**, *24*, 1725.
(18) Grob, C. A.; Renk, E. *Helv. Chim. Acta* **1954**, *37*, 1689.

Scheme V[a]



[a] Reagents: (a) $(i\text{-Pr})_3C_6H_2SO_2NHNH_2$, MeOH; (b) KCN, MeOH, reflux; (c) $NH_2OH{\cdot}HCl$, K_2CO_3, EtOH, reflux; (d) Ac_2O, reflux; (e) $NH_2NH_2{\cdot}H_2O$; MeOH, reflux; (f) $CH_3C(OMe)_3$, reflux; (g) KO-*t*-Bu, *n*-BuOH, reflux; (h) $(CH_3)_2C{=}NOH$, *n*-BuLi, THF; (i) H_2SO_4, THF, H_2O, reflux; (j) concentrated HCl; (k) $SOCl_2$; (l) propargylamine, CH_2Cl_2; (m) $Hg(OAc)_2$, HOAc, reflux.

Scheme VI[a]



[a] Reagents: (a) heterocycle; *n*-BuLi, THF; (b) $POCl_3$, Et_3N, CH_2Cl_2; (c) H_2, Pd–C, MeOH, 1 atm; (d) $SOCl_2$, heat; (e) Bu_3SnH, 2,2′-azobisisobutyronitrile (AIBN), THF, reflux.

V) or (b) direct coupling of a lithiated heterocycle with quinuclidinone (Scheme VI). In the former strategy, nitrile **32**, hydrazide **33**, ester **29**, or propargylic amide **34** provided the building blocks which could be cyclized by known methods to isomeric oxadiazoles **10** and **9**, isoxazole **7**, and oxazole **11**, respectively. The second, more convergent approach (Scheme VI) involved, for example, reaction of quinuclidinone with a 2-lithiofuran to yield alcohol **35**. In the case of **35a,b** this could be achieved by direct deprotonation of the readily available furan with *n*-butyllithium; for **35c**, however, the 2-bromofuran was employed to direct metalation to the required position. In this case it was important to remove the bromobutane byproduct to avoid quaternization of the quinuclidine during purification. Although **35** underwent elimination readily, the corresponding oxazole intermediates **36** were resistant to all conditions tried, presumably because of the electron-withdrawing nature of the oxazole, resulting in destabilization of the cationic transition state for elimination. Instead, chloro derivative **37** was efficiently reduced by tributyltin hydride.

Results

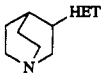
The dissociation constants of all of the compounds of the present study for both the high- and low-affinity states of the muscarinic receptor in rat cortical membranes were measured in a two-stage binding assay previously reported.[13] Briefly, this assay involved displacement by the test ligand of [^{3}H]oxotremorine-M (OXO-M) from the high-affinity state (the "agonist binding site") of the receptor and [^{3}H]-*N*-methylscopolamine (NMS) from predominantly the low-affinity state (the "antagonist binding site"). Most importantly, the ratio of these dissociation constants (the NMS/OXO-M ratio) gives a prediction of the cortical efficacy of the ligand since this ratio has been shown to correlate directly to the ability of the given ligand to stimulate cortical PI hydrolysis. Thus, antagonists exhibit ratios close to 1, whereas high-efficacy agonists possess values greater than 1000. The results are presented in Tables I and II.

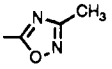
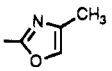
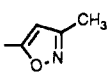
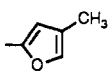
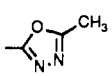
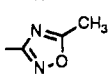
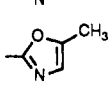
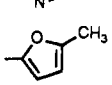
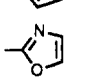
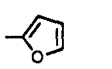
A comparison of the binding data for methyloxadiazole **5** with the parent ester **29** illustrates the suitability of this moiety as a bioisosteric replacement of potential general applicability. Since a 20-fold enhancement of binding with **5** was achieved at both receptor states, there was no accompanying gain in predicted efficacy. It was of interest however to understand which features of the oxadiazole ring contributed to this improvement in binding and whether some of these factors could be separately manipulated to cause structure–activity at the two affinity states to diverge. Progressive removal of the oxadiazole ring heteroatoms (**6–8**) caused a drastic reduction in predicted efficacy primarily through loss of OXO-M binding (greater than 50-fold). Binding to the low affinity state was relatively unchanged. This small set of compounds vindicated speculations based on data already reported in the literature that ligand efficacy may well be determined by hydrogen-bonding capability. Apparently two H-bonded acceptor sites on the ligand are necessary for high affinity at the agonist binding site. The exact position of these acceptor sites is also important for agonists (**9** and **10**) although clearly not for antagonist binding (**11** and **12**).

Within the oxadiazole series, differing only in the nature of the 3-substituent, lipophilicity and electronic factors markedly influence both affinity and efficacy (Table II). Increasing the size and lipophilicity of this substituent (**5** and **15–17**) favored low-affinity-state binding, resulting in compounds with a clear-cut antagonist profile. Most notable is **17**, conceived to be a QNB mimic, which had subnanomolar affinity at both receptor states and is thus one of the most potent, nonquaternized muscarinic antagonists known. Efficacy peaked with the electron-donating, hydrophilic, amino substituent as a result of increasing binding to the agonist state of the receptor. This observation gave added credibility to the role of hydrogen bonding in stabilizing the agonist binding state of the receptor since the electron-donating amino group would be expected to further augment the acceptor properties of the oxadiazole ring nitrogens. This electronic effect was swamped by N-alkylation (**19** and **20**) although, surprisingly, less so by N-acylation (**21**). A range of other substituents having opposing electronic and hydrophilic properties (**22–26**) are included in Table II. As anticipated from earlier published data on 3-acetoxyquinuclidine,[19]

(19) Ringdahl, B.; Ehler, F. J.; Jenden, D. J. *Mol. Pharmacol.* **1982**, *21*, 594.

Table I. In Vitro Binding Data for Quinuclidine-Based Ligands Compared to Standard Muscarinic Agents



compd	HET	binding data: K_{app},[a] μM [^{3}H]NMS[b]	[^{3}H]OXO-M[c]	ratio[d]
5		0.44 (0.39–0.48)	0.00090 (0.00052–0.0013)	490
6		1.4 (1.2–1.7)	0.027 (0.022–0.033)	52
7		1.4 (1.1–1.8)	0.036 (0.030–0.045)	39
8		1.4 (0.95–1.9)	0.057 (0.041–0.067)	25
9		7.5 (5.4–12)	0.060 (0.054–0.071)	130
10		2.9 (2.1–3.5)	0.054 (0.042–0.080)	54
11		0.73 (0.45–1.00)	0.040 (0.033–0.048)	18
12		0.25 (0.23–0.28)	0.013 (0.010–0.017)	19
13		6.7[e]	0.038[e]	180
14		3.3[e]	0.034[e]	97
	arecoline (1)	6.2 (5.1–9.0)	0.011 (0.0098–0.012)	560
	RS-86 (2)	5.0 (4.3–5.4)	0.040 (0.033–0.046)	130
	pilocarpine (3)	4.0 (2.6–5.3)	0.040 (0.034–0.043)	100
	atropine	0.0010 (0.00092–0.0012)	0.00048 (0.00040–0.00064)	2.1
	carbachol	24 (23–26)	0.0058 (0.0048–0.0072)	4100
4		1.8 (1.0–2.3)	0.0046 (0.0035–0.0063)	390
29		8.6[e]	0.023[e]	370

[a] Displacement of tritiated radioligand from rat cortical homogenates. Results are expressed as an affinity constant (K_{app}) which has been corrected for ligand occupancy with the Cheng and Prusoff equation.[34] Unless otherwise stated, each value is the geometric mean of at least three determinations performed on separate occasions. Each curve is typically 4–10 concentrations performed in triplate. Range of values obtained are given in parentheses with each result. [b] Displacement of [^{3}H]-*N*-methylscopolamine. [c] Displacement of [^{3}H]-oxotremorine-M. [d] The ratio of the K_{app}'s of NMS and OXO-M. [e] Value derived from a single determination.

quaternization (e.g., **27**) invariably diminished both affinity and efficacy at the receptor.

More detailed biochemical evaluation of these compounds has confirmed their ability to readily penetrate into the central nervous system following systemic administration and to display high efficacy at cortical sites. In agreement with earlier observations,[20] substituents into the quinuclidine ring have a pronounced effect upon the pK_a of the amine. For example, the methyloxadiazole ring in **5** causes a reduction in pK_a from 11.0 for quinuclidine itself to 8.5, to give a compound in which the nonprotonated form is sufficiently populated at physiological pH to ensure rapid absorption across the blood–brain barrier. Compounds with an NMS/OXO-M ratio below 200 failed to show a significant cortical PI response in vitro. Aminooxadiazole **18**, however, having a much greater binding ratio, was able to maximally stimulate PI in an atropine-sensitive manner to 66% of the value achievable with 1 mM carbachol. These results will be reported in full elsewhere.

(20) Grob, C. A. *Helv. Chim. Acta* **1985**, *68*, 882.

Receptor Modeling and Discussion

To rationalize the data presented in the previous section, a new interpretation of the sequence of events which underlie ligand binding and subsequent receptor activation is proposed. The model is entirely consistent with more recent information derived from molecular biological studies[21,22] with the homologous β-adrenergic receptor. As has been obvious for some considerable time,[23] the primary interaction between ligand and muscarinic receptor involves the cationic head group of the ligand (the quaternary ammonium or protonated-amine moiety) and an anionic group on the receptor presumably provided by an aspartate (ASP) or a glutamate (GLU) residue. For the β receptor, this has now been shown[24] to be ASP-113,

(21) Chung, F.; Wang, C.; Potter, P. C.; Venter, J. C.; Fraser, C. M. *J. Biol. Chem.* **1988**, *263*, 4052.
(22) Strader, C. D.; Sigal, I. S.; Candelore, M. R.; Rands, E.; Hill, W. S.; Dixon, R. A. F. *J. Biol. Chem.* **1988**, *263*, 10267.
(23) For a review, see: Schulman, J. M.; Sabio, M. L.; Disch, R. L. *J. Med. Chem.* **1983**, *26*, 817.
(24) Strader, C. D.; Sigal, I. S.; Register, R. B.; Candelore, M. R.; Rands, E.; Dixon, R. A. F. *Proc. Natl. Acad. Sci. U.S.A* **1987**, *84*, 4384.

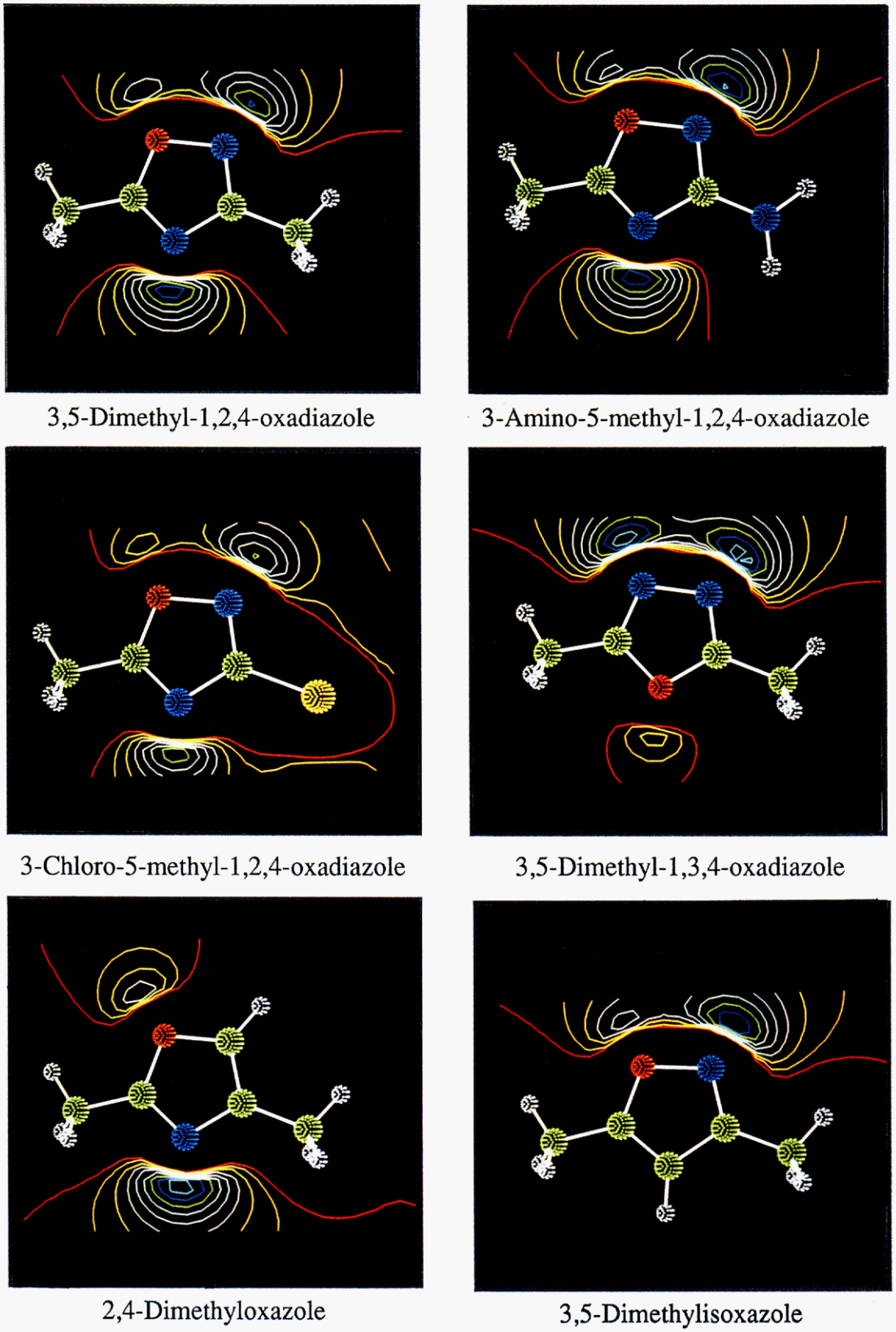
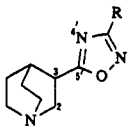


Figure 1. Two-dimensional molecular electrostatic-potential maps calculated for representative heterocycles. Contours are at increments of −10 starting from −30 kcal/mol (red).

buried within the membrane-spanning helical domains of the protein. We now propose that agonists but not antagonists are able to equilibrate with this site and a second, more deeply buried ASP, ASP-79, in the β-receptor. In confirmation of this proposal is the finding[21] that replacement of this residue by ASN-79 produced a receptor which bound antagonists with wild-type affinity but had up to a 200-fold reduced affinity for agonists and this

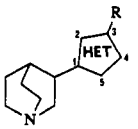
Table II. In Vitro Binding Data for Substituted Oxadiazoles

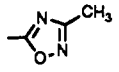
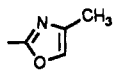
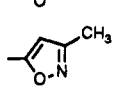
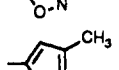
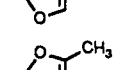
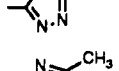
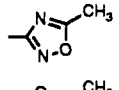
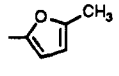
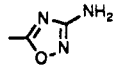


no.	R	binding data: K_{app},[a] μM [^{3}H]NMS[b]	[^{3}H]OXO-M[c]	ratio	V[f]	π[g]
5	CH_3	0.44 (0.39–0.48)	0.00090 (0.00052–0.0013)	490	64	0.56
15	CH_2CH_3	0.096 (0.08–0.11)	0.0056 (0.0047–0.0073)	17	74	1.02
16	CH_2Ph	0.070 (0.049–0.10)	0.021 (0.014–0.031)	3.3	117	2.01
17	$C(OH)Ph_2$	0.00012 (0.0001–0.00012)	0.000067 (0.000037–0.00015)	1.8	195	2.27
18	NH_2	0.60 (0.44–0.70)	0.00050 (0.00035–0.00067)	1200	59	−1.23
19	$NHCH_3$	2.0 (1.2–3.5)	0.053 (0.021–0.17)	38	71	−0.47
20	$N(CH_3)_2$	0.20 (0.13–0.37)	0.021 (0.014–0.025)	9.5	83	0.18
21	$NHCOCH_3$	23 (21–28)	0.12 (0.097–0.15)	190	86	−0.97
22	OCH_3	0.52 (0.50–0.56)	0.014 (0.012–0.015)	37	68	−0.02
23	Cl	0.19 (0.18–0.21)	0.00048 (0.00041–0.00054)	400	66	0.71
24	Br	0.19[e]	0.0011[e]	170	72	0.86
25	$CONH_2$	39[e]	1.7[e]	23	76	−1.49
26	CN	2.6 (2.2–2.8)	0.043 (0.041–0.045)	60	68	−0.57
27		6.6 (6.6–6.6)	0.079 (0.066–0.091)	84		
28		15 (15–16)	0.40 (0.38–0.43)	38		

[a–e] See Table I footnotes. [f] Van der Waals volume computed for the quinuclidine substituent as a whole. [g] Approximation of the hydrophobicity for the oxadiazole substituent using the Hansch aromatic substituent constant.[30]

Table III. Magnitude of the Electrostatic Potential Well Adjacent to Ring Atoms 2 and 4



no.	HET	log ratio[a]	V_2,[b] kcal/mol	V_4,[c] kcal/mol	V,[d] Å^3
5		2.69	−78	−72	63.5
6		1.72	−88	0	64.7
7		1.59	0	−80	63.5
8		1.18	0	0	65.8
9		2.11	−24	−87	62.4
10		1.73	−78	−37	59.0
12		1.28	−50	0	66.9
18		3.08	−78	−82	59.0
23		2.60	−67	−61	66.1

[a] log of the ratio of the K_{app}'s of NMS and OXO-M. [b] V_2 is the potential-well located adjacent to ring atom 2 in the plane of the heteroaromatic ring. [c] V_4 is the potential at ring atom 4. [d] Van der Waals volume computed for the quinuclidine substituent as a whole.

binding was not sensitive to guanine nucleotides. Both of these residues are conserved in all published[25] sequences of receptors for monoamine neurotransmitters linked to G-protein activation; in the human M-1 muscarinic receptor the equivalent residues are ASP-71 and ASP-105. Structural features which govern binding preferences to one site or the other begin to emerge from a critical assessment of the binding data from the current series of compounds and these will be discussed in the following paragraphs.

Conformation analysis using a molecular mechanics force field[26] on those molecules in Tables I and II lacking an "ortho" CH (e.g. **5** but not **7**) showed that the barrier to free rotation about the 3–5′ bond is less than 1 kcal/mol with energy minima at dihedral angles (2–3–5′–4′) of +143° and −40°. Restraining the mobility of this bond, by incorporation of a double bond at the quinuclidine 2,3-position, caused reductions in binding of over 20-fold and over 400-fold at the NMS- and OXO-M-labeled sites, respectively. Since the loss in binding was clearly different at the two states, a change in the pK_a of the quinuclidine nitrogen atom cannot account for the binding profile. However, the data is consistent with the view that a conformational change after the initial binding complex has been formed is necessary for subsequent binding at the high-affinity state of the receptor.

Within a subgroup of these compounds where the volume of the quinuclidine side chain (that is, the heteroaromatic ring and the substituent combined) does not vary significantly (Table III), it was shown that predicted efficacy correlated directly with the magnitude of the negative electrostatic potential in the vicinity of the oxadiazole ring nitrogen atoms (or equivalent atoms in the other heteroaromatic systems). For computational convenience,[27] the quinuclidine ring common to all molecules was

(25) Summarized in: Dixon, R. A. F.; Strader, C. D.; Sigal, I. S. *Annu. Rep. Med. Chem.* **1988**, *23*, 221.
(26) With use of the OPTIMOL program within the Merck molecular modeling facility (Dr. T. Halgren, Rahway; unpublished).
(27) All quantum mechanical calculations were performed with the CHEMQM interface withe the CHEMX program (Chemical Design Ltd., Oxford, U.K.).

replaced by methyl on the heteroaromatic rings constructed from either X-ray or microwave coordinates. This simplification is acceptable since, in all cases, the cationic head group presented to the receptor (i.e. the protonated quinuclidine species) will influence electron density on the heteroaromatic ring to the same extent. Electrostatic potential maps were generated by the DENPOT procedure[28] using wave functions computed by GAUSSIAN 80.[29] The variation of potential in the plane of the heteroaromatic ring may be most clearly demonstrated by reference to two-dimensional electrostatic-potential maps (Figure 1) from which the magnitude of the potential-well adjacent to the oxadiazole nitrogens (or equivalent atoms) may be estimated. Regression analysis of these potentials in relation to the NMS/OXO-M ratio (log) shows a significant correlation (Figure 2) according to the equation:

$$\log (\text{NMS/OXO-M}) = -0.0187(\pm 0.0018)(V\_2) - 0.0190(\pm 0.0019)(V\_4)$$

$$n = 8,\ R = 0.99,\ \text{SD} = 0.270,\ F = 303.47$$

where V_2 is the potential at ring atom 2 and V_4 is the potential at ring atom 4.

Taking a second subgroup of these ligands in which the oxadiazole ring remains constant, the influence of lipophilicity in the molecule at a position equivalent to the acetyl methyl group of acetylcholine becomes the predominant factor in binding to the NMS-labeled site (Table II). As an approximation to the substituent contribution to lipophilicity, the Hansch aromatic constants[30] are given in Table II. From this data it can be seen that an electronically neutral lipophilic substituent is favored for stabilization of the low-affinity state of the receptor. On the other hand, a blend of hydrophilic and electron-donating properties is necessary for optimal binding to the agonist binding site.

The conclusions to be drawn from this study are that two H-bonding interactions are necessary for binding with high affinity to the agonist binding site with little or no dependency on lipophilic binding energy. Either or both of these interactions are relatively unimportant in binding to the low-affinity state of the same receptor. By contrast, increased reliance upon lipophilic binding in the vicinity of the acetyl methyl group of the endogenous ligand characterizes antagonist behavior, with partial agonists falling between these two extremes. In terms of the binding model proposed above, antagonists are seen as ligands which bind to the more exposed ASP residue on the receptor. Both because of their size and lipophilicity, access of such compounds to the agonist binding domain of the protein, which is more deeply buried within the membrane-spanning helices, is severely impeded. Small hydrophilic ligands, that is, agonists, are able to equilibrate between these two ASP residues on the receptor by utilizing essentially hydrogen-bonding interactions in the shuttling process. During this equilibration, it is anticipated that the mutual conformational changes in both receptor and ligand that accompany receptor activation take place. Very recent[31] mutagenesis studies imply that a third anionic site (ASP-130 in the β-adrenergic receptor; conserved in the muscarinic receptor as ASP-122) may also be involved in agonist binding, and this finding may be accommodated by a continuation of the equilibration process with further movement of the ligand down the binding funnel of the receptor. These novel, centrally active compounds should help to elucidate the functional importance of cholinergic mechanisms in the normal brain and test the hypothesis that cholinergic enhancement will have clinical utility. Furthermore, it is proposed that similar, although of course not identical, binding models may be constructed for homologous receptor systems (e.g. β-adrenergic[32] and serotonergic[33] receptors) and such models may be of general value in ligand design.

Experimental Section

Chemical Methods. General Directions. In addition to those general directions previously described, the following procedures were adopted: Preparative chromatography was carried out with either gravity columns for both silica (Merck Art. 7734) and alumina (Woelm Grade III neutral) or medium-pressure Lobar columns (Merck Art. 10401). pK_a's were determined (with R. Williams) with a Radiometer Autotitration system (PHM84 Research pH meter, ABU80 Autoburette, and Hewlett-Packard 85B) and log P's by the shake-flask method.

3-(3-Methyl-1,2,4-oxadiazol-5-yl)quinuclidine Hydrochloride (5). Acetamide oxime[35] (3.5 g, 47.4 mmol) suspended in THF (150 mL) under N_2 was heated to 60 °C with NaH (1.42 g of a 60% dispersion in oil, 47.4 mmol) for 1 h in the presence of 4A molecular seives (10 g). Compound **29** (6.68 g, 39.5 mmol) in THF (25 mL) was added and the reaction was heated under reflux for 2.5 h. After cooling, the reaction was filtered and the solvent was removed under reduced pressure. Water was added to the residue, which was extracted (4×) with CH_2Cl_2. The extracts were evaporated to give an oil, which on treatment with ethereal HCl gave **5** (5.8 g, 64%): mp 185–187 °C (CH_2Cl_2/Et_2O); MS m/z 193 (M^+ of free base); ^1H NMR ($CDCl_3$) δ 1.81–1.93 and 2.07–2.27 (each 2 H, each m, 5-CH_2 and 8-CH_2), 2.41 (3 H, s, CH_3), 2.58–2.62 (1 H, m, 4-CH), 3.34–3.48 and 3.50–3.61 (4 H, each m, 6-CH_2 and 7-CH_2), 3.69–3.76 and 3.86–3.92 (1 H and 2 H, each m, 2-CH_2 and 3-CH). Anal. ($C_{10}H_{15}N_3O\cdot HCl\cdot 0.5H_2O$) C, H, N.

With use of the procedure above, but with acetamide oxime replaced by the appropriate amide oxime or hydroxyguanidine, the following were prepared. **15**: 58%; mp 113–115 °C. Anal. ($C_{11}H_{17}N_3O\cdot(COOH)_2$) C, H, N. **16**: 28%; mp 163–165 °C. Anal. ($C_{16}H_{19}N_3O\cdot(COOH)_2$) C, H, N. **19**: 12%; mp 154 °C dec. Anal. ($C_{10}H_{16}N_4O\cdot(COOH)_2$) C, H, N. **20**: 40%; mp 106–108 °C dec. Anal. ($C_{11}H_{18}N_4O\cdot(COOH)_2$) C, H, N.

3-Hydroxy-3-(4-methyloxazol-2-yl)quinuclidine (36a). A solution of n-butyllithium in hexane (1.6 M, 50 mL, 80 mmol) was added dropwise over 30 min to a stirred solution of 4-methyloxazole (7.26 g, 87.5 mmol) in THF (80 mL) under N_2, keeping the temperature below −65 °C. After a further 30 min at −70 °C, a solution of quinuclidin-3-one (9.10 g, 72.8 mmol) in THF (20 mL) was added over 5 min. The mixture was kept at −70 °C for 2 h and then warmed to 25 °C overnight. Saturated ammonium chloride solution (50 mL) was added, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The residue from the combined organic layers was dissolved in boiling EtOAc (250 mL), filtered, and concentrated to 100 mL. The product crystallized on cooling as colorless prisms (4.98 g, 33%): mp 176–177 °C; MS m/z 208 (M^+); ^1H NMR ($CDCl_3$) δ 1.32–1.57 (3 H, m, 5-CH and 8-CH_2), 2.11–2.19 (2 H, m, 4-CH and 5-CH), 2.17 (3 H, d, J = 1 Hz, CH_3); 2.76–2.88 (3 H, m, 6-CH_2 and 7-CH), 2.94–3.01 (1 H, m, 7-CH), 2.96 (1 H, dd, J = 1 and 14 Hz, 2-CH), 3.78 (1 H, dd, J = 2 and 14 Hz, 2-CH), 7.35 (1 H, q, J = 1 Hz, oxazole-H); IR ν_{max} (Nujol) 3200–2500, 1600, 1550

(28) Peeters, D.; Sana, M. DENPOT 80 program (QCPE 483).
(29) Chandra Singh, U.; Kollman, P. GAUSSIAN 80 program (QCPE 446).
(30) Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16*, 1207.
(31) Fraser, C. M.; Chung, F.; Wang, C.; Venter, J. C. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 5478.
(32) Donne-Op den Kelder, G. M.; Bultsma, T.; Timmerman, H.; Rademaker, B. *J. Med. Chem.* **1988**, *31*, 1069.
(33) Glennon, R. A. *J. Med. Chem.* **1986**, *30*, 1.
(34) Cheng, Y.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, 22, 3099.
(35) All amide oximes and related starting reagents were made by standard literature procedures (e.g., see: Hunkeler, W.; Kyburz, E. European Patent 150,040, 1985 and ref 16).

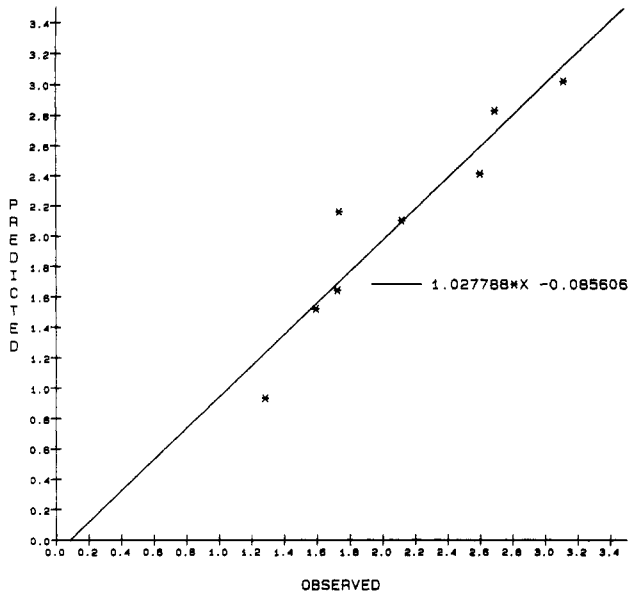


Figure 2. Plot of predicted versus observed log (NMS/OXO-M) with the line of best fit being $y = 1.028x - 0.086$.

cm^{-1}. Anal. ($C_{11}H_{16}N_2O_2$) C, H, N.

Compound **36b** was prepared from oxazole using the above procedure: 19% yield; mp 196–198 °C (EtOAc). Anal. ($C_{10}H_{14}N_2O_2$) C, H, N.

3-(4-Methyloxazol-2-yl)quinuclidine Hydrochloride (6). The foregoing hydroxyquinuclidine (**36a**, 1.50 g, 7.21 mmol) was added portionwise to stirred, ice-cooled thionyl chloride (15 mL), and the resulting solution was heated under reflux for 1.5 h. The cooled solution was evaporated, aqueous potassium carbonate (2 M, 50 mL) was added, and the mixture was extracted with CH_2Cl_2 to yield chloroquinuclidine **37** as a brown oil (1.21 g, 74%), which was used immediately in the next reaction: MS m/z 228, 226 (M^+ ^{37}Cl, ^{35}Cl); ^1H NMR ($CDCl_3$) δ 1.22–1.30 (1 H, m, 5-CH), 1.54–1.67 (3 H, m, 5-CH and 8-CH_2), 2.19 (3 H, d, J = 1 Hz, CH_3), 2.64–2.66 (1 H, m, 4-CH), 2.72–2.76 and 2.90–3.06 (each 2 H, each m, 6-CH_2 and 7-CH_2), 3.43 (1 H, d, J = 15 Hz, 2-CH), 4.30 (1 H, dd, J = 2 and 15 Hz, 2-CH), 7.39 (1 H, q, J = 1 Hz, oxazole-H).

A solution of the chloroquinuclidine (1.21 g, 5.34 mmol), tributyltin hydride (2.0 mL 7.4mmol) and 2,2′-azobisisobutyronitrile (AIBN, 50 mg) was heated under reflux under N_2. Further portions of AIBN were added after 3 and 5 h. After 8 h the cooled solution was partitioned between 2 M hydrochloric acid and CH_2Cl_2. The acid layer was basified with solid potassium carbonate and extracted with CH_2Cl_2. Chromatography of the residue isolated from the organic layer on alumina in CH_2Cl_2/MeOH (99:1) yielded the product (265 mg), which was converted to the hydrochloride (256 mg): mp 217–219 °C dec; R_f 0.4 in CH_2Cl_2/MeOH (95:5) on alumina; MS m/z 192 (M^+); ^1H NMR (D_2O) δ 1.78–1.92 (3 H, m, 5-CH and 8-CH_2), 2.08–2.13 (1 H, m, 5-CH), 2.12 (3 H, d, J = 1 Hz, CH_3), 2.55–2.58 (1 H, m, 4-CH), 3.28–3.41 (4 H, m, 6-CH_2 and 7-CH_2), 3.64–3.76 (3 H, m, 2-CH_2 and 3-CH), 7.58 (1 H, q, J = 1 Hz, oxazole-H). Anal. ($C_{11}H_{16}N_2O.1.4HCl$) C, H, N, Cl.

3-(3-Methylisoxazol-5-yl)quinuclidine Hydrochloride (7). A solution of *n*-butyllithium in hexane (2.5 M, 15 mL, 37.4 mmol) was added to a stirred solution of acetone oxime (1.4 g, 18.7 mmol) in dry THF (35 mL) at 0 °C. After 1 h, a solution of **29** (2.43 g, 14.4 mmol) in THF (30 mL), predried over molecular sieves, was added and the solution was allowed to warm to 22 °C over 18 h. The mixture was poured into a stirred solution of concentrated H_2SO_4 (8.2 g) in THF (40 mL) and water (10 mL) and was heated under reflux for 1 h. The cooled solution was basified with potassium carbonate and extracted with CH_2Cl_2. Column chromatography on alumina in CH_2Cl_2/MeOH (99:1) yielded the pure product (738 mg), which was converted to the hydrochloride and recrystallized from MeOH/Et_2O: mp 205–206 °C; R_f 0.46 in CH_2Cl_2/MeOH (95:5) on alumina; MS m/z 192 (M^+ of free base); ^1H NMR (D_2O) δ 1.86–1.96 and 2.08–2.20 (each 2 H, each m, 5-CH_2 and 8-CH_2), 2.30 (3 H, s, CH_3), 2.50 (1 H, q, J = 3.2 Hz, 4-CH), 3.32–3.46 (4 H, m, 6-CH_2 and 7-CH_2), 3.57 (1 H, ddd, J = 2, 6, and 14 Hz, 2-CH), 3.66–3.74 (1 H, m, 3-CH), 3.80 (1 H, ddd, J = 2, 10, and 12 Hz, 2-CH), 6.34 (1 H, s, ArH). Anal. ($C_{11}H_{16}N_2O$·HCl·0.1H_2O) C, H, N.

3-Hydroxy-3-(4-methylfuran-2-yl)quinuclidine (35a). A solution of *n*-butyllithium in hexane (5.5 mL, 1.6 M, 8.8 mmol) was added dropwise to a solution of 2-bromo-4-methylfuran (1.42 g, 8.8 mmol) in dry THF (10 mL) at −75 °C over 10 min. After 5 min a solution of 3-quinuclidinone (1.0 g, 8 mmol) in THF (5 mL) was added and the mixture was stirred at −70 °C for 2 h. Water (2 mL) was added at −70 °C, and the mixture was poured into 2 M hydrochloric acid and washed with CH_2Cl_2. The aqueous layer was basified with sodium carbonate; the product was extracted with CH_2Cl_2 and crystallized from EtOAc/petroleum ether to yield the title compound (1.17 g, 71%): mp 124–126 °C; R_f 0.30 in CH_2Cl_2/MeOH (9:1) on alumina; MS m/z 207 (M^+); ^1H NMR ($CDCl_3$) δ 1.28–1.53 (3 H, m, 5-CH and 8-CH_2), 2.01 (3 H, d, J = 1 Hz, CH_3), 2.09–2.18 (1 H, m, 5-CH), 2.15–2.19 (1 H, m, 4-CH), 2.45 (1 H, br, OH), 2.62–2.87 (3 H, m, 6-CH_2 and 7-CH), 2.95–3.01 (2 H, m, 2-CH and 7-CH), 3.36 (1 H, dd, J = 2 and 14 Hz, 2-CH), 6.14 (1 H, s, furan 3-CH), 7.14 (1 H, q, J = 1 Hz, furan 5-CH). Anal. ($C_{12}H_{17}NO_2$) C, H, N.

With use of the above procedure, the following were prepared from the appropriate furan. **35b**: 45% yield; mp 117–120 °C (EtOAc). Anal. ($C_{11}H_{15}NO_2$) C, H, N. **35c**: 42% yield; mp 152–156 °C (EtOAc). Anal. ($C_{12}H_{17}NO_2$) C, H, N.

3-(4-Methylfuran-2-yl)quinuclidine Hydrochloride (8). A stirred solution of hydroxyquinuclidine **35c** (900 mg, 4.35 mmol) in CH_2Cl_2 (9 mL) at 0 °C was treated with triethylamine (1.6 mL, 11.6 mmol) and phosphorus oxychloride (0.8 mL, 8.7 mmol). After 4 h at 0 °C and a further 1 h at 22 °C, the mixture was partitioned between aqueous potassium carbonate and CH_2Cl_2. The organic layer was evaporated to yield the crude product (768 mg). A portion of this material (586 mg) was hydrogenated over Pd/C (100 mg) in ethanol (50 mL) at atmospheric pressure. After filtration through Hyflo and evaporation, column chromatography on alumina in CH_2Cl_2/MeOH (99:1) yielded the title compound (264 mg). The hydrochloride was crystallized from MeOH/Et_2O (258 mg): mp 153–157 °C; R_f 0.30 in CH_2Cl_2/MeOH (95:5) on alumina; MS m/z 191 (M^+); ^1H NMR (D_2O) 1.80–1.98 and 2.04–2.16 (each 2 H, each m, 5-CH_2 and 8-CH_2), 2.01 (3 H, s, CH_3), 2.38–2.43 (1 H, m, 4-CH), 3.28–3.56 (5 H, m, 3-CH, 6-CH_2, and 7-CH_2), 3.60–3.76 (2 H, m, 2-CH_2), 6.27 (1 H, m, furan 3-CH), 7.30 (1 H, s, furan 5-CH). Anal. ($C_{12}H_{17}NO$·HCl·0.25H_2O) C, H, N.

Quinuclidine-3-carboxyhydrazide Dihydrochloride (33). Methyl quinuclidine-3-carboxylate hydrochloride (10 g, 4.87 mmol) was partitioned between CH_2Cl_2 and 2 M potassium carbonate solution. The material isolated from the organic layer was dissolved in MeOH (10 mL) and hydrazine hydrate (2 mL) and the solution heated under reflux for 22 h. Evaporation of the solvents yielded the hydrazide (0.85 g), which was characterized as its dihydrochloride salt: mp 227–230 °C; R_f 0.3 in CH_2Cl_2/MeOH (9:1) on alumina; MS m/z 169 (M^+ of free base); ^1H NMR (D_2O) δ 1.85–1.93 (2 H, m, 5-CH_2), 2.00–2.09 (2 H, m, 8-CH_2), 2.41–2.46 (1 H, m, 4-CH), 3.19–3.21 (1 H, m, 3-CH), 3.30–3.37 (4 H, m, 6-CH_2 and 7-CH_2), 3.44 (1 H, ddd, J = 13, 13, and 2 Hz, 2-CH anti to CO) and 3.72 (1 H, ddd, J = 13, 5.5, and 1.5 Hz, 2-CH syn to CO); IR ν_{max} (Nujol) 3300–2500, 2040, 1980, 1700 cm^{-1}. Anal. ($C_8H_{15}N_3O$·2HCl·0.2H_2O) C, H, N, Cl.

3-(5-Methyl-1,3,4-oxadiazol-2-yl)quinuclidine Hydrogen Fumarate (9). A solution of the foregoing hydrazide (862 mg, 5.1 mmol) in MeOH (20 mL) and trimethyl orthoacetate (6.5 mL, 51 mmol) was heated under reflux for 4 h and cooled, and the solvent was evaporated in vacuo. The residue was dissolved in *tert*-butanol (20 mL), potassium *tert*-butoxide (0.86 g, 7.7 mmol) was added, and the solution was heated under reflux for 17 h. After removal of the solvent in vacuo, the residue was partitioned between CH_2Cl_2 and 2 M potassium carbonate solution. The material isolated from the organic layer was purified by chromatography on alumina in CH_2Cl_2/MeOH (99:1) to yield the desired oxadiazole (170 mg), which was characterized as its hydrogen fumarate: mp 167–168 °C; R_f 0.2 in CH_2Cl_2/MeOH (98:2) on alumina; MS m/z 193 (M^+ of free base); ^1H NMR (D_2O) δ 1.81–1.98 (2 H, m, 8-CH_2), 2.11–2.18 (2 H, m, 5-CH_2), 2.54 (3 H, s, CH_3), 2.58–2.61 (1 H, m, 4-CH), 3.31–3.45 (4 H, m, 6-CH_2 and 7-CH_2) and 3.75–3.83 (3 H, m, 2-CH_2 and 3-CH), 6.67 (2 H, s,

$HO_2CCH{=}CHCO_2H$). Anal. ($C_{10}H_{15}N_3O{\cdot}C_4H_4O_4$) C, H, N.

3-(5-Methyl-1,2,4-oxadiazol-3-yl)quinuclidine Hydrochloride (10). 3-Quinuclidinone (24.2 g, 0.19 mol) and 2,4,6-triisopropylbenzenesulphonohydrazide (72 g, 0.24 mol) were stirred together in anhydrous MeOH (250 mL) for 3 h. Potassium cyanide (33.8 g, 0.51 mol) was added and the mixture was heated under reflux for 5 h. The residue after evaporation of the solvent was partitioned between water and CH_2Cl_2. The organic phase was dried and evaporated and the residue was fractionally distilled under reduced pressure to give 3-cyanoquinuclidine (**32**, 6.1 g), bp 95–100 °C (0.1 mmHg).

The foregoing nitrile (1.36 g, 10 mmol) was treated in refluxing ethanol (40 mL) for 16 h with hydroxylamine hydrochloride (2.08 g, 30 mmol) and potassium carbonate (2.8 g, 20 mmol). The residue obtained after evaporation of the ethanol was dried over phosphorus pentoxide and then treated at 0 °C with acetic anhydride (40 mL). The mixture was heated under reflux for 3 h, excess acetic anhydride was removed, and the residue was partitioned between CH_2Cl_2 and saturated potassium carbonate solution. The material isolated from the organic phase was purified by chromatography on alumina in CH_2Cl_2/MeOH (99:1). Treatment of the resulting oil with ethereal hydrogen chloride followed by recrystallization of the salt from 2-propanol/Et_2O gave the required oxadiazole hydrochloride (610 mg); mp 191 °C dec; MS m/z 193 (M^+ of free base); ^1H NMR (D_2O) δ 1.85–1.91 and 2.15–2.19 (each 2 H, each m, 5-CH_2 and 8-CH_2), 2.54 (1 H, dd, J = 4.5 Hz, 4-CH), 2.63 (3 H, s, CH_3), 3.3–3.47 (4 H, m, 6-CH_2 and 7-CH_2), 3.6–3.71 (1 H, m, 3-CH) and 3.76–3.82 (2 H, m, 2-CH_2). Anal. ($C_{10}H_{15}N_3O{\cdot}HCl{\cdot}0.25\ H_2O$) C, H, N.

3-(5-Methyloxazol-2-yl)quinuclidine Hydrogen Fumarate (11). Quinuclidine-3-carboxylic acid hydrochloride (4.88 g, 25.5 mmol) was added to stirred thionyl chloride (60 mL) with ice cooling, and the resulting solution was heated to reflux for 2.5 h. The cooled mixture was evaporated, and the last traces of thionyl chloride were removed as a toluene azeotrope. The residue was suspended in dry CH_2Cl_2 (50 mL) under nitrogen, propargylamine (3.5 mL, 51 mmol) and triethylamine (6.0 mL, 43 mmol) were added, and the mixture was stirred at 20 °C for 16 h. Aqueous potassium carbonate (2 M, 30 mL) was added, and the solution was extracted with CH_2Cl_2 to yield the crude propargyl amide (2.8 g). This material was dissolved in acetic acid (45 mL), mercuric acetate (262 mg, 0.82 mmol) was added, and the mixture was heated under reflux for 3 h. The cooled solution was evaporated, aqueous potassium carbonate was added, and the product was extracted with CH_2Cl_2. Column chromatography on alumina in CH_2Cl_2/MeOH (99:1) gave the free base of the title compound as a colorless gum (748 mg, 16% overall). The hydrogen fumarate salt: mp 123–125 °C (2-propanol/Et_2O); MS m/z 192 (M^+); ^1H NMR (D_2O) δ 1.78–1.88 (2 H, m, 8-CH_2), 2.07–2.15 (2 H, m, 5-CH_2), 2.29 (3 H, d, J = 1 Hz, CH_3), 2.54–2.57 (1 H, m, 4-CH), 3.31–3.42 (4 H, m, 6-CH_2 and 7-CH_2), 3.62–3.76 (3 H, m, 2-CH_2 and 3-CH), 6.66 (2.2 H, s, $HO_2CCH{=}CHCO_2H$), 6.76 (1 H, q, J = 1 Hz, $NCH{=}CO$). Anal. ($C_{11}H_{16}N_2O{\cdot}1.1C_4H_4O_4$) C, H, N.

3-(5-Methylfuran-2-yl)quinuclidine hydrochloride (12) was prepared from **35a** as for **8**: 45% yield, hydrochloride mp 161–163 °C (2-propanol/Et_2O); R_f 0.40 in CH_2Cl_2/MeOH (95:5) on alumina; MS m/z 191 (M^+); ^1H NMR (CD_3OD) δ 1.76–1.85 (1 H, m, 5-CH), 1.92–2.03 (1 H, m, 5-CH), 2.06–2.15 (2 H, m, 8-CH_2), 2.26 (3 H, s, CH_3), 2.30–2.37 (1 H, m, 4-CH), 3.25–3.48 (5 H, m, 3-CH, 6-CH_2, and 7-CH_2), 3.60–3.77 (2 H, m, 2-CH_2), 5.98 (1 H, d, J = 3 Hz, furan 4-CH), 6.20 (1 H, d, J = 3 Hz, furan 3-CH). Anal. ($C_{12}H_{17}NO{\cdot}HCl{\cdot}0.5H_2O$) C, H, N, Cl.

3-Furan-2-ylquinuclidine hydrochloride (14) was prepared from **35b** as for **8**: 15% yield; mp 175–180 °C dec; R_f 0.30 in CH_2Cl_2/MeOH (95:5) on alumina; MS m/z 177 (M^+); ^1H NMR (D_2O) δ 1.78–1.98 and 2.04–2.20 (each 2 H, each m, 5-CH_2 and 8-CH_2), 2.40–2.44 (1 H, m, 4-CH), 3.27–3.43 (4 H, m, 6-CH_2 and 7-CH_2), 3.47–3.62 (2 H, m, 2-CH and 3-CH), 3.66–3.78 (1 H, m, 2-CH), 6.37 (1 H, d, J = 3.3 Hz, furan 3-CH), 6.48 (1 H, dd, J = 1.6 and 3.3 Hz, furan 4-CH), 7.52 (1 H, d, J = 1.6 Hz, furan 5-CH). Anal. ($C_{11}H_{15}NO{\cdot}HCl{\cdot}0.3H_2O$) C, H, N.

3-Oxazol-2-ylquinuclidine hydrogen oxalate (13) was prepared from **36b** as for **6**: 17% yield; mp 89–92 °C (2-propanol/Et_2O); R_f 0.39 in CH_2Cl_2/MeOH (95:5) on alumina; MS m/z 178 (M^+); ^1H NMR (D_2O) 1.73–1.94 and 2.06–2.10 (each 2 H, each m, 5-CH_2 and 8-CH_2), 2.56–2.63 (1 H, m, 4-CH), 3.29–3.45 (4 H, m, 6-CH_2 and 7-CH_2), 3.69–3.84 (3 H, m, 2-CH_2 and 3-CH), 7.17 (1 H, d, J = 0.7 Hz, oxazole 4-CH), 7.87 (1 H, d, J = 0.7 Hz, oxazole 5-CH). Anal. ($C_{10}H_{14}N_2O{\cdot}1.4C_2H_2O_4$) C, H, N.

3-(3-Amino-1,2,4-oxadiazol-5-yl)quinuclidine (18). Sodium metal (1.56 g, 68 mmol) was added to a suspension of molecular sieves (type 4A, 12 g) in absolute EtOH (60 mL) stirred under N_2. After 15 min at room temperature, hydroxyguanidine hemisulphate hemihydrate (4.72 g, 35 mmol) was added and the stirring was continued a further 1 h. Compound **29** (1 g, 5.9 mmol) was added to the mixture, which was then heated under reflux for 2 h. After removal of the molecular sieves by filtration, the filtrate was evaporated, and the resulting gum was partitioned between CH_2Cl_2 and water. The material isolated from the organic layer was recrystallized from isopropyl alcohol/petroleum ether (*i*-PA/PE) to afford the required aminooxadiazole (490 mg, 43%); mp 158–160 °C; MS m/z 194 (M^+); ^1H NMR ($CDCl_3$) δ 1.36–1.48 (1 H, m, 8-CH), 2.60–2.73 (3 H, m, 8-CH and 5-CH_2), 2.17-2.23 (1 H, m, 4-CH), 2.79–3.08 (5 H, m, 6-CH_2, 7-CH_2, and 2-CH), 3.21-3.38 (2 H, m, 3-CH and 2-CH), 4.43 (2 H, b s, NH_2). Anal. ($C_9H_{14}N_4O$) C, H, N.

3-(3-Acetamido-1,2,4-oxadiazol-5-yl)quininuclidine (21). Compound **18** (1.75 g, 9.0 mmol) was headed under reflux for 40 min in a mixture (1:1) of AcOH and Ac_2O (35 mL). The reaction was cooled and concentrated under reduced pressure. The residue was dissolved in water (50 mL), adjusted to pH 10 with K_2CO_3, and extracted with CH_2Cl_2 (4 × 50 mL). The combined extracts were evaporated, and the residue was chromatographed on alumina eluting with CH_2Cl_2/MeOH (97:3). The title product thus obtained was further purified by recrystallization from CH_2Cl_2/Et_2O (320 mg, 15%): mp 192–193 °C; MS m/z 236 (M^+); ^1H NMR ($CDCl_3$) δ 1.44–1.53 and 1.78–1.86 (each 2 H, each m, 5-CH_2 and 8-CH_2), 2.20 (3 H, b s, CH_3), 2.29–2.36 (1 H, m, 4-CH), 2.75–2.85, 2.98–3.06, and 3.12–3.28 (each 2 H, each m, 2-CH_2, 6-CH_2, and 7-CH_2), 4.00–4.18 (1 H, m, 3-CH); IR ν_{max} (nujol) 1715 cm^{-1} (C=O); Anal. ($C_{11}H_{16}N_4O_2$) C, H, N.

3-(3-Chloro-1,2,4-oxadiazol-5-yl)quinuclidine Hydrochloride (23). To a solution of **18** (4.0 g, 20 mmol) in concentrated HCl (40 mL) at 0 °C was added dropwise $NaNO_2$ (2.0 g, 30 mmol) in water (1 mL). After complete addition, the solution was stirred for 0.5 h and then filtered and concentrated under reduced pressure. The residue was treated with cold K_2CO_3 solution and extracted with CH_2Cl_2. The extracts were dried and then treated with ethereal HCl to give the title compound as a white solid (3.36 g, 67%) mp 179–182 °C; MS m/z 214 (FAB+, $[M + H]^+$ of free base); ^1H NMR (D_2O) δ 1.85–2.01 and 2.10–2.25 (each 2 H, each m, 5-CH_2 and 8-CH_2), 2.66–2.72 (1 H, m, 4-CH), 3.35–3.52 (4 H, m, 6-CH_2 and 7-CH_2), 3.77–3.90 and 3.95–4.02 (2 H and 1 H, respectively, each m, 2-CH_2 and 3-CH). Anal. ($C_9H_{12}ClN_3O{\cdot}HCl$) C, H, N.

3-(3-Bromo-1,2,4-oxadiazol-5-yl)quinuclidine Sesquioxalate (24). This was prepared by the above procedure using aqueous HBr (49%) instead of concentrated HCl in 10% yield, mp 144–145 °C (MeOH/Et_2O). Anal. ($C_9H_{12}BrN_3O{\cdot}1.5(COOH)_2$) C, H, N.

3-(3-Methoxy-1,2,4-oxadiazol-5-yl)quinuclidine Hydrochloride (22). Compound **23** (700 mg, 2.8 mmol) was heated under reflux with NaOMe (280 mg, 5.2 mmol) in MeOH (15 mL) for 5 h. The solvent was removed and the residue was purified by chromatography on alumina with CH_2Cl_2/MeOH (99:1). The product thus obtained was treated with ethereal HCl to give **22** (250 mg, 35%), mp 146–147 °C (CH_2Cl_2/Et_2O); MS m/z 209 (M^+ of free base); ^1H NMR (D_2O) δ 1.82–2.00 and 2.10–2.20 (each 2 H, each m, 5-CH_2 and 8-CH_2), 2.62–2.67 (1 H, m, 4-CH), 3.34–3.47 (4 H, m, 6-CH_2 and 7-CH_2), 3.76–3.88 (3 H, m, 2-CH_2 and 3-CH), 4.06 (3 H, s, OCH_3). Anal. ($C_{10}H_{15}N_3O_2{\cdot}HCl{\cdot}0.33H_2O$) C, H, N.

3-(3-Cyano-1,2,4-oxadiazol-5-yl)quinuclidine Hydrogen Oxalate (26). Compound **18** (780 mg, 4.0 mmol) in dry DMF (40 mL) was cooled to 10 °C and treated with dry HCl (14 mL of a 0.85 M solution in DMF, 12 mmol) and isoamyl nitrite (1.6 mL, 12 mmol) for 3.5 h. Bu_4NCN (3.2 g, 12 mmol) in DMF (10 mL) was added and the mixture was allowed to warm slowly to room temperature. The residue obtained after removal of the solvent was partitioned between ether and aqueous K_2CO_3. The ether was dried and evaporated and the residue was purified by chromatography on alumina. The product thus obtained was crystallized as the hygroscopic oxalate salt (35 mg, 4%); MS m/z

204 (M^+ of free base); ^1H NMR (D_2O) δ 1.78–2.00 and 2.08–2.26 (each 2 H, each m, 5-CH_2 and 8-CH_2), 2.65–2.71 (1 H, m, 4-CH), 3.32–3.50 (4 H, m, 6-CH_2 and 7-CH_2), 3.85 (2 H, d, J = 8 Hz, 2-CH_2), 4.08 (1 H, t, J = 8 Hz, 3-CH). Anal. ($C_{10}H_{12}N_4O$·(CO-$OH)_2$·1.8H_2O)C, N; H: calcd., 5.4; found, 4.9.

3-(3-Ethoxycarbonyl-1,2,4-oxadiazol-5-yl)quinuclidine Hydrochloride (38). Compound **29** (9.3 g, 45.2 mmol) was heated under reflux in concentrated HCl (100 mL) for 16 h. The reaction was concentrated and the residue was heated under reflux in $SOCl_2$ (150 mL) for 2.5 h. The solution was concentrated in vacuo and the remaining solid was suspended in dry THF (150 mL) under N_2. (Ethoxycarbonyl)formamide oxime (7.8 g, 59.0 mmol), in THF (150 mL), was added dropwise and the reaction was stirred for 16 h. The solution was evaporated under reduced pressure and the residue was dissolved in H_2O which was made basic with K_2CO_3. The solution was extracted with CH_2Cl_2 (3×) and the combined extracts were evaporated. The residue was dissolved in dry dioxane (200 mL) and heated under reflux over type 4A molecular sieves (70 g) for 24 h. The reaction was filtered and concentrated to give a residue which was treated with ethereal HCl to give the title compound (2.50 g, 16%): mp 170–171 °C (*i*-PA); MS m/z 251 (M^+ of free base); ^1H NMR (D_2O) δ 1.42 (3 H, t, J = 7.2 Hz, CH_3), 1.80–2.01 and 2.10–2.28 (each 2 H, each m, 5-CH_2 and 8-CH_2), 2.68–2.73 (1 H, m, 4-CH), 3.34–3.52 (4 H, m, 6-CH_2 and 7-CH_2), 3.88 (2 H, d, J = 8.2 Hz, 2-CH_2), 4.00–4.08 (1 H, m, 3-CH), 4.52 (2 H, q, J = 7.2 Hz, OCH_2); IR ν_{max} (Nujol) 1748 cm^{-1} (C=O). Anal. ($C_{12}H_{17}N_3O_3$·HCl) C, H, N.

3-(3-Carboxamido-1,2,4-oxadiazol-5-yl)quinuclidine Hydrochloride (25). The preceding compound (1.0 g, 4.0 mmol) was cooled to 0 °C in EtOH (50 mL) and NH_3 was bubbled through for 1.5 h. The solvent was removed and the residue was treated with K_2CO_3 solution and extracted with CH_2Cl_2. The extracts were concentrated, and the residue was treated with ethereal HCl to give **25** (150 mg, 14%); mp 208–210 °C ($MeOH/Et_2O$); MS m/z 223 ($[CI]^+$, M^+ of free base); ^1H NMR (D_2O) δ 1.83–2.01 and 2.12–2.28 (each 2 H, each m, 5-CH_2 and 8-CH_2), 2.68–2.75 (1 H, m, 4-CH), 3.36–3.54 (4 H, m, 6-CH_2 and 7-CH_2), 3.82–3.96 (2 H, m, 2-CH_2), 4.00–4.07 (1 H, m, 3-CH). Anal. ($C_{10}H_{14}N_4O_2$·HCl·0.75 H_2O) C, H; N: calcd, 20.6, found, 21.2.

α-(Tetrahydropyranyloxy)phenylacetamide Oxime (39). To a solution of sodium (6.9 g, 0.3 mol) in MeOH (1 L) was added hydroxylamine hydrochloride (20.8 g, 0.3 mol) followed by α-(tetrahydropyranyloxy)benzyl cyanide (43.4 g, 0.2 mol). After stirring for 16 h, the reaction was filtered, evaporated, and dissolved in dry ether (1 L). The following day, a white precipitate formed (35.4 g, 71%); mp 90–92 °C; R_f 0.47 in CH_2Cl_2/MeOH) (9:1) on silica; MS m/z 251 (M + H)$^+$; ^1H NMR (DMSO-d_6) δ 1.46–1.82 (6 H, m, 3 × CH_2), 3.25–3.32 and 3.40–3.46 (0.33 H and 0.67 H, each m, one of CH_2O), 3.64–3.71 and 3.78–3.84 (0.67 H and 0.33 H, each m, one of CH_2O), 4.49 and 4.71 (0.33 H and 0.67 H, each t, each J = 3 Hz, CHO), 5.01 and 5.03 (0.67 H and 0.33 H, each s, PhCH), 5.22 and 5.26 (0.67 H and 1.33 H, each s, NH_2), 7.25–7.46 (5 H, m, C_6H_5), 9.10 and 9.24 (0.33 H and 0.67 H, each s, (=NOH). Anal. ($C_{13}H_{18}N_2O_3$) C, H, N.

3-[3-[1-Phenyl-1-(tetrahydropyranyloxy)methyl]-1,2,4-oxadiazol-5-yl]quinuclidine (40). The foregoing amide oxime (15.5 g, 60 mmol) was stirred in dry THF (200 mL) with powdered 4A molecular sieves (5 g) under N_2 for 1 h. NaH (2.4 g of a 60% dispersion in oil, 60 mmol) was added and the reaction was heated at 50 °C for 0.5 h. A solution of **29** (8.0 g, 48 mmol) in THF (50 mL) was added and the reaction mixture was heated under reflux for 4 h. The oil obtained after filtration and evaporation of the solvent was purified by column chromatography on silica in CH_2Cl_2/MeOH (20:1) to yield the title compound as a pale yellow oil (12.7 g, 72%); MS m/z 370 (M + H)$^+$; ^1H NMR ($CDCl_3$) δ 1.36–1.93 (10 H, m, 5 × CH_2), 2.21–2.23 (1 H, m, 4-CH), 2.83–3.54 (8 H, m, 3 × CH_2N and CH_2O), 3.75–3.82 and 3.91–3.97 (1 H, each m, 3-CH), 4.69–4.71 and 4.85–4.86 (1 H, each m, OCH), 5.96 and 6.01 (1 H, each m, PhCH), and 7.27–7.55 (5 H, m, C_6H_5).

A small portion of the above product was precipitated from ether as the hydrogen oxalate salt, mp 95–100 °C. Anal. (C_{21}-$H_{27}N_3O_3$·$(COOH)_2$) C, H, N.

3-[3-(1-Hydroxy-1-phenylmethyl)-1,2,4-oxadiazol-5-yl]quinuclidine Hydrogen Oxalate (41). The foregoing tetrahydropyranyl ether (**40**, 11.0 g, 29.8 mmol) in MeOH (250 mL) was treated with 2 N HCl (30 mL, 60 mmol) for 1 h. The residue, after evaporation of the solvents, was taken up in CH_2Cl_2 and water, cooled, and then basified with K_2CO_3. The organic layer was separated and the aqueous layer was reextracted several times with CH_2Cl_2. Evaporation of the combined organic extracts gave the title product as its free base (8.1 g, 95%) from which the hydrogen oxalate salt was prepared: mp 105–107 °C; MS m/z 286 [(M + H)$^+$]; ^1H NMR (D_2O) δ 1.6–1.8 (1 H, m, one of CH_2), 1.85–1.96 (1 H, m, one of CH_2), 2.06–2.22 (2 H, m, CH_2), 2.10–2.14 (1 H, m, 4-CH), 3.34–3.43 (4 H, m, 6-CH_2 and 7-CH_2), 3.77–3.79 (2 H, m, CH_2N), 3.88–3.89 (1 H, m, 3-CH), 6.06 (1 H, s, PhCH), 7.43–7.49 (5 H, m, C_6H_5). Anal. ($C_{16}H_{19}N_3O_2$·$(COOH)_2$·1.5H_2O) C, H, N.

3-(3-Benzoyl-1,2,4-oxadiazol-5-yl)quinuclidine Sesquioxalate (31). Compound **41** (free base, 8.1 g, 28.4 mmol) in CH_2Cl_2 (500 mL) was stirred with activated MnO_2 (50 g). After 0.5 h, the reaction mixture was filtered and the MnO_2 was repeatedly washed with CH_2Cl_2. The solution obtained was again filtered through Florisil (100–120 mesh) and evaporated to yield the title compound as its free base (6.1 g, 75%). This material in ether was crystallized as the sesquioxalate salt: mp 82–85 °C; ^1H NMR (D_2O) δ 1.90–1.97 and 2.16–2.23 (each 2 H, each m, 5-CH_2 and 8-CH_2), 2.73–2.76 (1 H, m, 4-CH), 3.40–3.52 (4 H, m, 6-CH_2 and 7-CH_2), 3.79–3.92 (2 H, m, 2-CH_2), 4.10–4.11 (1 H, m, 3-CH), 7.6 (2 H, t, J = 8 Hz, 3-H and 5-H of C_6H_5), 7.84 (1 H, t, J = 7 Hz, 4-H of C_6H_5), 8.20–8.22 (2 H, dd, J = 7 and 1 Hz, 2-H and 6-H of C_6H_5). Anal. ($C_{16}H_{17}N_3O_2$·1.5$(COOH)_2$·0.5H_2O) C, H, N.

3-[3-(-1,1-Diphenyl-1-hydroxymethyl)-1,2,4-oxadiazol-5-yl]quinuclidine Hydrogen Oxalate (17). 3-(3-Benzoyl-1,2,4-oxadiazol-5-yl)quinuclidine (566 mg, 2 mmol) in dry THF under N_2 was treated with phenylmagnesium bromide (2 mL of a 3 M solution, 6 mmol) at room temperature for 0.5 h. Saturated ammonium chloride was added and the mixture was partitioned and extracted twice with CH_2Cl_2. The material isolated from the combined organic extracts was purified by column chromatography on alumina in CH_2Cl_2/MeOH (99:1) to yield the free base of the title compound as a pale yellow oil (361 mg, 58%), which was crystallized as the hydrogen oxalate salt: mp 65–70 °C; MS m/z 362 (M + H)$^+$; ^1H NMR (D_2O) δ 1.72–2.24 (4 H, m, 5-CH_2 and 8-CH_2), 2.63–2.64 (1 H, m, 4-CH), 3.35–3.42 and 3.77–3.82 (6 H, m, 2-CH_2, 6-CH_2, and 7-CH_2), 3.92–3.94 (1 H, m, -3-CH), 7.36–7.44 (10 H, m, 2 × C_6H_5). Anal. ($C_{22}H_{23}N_3O_2$·$(COOH)_2$·1.1H_2O) C, H, N.

3-(3-Methyl-1,2,4-oxadiazol-5-yl)-2,3-dehydroquinuclidine Hydrochloride (28). Acetamide oxime (650 mg, 8.8 mmol) in ethanol (30 mL) was treated with sodium metal (180 mg, 8.0 mmol) in the presence of molecular sieves (type 4A, 3 g). 3-(Methoxycarbonyl)-2,3-dehydroquinuclidine (250 mg, 1.5 mmol) was added and the mixture was heated under reflux for 4 h, cooled, filtered, and evaporated to dryness. The residue was partitioned between aqueous K_2CO_3 and CH_2Cl_2 and the organic solution was separated and dried (Na_2SO_4). The CH_2Cl_2 solution was treated with potassium *tert*-butoxide (1 g) for 1 h at room temperature and then washed with water and again dried and concentrated. Chromatography on alumina (eluting with 4% MeOH in CH_2Cl_2) gave **28** as the hydrochloride salt (110 mg, 32%); mp 167–169 °C; MS m/z 191 (M^+ of free base); ^1H NMR (D_2O) δ 1.84–1.95 and 2.16–2.28 (each 2 H, each m, 5-CH_2 and 8-CH_2), 2.46 (3 H, s, CH_3), 3.21–3.32 and 3.69–3.78 (2 H and 3 H, each m, 4-CH, 6-CH_2, and 7-CH_2), 7.69 (1 H, d, J = 1.4 Hz, 2-CH). Anal. ($C_{10}H_{13}N_3O$·HCl) C, H, N.

Registry No. **5**, 114724-64-0; **5**·HCl, 114724-63-9; **6**, 112829-23-6; **6**·$^3/_2$ HCl, 123837-07-0; **7**, 123836-83-9; **7**·HCl, 123837-08-1; **8**, 123836-84-0; **8**·HCl, 123837-12-7; **9**, 114724-71-9; **9**·fumarate, 123837-15-0; **10**, 114724-62-8; **10**·HCl, 114724-61-7; **11**, 122829-24-7; **11**·fumarate, 122829-47-4; **12**, 123836-85-1; **12**·HCl, 123837-17-2; **13**, 123836-86-2; **13**·oxalate, 123837-19-4; **14**, 123836-87-3; **14**·HCl, 123837-18-3; **15**, 123836-88-4; **15**·oxalate, 123837-03-6; **16**, 123836-89-5; **16**·oxalate, 123837-04-7; **17**, 123836-90-8; **17**·oxalate, 123837-28-5; **18**, 114724-42-4; **19**, 123836-91-9; **19**·oxalate, 123837-05-8; **20**, 123836-92-0; **20**·oxalate, 123837-06-9; **21**, 121024-67-7; **22**, 123836-93-1; **22**·HCl, 123837-21-8; **23**, 123836-94-2; **23**·HCl, 114724-93-5; **24**, 123836-95-3; **24**·$^3/_2$ oxalate, 123837-20-7; **25**, 123836-96-4; **25**·HCl, 123837-23-0; **26**, 123836-97-5; **26**·oxalate, 123837-22-9; **27**, 123836-98-6; **28**, 114724-66-2; **28**·HCl, 114724-65-1; **29**, 38206-86-9; **29**·HCl, 54954-73-3; **30a**, 83598-29-2; **31**, 123836-

99-7; **31**·$^3/_2$ oxalate, 123837-27-4; **32**, 51627-76-0; **33**, 114725-06-3; **33**·2HCl, 123837-13-8; **34**, 122829-77-0; **35a**, 123837-00-3; **35b**, 123837-10-5; **35c**, 114724-65-1; **36a**, 122829-26-9; **36b**, 122829-29-2; **37a**, 122829-60-1; **38**, 114724-81-1; **38**·HCl, 114724-80-0; **39**, 123837-01-4; **40**, 123837-02-5; **40**·oxalate, 123837-24-1; **41**, 123837-25-2; **41**·oxalate, 123837-26-3; $H_3CC(=NOH)NH_2$, 22059-22-9; $EtC(=NOH)NH_2$, 29335-36-2; $PhCH_2C(=NOH)NH_2$, 19227-11-3; $H_3CC(=NOH)CH_3$, 127-06-0; $HC{\equiv}CCH_2NH_2$, 2450-71-7; $HONHC(NH_2){=}NH$, 6345-29-5; $EtOCOC(=NOH)NH_2$, 10489-74-4; PhMgBr, 100-58-3; $MeNHC(=NH)NHOH$, 123837-29-6; $Me_2NC(=NH)NHOH$, 29044-27-7; 3-quinuclidinone, 3731-38-2; 2-bromo-5-methylfuran, 123837-09-2; 2-bromofuran, 584-12-3; 2-bromo-4-methylfuran, 78259-59-3; 3-(4-methylfuran-2-yl)-2,3-dehydroquinuclidine, 123837-11-6; *N*-[(1-methoxyethylidine)amino]-3-quinuclidinecarboxamide, 123837-14-9; 3-(*N*-hydroxyamidino)quinuclidine, 123837-16-1; quinuclidine-3-carboxylic acid hydrochloride, 6238-34-2; oxazole, 288-42-6; α-(tetrahydroxypyranyloxy)benzyl cyanide, 41865-47-8; 3-(methoxycarbonyl)-2,3-dehydroquinuclidine, 31539-88-5; 4-methyloxazole, 693-93-6.

Supplementary Material Available: Table of microanalytical data for novel compounds (2 pages). Ordering information is given on any current masthead page.

Synthesis and α_2-Adrenoceptor Effects of Substituted Catecholimidazoline and Catecholimidazole Analogues in Human Platelets

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It is known that the steric requirements for the interactions of catecholamines and catecholimidazolines with α_1- and α_2-adrenoceptors are different. New analogues of desoxycatecholimidazoline (**1**), desoxycatecholimidazole (**3**), benzylic hydroxyl substituted imidazole (**4**), and the aromatic fluorine substitution analogues of **1** at the 2 (**5**), 5 (**6**), and 6 (**7**) positions, and a set of asymmetric 4-substituted catecholimidazolines, *S*-**8** and *R*-**8**, were prepared and tested for interaction with α_2-adrenoceptors in human platelets. With the exception of **3**, all compounds were selective for α-adrenoceptor-mediated responses in human platelets. Introduction of a double bond in imidazoline **1** to give an imidazole **3** or the introduction of a benzylic hydroxyl group to **3**, as in **4**, reduced the inhibition of platelet aggregation with a rank order potency of **1** > **3** > **4**. Fluorine atom substitution at the 2-, 5-, or 6-positions only slightly modified the inhibitory activity of **1**. Each analogue (**1**, **3**–**7**) produced α_2-mediated inhibition of platelet adenylate cyclase and can be classified as a partial agonist. The inhibition potency of *S*-**8** and *R*-**8** against epinephrine-induced aggregatory responses were greatly different, and only *R*-**8** and **4** were α_2-agonists on human platelet function. Our studies provide further evidence for the differential interaction of catecholamines and catecholimidazolines in α_1- and α_2-adrenoceptor systems.

Phenethylamines and benzylimidazolines constitute the two major classes of drugs that are known to interact with α-adrenoceptors.[1] In our previous studies we have found 3,4-dihydroxytolazoline (**1**) to be a potent full agonist on α_1-adrenergic receptors while it has shown only partial agonist activity on α_2-adrenoceptors. We have found that the introduction of a hydroxyl group at the benzylic position of **1** to give 3,4,α-trihydroxytolazoline (**2**) leads to a compound with full agonist activity on the α_2-adrenergic receptor but brings about a reduction in affinity for α_1-adrenoceptor activity. Moreover, the phenylethylamines always follow the Easson–Stedman theory, while imidazolines do not.[2,3] Thus, the structure–activity relationships for activation of α-adrenergic receptors within the imidazoline class are considerably different from that of phenylethylamines.

The present study was directed at investigating the effects of structural modification of 3,4-dihydroxytolazoline on α_2-adrenergic activity in human platelets. It has been shown previously that certain imidazole derivatives do possess potent and selective antagonist activity on α_2-adrenergic receptors.[4] We have also prepared and investigated the replacement of the imidazoline ring of **1** with an imidazole group to give **3** and we also added a hydroxyl group to give **4** so we could compare its activity to that in the imidazoline series. Fluorine substitution on norepinephrine,[5] a classical phenylethylamine compound, resulted in a 2-fluoro analogue that was a selective agonist for β-adrenergic receptors, while the 6-fluoro analogue was a selective agonist on α-adrenergic receptors. Our objective was to prepare 2-, 5-, and 6-fluoro analogues of **1** to give **5**, **6**, and **7**, respectively, and to investigate the effect of fluorine substitutions on α_2-adrenoceptor activity. Due to the paucity of information available on 4-substituted imidazolines in which the 4-substituent possessed a catechol functional group, we prepared the *R* and *S* isomers of 4-(3,4-dihydroxybenzyl)imidazoline (**8**). These three sets of analogues were studied in human platelets for α_2-adrenergic activity as agonists or as antagonists of epinephrine-mediated responses.

Chemistry

Synthesis of imidazoles **3** and **4** is outlined in Scheme I. *N*-(Diethoxymethyl)imidazole[6] (**9**) was treated with

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