Synthesis and Muscarinic Activities of 1,2,4-Thiadiazoles

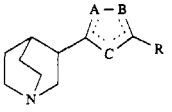
Angus M. MacLeod,*,† Raymond Baker,† Stephen B. Freedman,‡ Shailendra Patel,‡ Kevin J. Merchant,† Michael Roe,† and John Saunders†

Chemistry and Biochemistry Departments, Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, U.K. *Received November 17, 1989*

A series of novel 1,2,4-thiadiazoles bearing a mono- or bicyclic amine at C5 were prepared. Quinuclidine and 1-azabicyclo[2.2.1]heptane derivatives were synthesized by reaction of the lithium enolate of the 3-methoxycarbonyl compounds followed by ester hydrolysis and decarboxylation. The receptor-binding affinity and efficacy of these compounds as muscarinic ligands was assessed by radioligand binding assays using [^{3}H]-*N*-methylscopolamine and [^{3}H]oxotremorine-M. Optimal agonist affinity was observed for 3'-methyl compounds. Smaller substituents (H) retained efficacy with reduced affinity while larger groups led to substantially lower efficacy. The observed binding affinity was influenced both by the conformational energy of rotation around the C3–C5' bond and the steric requirement of the mono- or bicyclic amine.

The characteristic deficit of the neurotransmitter acetylcholine which occurs in Alzheimer's disease[1] has stimulated interest in muscarinic pharmacology and led to the hypothesis that a clinically induced elevation of cholinergic transmission may be capable of reducing the effects of this disease, including the loss of memory and impaired cognitive function. Clinical studies with directly acting muscarinic agonists such as arecoline,[2] RS86,[3] and pilocarpine[4] have produced disappointing results in contrast to those seen with cholinesterase inhibitors.[2] We have suggested[5] that this may be due to the low efficacy of these drugs at cortical muscarinic receptors and that the strategy of treating the disease through an agonist replacement therapy will only be fully tested with compounds which show a significant stimulation of phosphatidylinositol hydrolysis in the cortex. Cortical muscarinic efficacy[6] may be predicted from the ratio of affinity constants of compounds in displacement of the antagonist *N*-methylscopolamine (NMS) and agonist oxotremorine-M (the NMS/OXO-M ratio). Antagonists give a ratio close to 1 and high-efficacy agonists give ratios >1000 while partial agonists have intermediate values (Table I).

We have described[5] a series of novel muscarinic agonists with high affinity and efficacy which lack the quaternary amine of the endogenous and classical ligands and can readily penetrate the blood–brain barrier to achieve significant concentrations in the CNS. From a range of heteroaromatic substituted quinuclidines 1 it was demonstrated that agonist activity was optimal in compounds capable of participating in two hydrogen-bonding interactions with the receptor in addition to the primary electrostatic binding of the cationic head. Efficacy correlated in a quantitative manner with the hydrogen bonding acceptor abilities of the two heteroatoms B and C according to the equation



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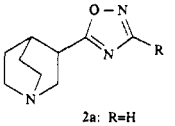
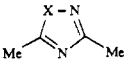
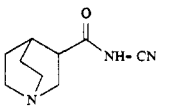


2a: R=H
2b: R=Me



3: X=S
4: X=O



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$$\log \text{NMS/OXO-M} = -0.0190\ (\pm 0.0019)V_B - 0.0187\ (\pm 0.0018)V_C$$

where V_B and V_C are the minimum electrostatic potentials adjacent to B and C, respectively. The lack of a constant term in this equation indicates that, when there are no unfavorable steric effects, ligand efficacy (but not affinity) depends entirely on hydrogen bonding since in the absence of negative potentials exerted by B and C the equation predicts a pure antagonist (NMS/OXO-M = 1). Efficacy in this series was found to be greatest for 1,2,4-oxadiazoles **2** with the NMS/OXO-M ratio critically dependent on the electron-withdrawing or -donating effect of the 3' substituent.

Examination of other 5-membered heteroaromatic rings has revealed that 3,5-dimethyl-1,2,4-thiadiazole (**3**) displays similar negative potentials (Figure 1) adjacent to N2 and N4 (−77 and −78 kcal mol^{-1}, respectively) compared to its oxa analogue **4** (−74 and −77 kcal mol^{-1}). With these values in the correlation above, a predicted log (NMS/OXO-M) of 2.91 is obtained for 3-methyl-5-(3-quinuclidinyl)-1,2,4-thiadiazole. This assumes the greater bulk introduced with sulfur would not cause unfavorable steric interactions at

Table I. In Vitro Binding Data for Standard Muscarinic Ligands and 1,2,4-Oxadiazoles

compd	binding data (K_{app}, μM)[a] [^{3}H]NMS[b]	[^{3}H]OXO-M[c]	ratio[d]
atropine	0.0010	0.00048	2.1
arecoline	6.2	0.011	560
37	20[e]	0.017[e]	1200
carbachol	22	0.0049	4100
2b[f]	0.44	0.00090	490

[a] Displacement of tritiated radioligand from rat cortical homogenate. Results are expressed as an affinity constant (K_{app}) which has been corrected for ligand occupancy with the Cheng–Prusoff equation.[2] Except where otherwise stated, each value is the geometric mean of at least three determinations performed on separate occasions; the standard error in the geometric mean was not greater than ±4.5%. [b] Displacement of [^{3}H]-*N*-methylscopolamine. [c] Displacement of [^{3}H]oxotremorine-M. [d] The ratio of NMS/OXO-M K_{app}'s. [e] Value derived from a single determination. [f] Reference 1.

† Chemistry Departments.
‡ Biochemistry Department.

(1) Perry, E. K. *Br. Med. Bull.* **1986**, *42*, 63.
(2) Christie, J. E.; Shering, A.; Ferguson, J.; Glen, A. I. M. *Br. J. Psychiatry* **1981**, *138*, 46.
(3) Mouradian, M. M.; Mohr, E.; Williams, J. A.; Chase, T. N. *Neurology* **1988**, *38*, 606.
(4) Caine, R. D. *N. Engl. J. Med.* **1980**, *303*, 585.
(5) Saunders, J.; Cassidy, M.; Freedman, S. B.; Harley, E. A.; Iversen, L. L.; Kneen, C.; MacLeod, A.; Merchant, K.; Snow, R. J.; Baker, R. *J. Med. Chem.* **1990**, *33*, 1128.
(6) Freedman, S. B.; Harley, E. A.; Iversen, L. L. *Br. J. Pharmacol.* **1988**, *93*, 437.
(7) Quantum mechanical calculations were carried out using the CHEMQM interface with the CHEMX program (Chemical Design Ltd., Oxford, UK).
(8) DENPOT 80 (*QCPE* 483) by Peeters, D.; Sana, M.
(9) GAUSSIAN 80 (*QCPE* 446) by Singh, U. C.; Kollman, P.

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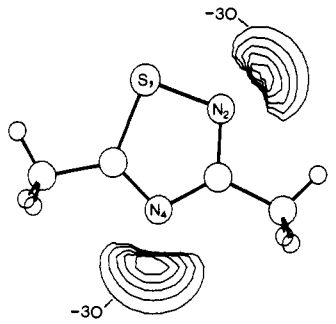


Figure 1. Two-dimensional molecular electrostatic potential map calculated[7] for 3,5-dimethyl-1,2,4-thiadiazole in the plane of the ring. Contours are in increments of −10 starting from −30 kcal/mol. Maps were generated by the DENPOT[8] procedure using wave functions computed by GAUSSIAN 80.[9]

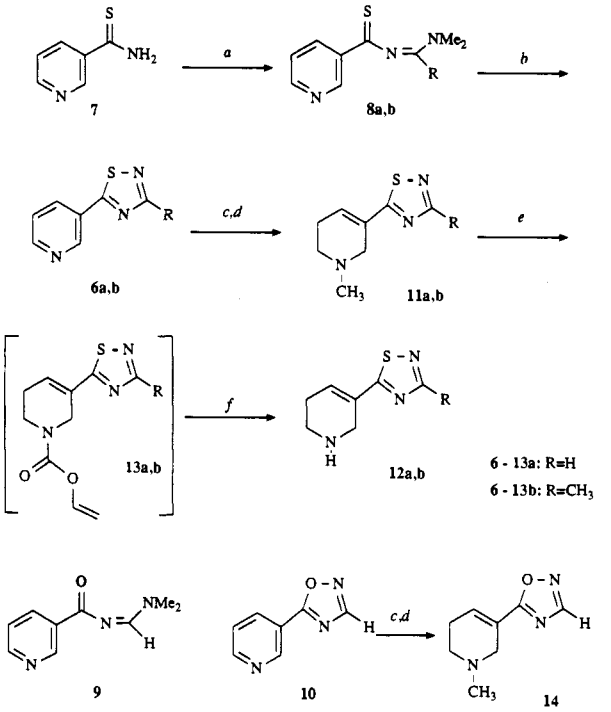
the active site or restrict rotational freedom of the molecule to adopt the preferred conformation for agonist binding. On the basis of this prediction of efficacy, a number of 3-methyl-1,2,4-thiadiazoles have been synthesized attached to a variety of heterocyclic bases including quinuclidine. The homologous compounds unsubstituted at C3′ have also been made to assess the contribution to affinity and efficacy of the methyl group. In general 1,2,4-oxadiazoles unsubstituted at C3 are unstable[10] and readily isomerize so that attempts to make, for example, quinuclidine **2a** lead only to isolation of acylcyanamide **5**. In contrast the corresponding thiadiazoles are stable and provide a suitable alternative series in which to evaluate substituent effects in this general class of muscarinic ligands. The choice of thiadiazole 3-substituent has also been extended to include a range of larger lipophilic groups which have a profound influence on efficacy.

Synthesis

The preferred literature method[11] for synthesis of 1,2,4-thiadiazoles is by oxidative cyclization of a thioacylamidine prepared from the corresponding thioester or thioamide. Pyridylthiadiazoles **6** were made from thionicotinamide **7** by using the reported procedure[12] of cyclization of **8** with hydroxylamine-*O*-sulfonic acid (HOSA) in methanol (Scheme I). Under these reaction conditions, competing oxidation of **8** (where R = H) to acylamidine **9** occurred prior to cyclization since pyridyloxadiazole **10** was produced together with **6a** in equal proportions. Characterization of **10** was subsequently confirmed by unambiguous synthesis under the same conditions starting from nicotinamide. Quaternization of **6** followed by reduction with $NaBH_4$ gave heteroaromatic arecoline analogues **11** after fractional crystallization of the hydrochloride salts to remove small amounts of the Δ^2- and Δ^5-isomers. Secondary amines **12** were also made by demethylation of **11** with vinyl chloroformate[13] and acid-catalyzed decomposition of the intermediate vinyl carbamates **13**. With **10** in hand, it was found that quaternization and reduction also gave a stable 3′-unsubstituted 1,2,5,6-tetrahydropyridyl oxadiazole, **14**. To our knowledge this is the only example of a stable 5-monosubstituted oxadiazole other than those linked to an aromatic or heteroaromatic ring.[14] Apparently the extended conjugation provided by the unsaturated linkage in **14** is sufficient to reduce the tendency to rearrange.

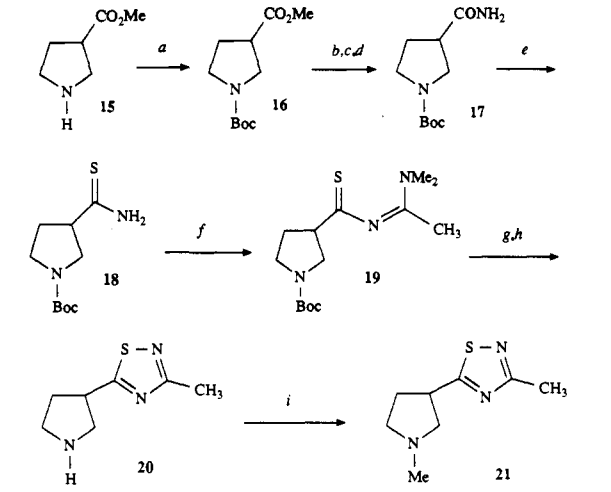
Thiadiazoles having alternative tertiary amino mono- or bicyclic rings were not accessible by the same process since treatment of 1-methyl-3-carbamoylpyrrolidine with Lawesson's reagent or P_2S_5 failed to give the corresponding thioamide. Since it was reasoned that these thionylations failed because of competing reaction of the tertiary amine with the reagents, BOC-protected pyrrolidine **17** was prepared (Scheme II) and reacted satisfactorily with

Scheme I[a]



[a] Reagents: (a) $RC(OMe)_2NMe_2$/MeOH; (b) HOSA/MeOH; (c) MeI/acetone; (d) $NaBH_4$/EtOH/H_2O; (e) CH_2=CHOCOCl/CH_2ClCH_2Cl; (f) HCl/MeOH.

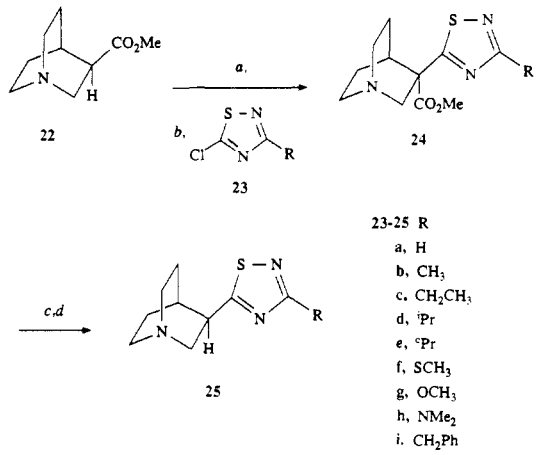
Scheme II[a]



[a] Reagents: (a) Boc_2O/CH_2Cl_2; (b) NaOH/H_2O/MeOH; (c) EtOCOCl/Et_3N/CH_2Cl_2; (d) NH_3/CH_2Cl_2 (e) Lawesson's reagent/C_6H_6; (f) $Me(MeO)_2CNMe_2/CH_2Cl_2$; (g) HOSA/pyridine/MeOH; (h) 2 N HCl/EtOH; (i) HCHO/HCO_2H.

(10) Clapp, L. B. *Adv. Heterocycl. Chem.* **1976**, *20*, 65.
(11) Franz, J. E.; Dhingra, O. P. *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Ed.; Pergamon Press: New York, 1984; Vol. 4, p 463.
(12) (a) Lin, Y.; Lang, S. A.; Petty, S. R. *J. Org. Chem.* **1980**, *45*, 3750. (b) Kristiansen, O.; Drabek, J. European Pat. Appl. 116515, 1984.
(13) Olofson, R. A.; Schnur, R. C.; Bunes, L.; Pepe, J. P. *Tetrahedron Lett.* **1977**, 1567.
(14) Lin, Y.; Lang, S. A.; Lovell, M. F.; Perkinson, N. A. *J. Org. Chem.* **1979**, *44*, 4160.

Scheme III[a]

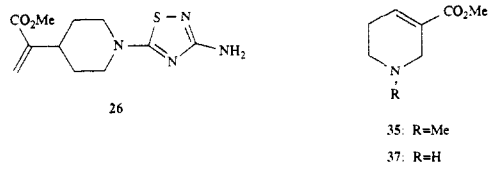


[a] Reagents: (a) LDA/THF/−78 °C; (c) 2 N NaOH/MeOH; (d) HCl/pH 2.

Lawesson's reagent to give **18** in 50% yield. Condensation with dimethylacetamide dimethyl acetal gave thioacylamidine **19**, which was cyclized to the thiadiazole with HOSA and deprotected to give **20**. N-Methylation with formic acid/formaldehyde then gave the target pyrrolidine **21**.

Since the protection strategy adopted above was not applicable to quinuclidine, an alternative method was developed involving addition of a preformed thiadiazole to the lithium enolate of 3-(methoxycarbonyl)quinuclidine (Scheme III). Thus treatment of **22** with LDA followed by a 5-chloro-1,2,4-thiadiazole gave 3,3-disubstituted quinuclidines **24**. After hydrolysis with NaOH, adjusting the solution to pH 1.5 resulted in rapid decarboxylation to **25**. The intermediate thiadiazole ester **24** was isolated and characterized only in the case where R = CH_3 since the sequence from **23** to **25** could conveniently be carried out without intermediate purification typically in a 30% yield.

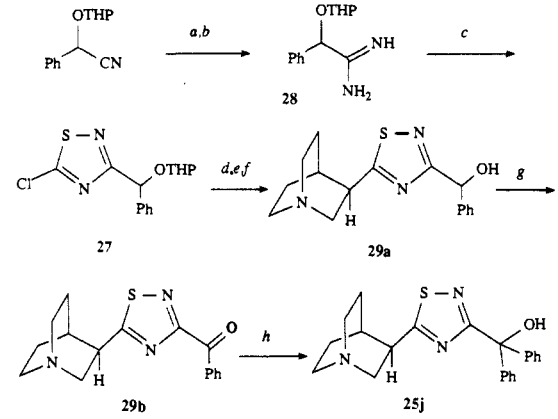
This was a general procedure for preparing a range of compounds with a variety of chlorothiadiazoles[15,16] and was unsuccessful only where R = NH_2.[17] In this last instance piperidine **26** was isolated, arising from ring opening of the



quinuclidine azabicycle. By contrast (dimethylamino)thiadiazole **25h** could be made by the same process but in low yield (17%). For quinuclidinyl benzylate analogue **25j** the THP-protected (hydroxybenzyl)thiadiazole **27** was made (Scheme IV) by cyclization of amidine **28** with perchloromethyl mercaptan. The derived quinuclidine **29a** was oxidized to benzoylthiadiazole **29b** and reacted with phenylmagnesium bromide to give **25j** in 55% yield.

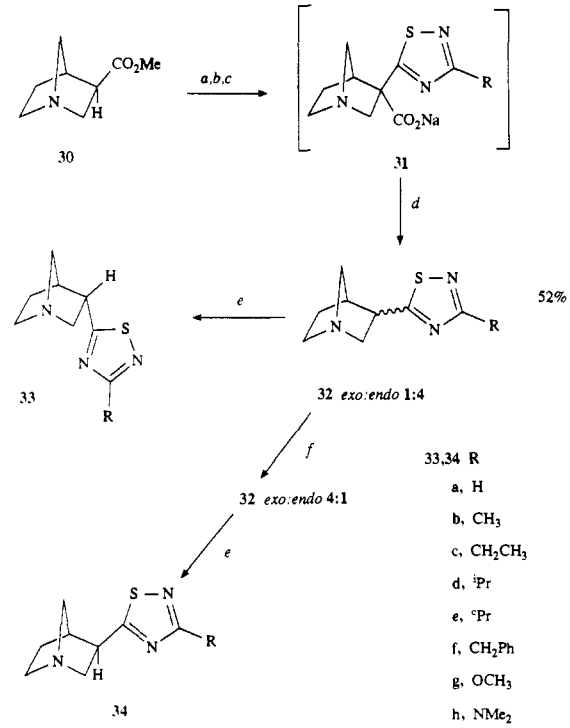
The same methodology applied to the 1-azanorbornane system invariably gave higher yields of products by presenting lower steric hindrance to the incoming electrophile. 3-(Methoxycarbonyl)-1-azabicyclo[2.2.1]heptane[18] (**30**,

Scheme IV[a]



[a] Reagents: (a) Na/EtOH; (b) NH_3/NH_4Cl; (c) Cl_3CSCl/CH_2Cl_2, $NaOH/H_2O$; (d) 3-Lithio-3-(methoxycarbonyl)quinuclidine/THF; (e) $NaOH/H_2O$/THF; (f) HCl/pH 2; (g) MnO_2/CH_2Cl_2; (h) PhMgBr/THF.

Scheme V[a]

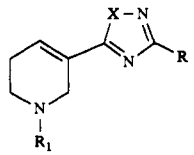


[a] Reagents: (a) LDA/THF/−78 °C; (b) **23**; (c) 2 N NaOH/MeOH; (d) HCl/pH 2; (e) $(COOH)_2$; (f) NaOMe/MeOH.

prepared as a 9:1 exo/endo mixture) treated sequentially with LDA, **23**, and NaOH gave sodium salts **31** (not isolated) in aqueous solution from which all impurities could be removed by washing with EtOAc. Decarboxylation with HCl at pH 1.5 gave **32** in ca. 50% overall yield from **30** as a 4:1 endo/exo mixture (by GC) arising from preferential protonation from the exo face. The diastereomers could be separated by chromatography on alumina but, more conveniently, fractional crystallization of the oxalate salts gave the pure major endo isomer **33** with stereochemistry assigned by COSY NMR. Base-catalyzed epimerization of mixture **32** resulted in a 1:4 endo/exo ratio at equilib-

(15) Goerdeler, J.; Ohm, J.; Tegtmeyer, O. *Chem. Ber.* **1956**, *89*, 1534.
(16) Goerdeler, J.; Groschopp, H.; Sommerlad, U. *Chem. Ber.* **1957**, *90*, 182.
(17) Krenzer, J.; Richter, S. B. U.S. Patent 3764685, 1973.
(18) (a) 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. (b) MacLeod, A. M.; Saunders, J.; Baker, R.; Merchant, K. European Pat. Appl. 0307142.

Table II. In Vitro Binding Data for Monocyclic Amines



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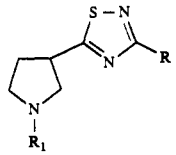
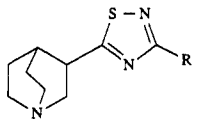


20,21

compd	R	R_1	X	binding data (K_{app}, μM)[a] [3H]NMS[b]	[3H]OXO-M[c]	ratio[d]
14	H	Me	O	8.9[e]	0.0077[e]	1200
36[f]	Me	Me	O	1.8	0.0046	390
11a	H	Me	S	11	0.027	410
11b	Me	Me	S	1.4	0.0089	160
12a	H	H	S	11	0.014	790
12b	Me	H	S	0.95[e]	0.0021[e]	450
20	Me	H	S	18	0.054	330
21	Me	Me	S	36	0.15	240

[a-f] See the footnotes for Table I.

Table III. In Vitro Binding Data For Quinuclidines



no. compd	R	binding data (K_{app}, μM)[a] [3H]NMS[b]	[3H]OXO-M[c]	ratio[d]
25a	H	3.3	0.0077	430
25b	Me	0.36	0.00078	460
25c	Et	0.082	0.0090	9.1
25d	iPr	0.033	0.0031	11
25e	cPr	0.023[e]	0.0028[e]	8.2
25f	SMe	0.12	0.012	10
25g	OMe	0.90	0.033	27
25h	NMe_2	0.14	0.023	6.1
25i	CH_2Ph	0.082	0.014	5.9
25j	$C(OH)Ph_2$	0.00020	0.000068	2.9

[a-e] See the footnotes for Table I.

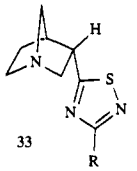
rium from which the exo isomer **34** was again obtained pure by salt formation and fractional crystallization (Scheme V).

Results

The dissociation constants at cortical muscarinic receptors for the novel thiadiazoles of this study were measured as described previously by their displacement of [3H]oxotremorine-M and [3H]-*N*-methylscopolamine from the high- and low-affinity states of the receptor, respectively, and are tabulated with the resulting NMS/OXO-M ratios (Tables II–IV). The 1,2,4-thiadiazole analogue (**11b**) of arecoline (**35**) proved to be a partial agonist with higher affinity than the natural product but lower efficacy as assessed by the binding ratio. Removal of the C3′-methyl substituent from **11b** or the equivalent oxadiazole **36** (Table II) gave compounds **11a** and **14**, respectively, having lower affinity but substantially greater efficacy. In the tetrahydropyridines efficacy was also significantly increased on removal of the *N*-methyl group (**12a,b**). This resulted mainly from improved displacement of OXO-M in the thiadiazoles whereas a 3-fold reduction in displacement of NMS was responsible for the higher ratio of **37** compared to that of arecoline. By contrast, a 2-fold increase in affinity in both binding assays was observed by N-demethylation of the pyrrolidine **21** to **20** with no significant change in the level of efficacy.

Quinuclidinylthiadiazole **25b** had affinity and efficacy similar to those of the corresponding oxadiazole **2b** with

Table IV. In Vitro Binding Data For 1-Azanorbornanes



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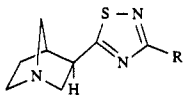


34

no. compd	R	binding data (K_{app}, μM)[a] [3H]NMS[b]	[3H]OXO-M[c]	ratio[d]
33a	H	6.4	0.0056	1100
33b	Me	0.62	0.00062	1000
33c	Et	0.29	0.0050	58
33d	iPr	0.29	0.041	7.1
33e	cPr	0.21	0.0040	53
33f	CH_2Ph	0.34	0.074	4.6
33g	OMe	2.0	0.0060	330
33h	NMe_2	0.84	0.062	14
34a	H	1.4	0.0013	1100
34b	Me	0.37	0.00045	820
34c	Et	0.51	0.033	15
34d	iPr	0.40	0.055	7.3
34e	cPr	0.16	0.019	8.4
34f	CH_2Ph	0.54	0.061	8.9
34g	OMe	1.8	0.017	110
34h	NMe_2	0.99	0.098	10

[a-d] See the footnotes for Table I.

a log (NMS/OXO-M) of 2.63, which is within 95% confidence limits of the predicted value in the correlation described above. The electron-withdrawing effects of the oxadiazole and thiadiazole rings were similar, giving pK_a values of 8.6 and 8.7 for **2a** and **25b**, respectively, but it was surprising to note that lipophilicity for **25b** (log P = 0.0) was actually lower than that for **2a** (log P = +0.6).

Higher NMS/OXO-M ratios were observed for both the analogous *exo*- and *endo*-azanorbornanes, with that for the endo isomer **33b** indicating higher efficacy than for its diastereomer **34b**. Consistent with these binding ratios, **33b** produced a higher maximum response in stimulation of phosphatidylinositol turnover in cortical tissue [76 (±5)% of the response evoked by 1 mM carbachol; EC_{50} = 2.7 (±0.9) μM] compared to **34b** [52 (±3)%; EC_{50} = 0.51 (±0.15) μM]. The 3′-unsubstituted thiadiazoles in the azanorbornane and quinuclidine series retained or had higher efficacy than their 3′-methyl analogues but invariably with lower affinity.

As observed with the oxadiazole studies, and other classes of muscarinic ligands, introduction of large substituents at C3′ of the thiadiazoles (**25c–f**) caused a profound reduction in the efficacy of these compounds generally consequent on improved displacement of NMS binding and lower affinity at the agonist binding state of the receptor. The sensitivity to steric effects was most marked with the quinuclidines while slightly greater bulk tolerance at C3′ was demonstrated for the smaller azanorbornanes, particularly the endo isomers. The electron-donating methoxy substituent conferred higher efficacy on these compounds than the isosteric ethyl group but this electronic effect could not outweigh or, in higher homologues, influence the steric factor in reducing efficacy (compare 3′-isopropyl with 3′-dimethylamino). Finally at the lowest extreme of the efficacy range, the diphenylhydroxymethyl moiety found in quinuclidinyl benzylate again showed its remarkable complimentarity to the muscarinic receptor in the high affinity of thiadiazole analogue **25j**.

Discussion

The importance of the C3′-methyl substituent equivalent to the acetyl methyl group of acetylcholine is clearly

Table V. Data for Quinuclidines[a]

no.	empirical formula	mp, °C	no.	empirical formula	mp, °C
25a	$C_9H_{13}N_3S \cdot 1.5(COOH)_2$	131–132	**25e**	$C_{12}H_{17}N_3S \cdot (COOH)_2$	175–176
25b	$C_{10}H_{15}N_3S \cdot 1.5(COOH)_2$	159–160	**25f**	$C_{10}H_{15}N_3S_2 \cdot HCl$	194–195
25c	$C_{11}H_{17}N_3S \cdot HCl \cdot 0.25H_2O$	174–175	**25g**	$C_{10}H_{15}N_3OS \cdot (COOH)_2$	gum
25d	$C_{12}H_{19}N_3S \cdot (COOH)_2$	115–117	**25h**	$C_{11}H_{18}N_4S \cdot HCl \cdot 0.75H_2O$	153–156

[a] All compounds were crystallized from MeOH/Et_2O or CH_2Cl_2/Et_2O and gave satisfactory microanalysis for C, H, and N except **25g**: MS m/z 225.0922; $C_{10}H_{15}N_3OS$ (free base) requires m/z 225.0935.

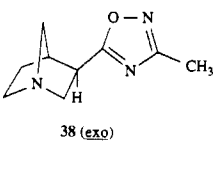
Table VI. Data for 1-Azanorbornanes[a]

no.	empirical formula	mp, °C	no.	empirical formula	mp, °C
33b	$C_9H_{13}N_3S \cdot (COOH)_2$	143–144	**34b**	$C_9H_{13}N_3S \cdot (COOH)_2$	155–156
33c	$C_{10}H_{15}N_3S \cdot (COOH)_2$	142–143	**34c**	$C_{10}H_{15}N_3S \cdot (COOH)_2$	133–135
33d	$C_{11}H_{17}N_3S \cdot (COOH)_2$	127	**34d**	$C_{11}H_{17}N_3S \cdot (COOH)_2$	131
33e	$C_{11}H_{15}N_3S \cdot (COOH)_2 \cdot 0.25H_2O$	133–134	**34e**	$C_{11}H_{15}N_3S \cdot (COOH)_2$	159–160
33f	$C_{15}H_{17}N_3S \cdot HCl \cdot H_2O$	108–109	**34f**	$C_{15}H_{17}N_3S \cdot (COOH)_2$	110–112 dec
33g	$C_9H_{13}N_3OS \cdot (COOH)_2 \cdot 0.75H_2O$	113–114	**34g**	$C_9H_{13}N_3OS \cdot (COOH)_2$	115–116 dec
33h	$C_{10}H_{16}N_4S \cdot (COOH)_2$	134–136	**34h**	$C_{10}H_{16}N_4S \cdot 2HCl \cdot 0.67H_2O$	155–156

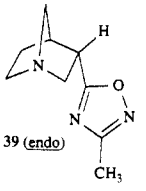
[a] All compounds were crystallized from MeOH/^{i}PrOH or MeOH/Et_2O and gave satisfactory microanalysis for C, H, and N.

demonstrated from the lower binding at both high and low affinity states of the receptor with the 3′-H analogues. Previous studies[1] concluded that hydrogen bonding of the heterocyclic ring plays a vital role in agonist binding but contributes little or nothing to binding at the low-affinity state of the receptor. Assuming the difference in displacement of NMS seen with pairs of 3′-H and 3′-Me thiadiazoles (**11a,b**, **12a,b**, **25a,b**, **33a,b**, **34a,b**) or oxadiazoles (**14**, **36**) is due largely to changes in lipophilic binding, the average contribution to binding energy[19] of the methyl substituent in this class of compounds is 1.2 kcal mol^{-1}. In antagonist binding the receptor is able to accommodate larger lipophilic substituents while the affinity of these ligands is maintained (**34c–f**) or increased (**25c–j**, **33c–f**). However, the receptor exhibits a definite preference for the methyl substituent in high-affinity binding, suggesting there is a specific recognition pocket for groups of this size. The loss in agonist binding observed by increasing in size to 3′-ethyl is seen as an incomplete fit of this substituent into the lipophilic pocket, resulting in an attenuation or disabling of hydrogen bonding.

The small difference in affinity of the *endo* and *exo*-azanorbornanes **33b** and **34b** (2-fold) contrasts with the analogous oxadiazoles **38** and **39**, where the exo isomer is



38 (exo)



39 (endo)

23- and 36-fold greater in affinity at the OXO-M and NMS binding sites, respectively.[20] Conformational analysis (Figure 2) indicates that there is essentially free rotation of the oxadiazole ring in **38**, but in the endo isomer two energy maxima exist where the heteroatoms O1′ and N4′ pass close to the endo proton on C5 with respective energies 1.7 and 1.8 kcal mol^{-1} higher than the global minimum. This may suggest that the difference in potency of these compounds is due to the required binding conformation being at, or close to, one of these energy maxima. The bulkier sulfur atom in thiadiazole **33b** presents a much higher energy barrier to passing this proton (3.6 kcal mol^{-1}) while the second rotational barrier is unchanged. The small potency difference between the diastereomeric pair of thiadiazoles excludes the highest energy conformer of **33b** from being close to the receptor-binding conformation. However, since the second energy maximum for **33b** is at a dihedral angle (C2–C3–C5′–S1′) equivalent to the global energy minimum for **34b**, a larger potency difference should be expected for this pair of diastereomers if this conformation is optimal for activity. Consequently, the binding of these ligands cannot be explained entirely on the basis of rotational energies and is likely to depend on a combination of conformational mobility and the steric influence of the azanorbornane ring system at the receptor.

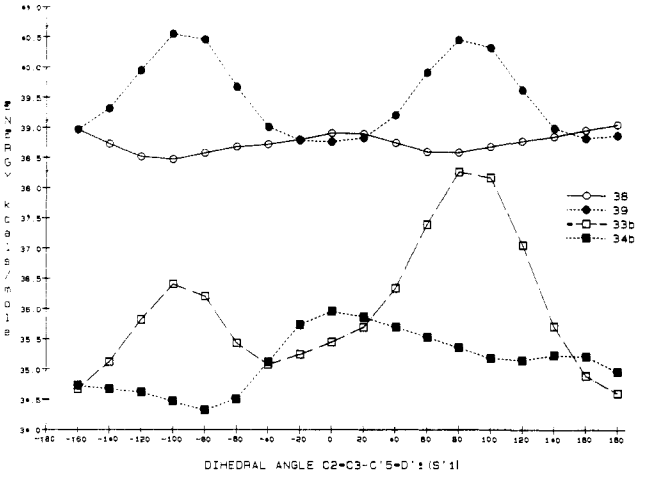


Figure 2. Conformational analysis of 1-azabicyclo[2.2.1]heptanyl-1,2,4-oxadiazoles and -1,2,4-thiadiazoles. Energies were calculated at each 20° rotation around C3–C5′ after minimization using a molecular mechanics force field.[21]

Conclusions

The 1,2,4-thiadiazole ring represents an ester mimic in the binding of muscarinic ligands capable of displaying high receptor affinity over a wide efficacy range. As with the endogenous ligand, a methyl group is the preferred size of lipophilic substituent for binding to the high-affinity state of the receptor. Within the present series of com-

(19) For average contributions of functional groups to binding energies, see: Andrews, P. R.; Craik, D. J.; Martin, J. L. *J. Med. Chem.* **1984**, *27*, 1648.

(20) (a) Saunders, J.; Freedman, S. B. In *Subtypes of Muscarinic Receptors IV*; Proceedings of the Fourth International Symposium on Subtypes of Muscarinic Receptors; Levine, R, R., Birdsall, N. J. M., Eds.; Elsevier Publications: Cambridge, 1989. (b) Street, L. J.; Baker, R.; Book, T.; Kneen, C. O.; MacLeod, A. M.; Merchant, K. J.; Showell, G. A.; Saunders, J.; Freedman, S. B.; Harley, E. A. *J. Med. Chem.*, in press.

pounds the conformation required for optimal binding to the receptor cannot be defined with certainty although some of the available conformational space may be ruled out. Potency of these ligands is affected both by the steric requirement of the amine-containing moiety and rotational freedom of the heteroaromatic ring. In vivo pharmacological evaluation of these compounds will be reported at a later date.

Experimental Section

Melting points were determined with a Büchi capillary melting point apparatus and are uncorrected. NMR spectra were recorded at 360 MHz on a Bruker AM360 instrument and mass spectra were recorded with a VG-70-250 mass spectrometer. GC was carried out on a 12-m SE30 capillary column with a Perkin-Elmer gas chromatograph (8320). The term "dried" refers to drying of an organic phase over anhydrous sodium sulfate, and organic solvents were evaporated on a Büchi rotary evaporator at reduced pressure. Column chromatography was carried out on neutral alumina (Merck Art. 1077, activity Brockman Grade III) and silica gel (Merck Art. 7734). Medium-pressure liquid chromatography was performed with a Lobar Lichroprep Si 60 (40–63 mm) column (Merck Art. 10401). Elemental analyses were performed by C.H.N. Analysis Ltd., Leicester, England.

3-(1,2,4-Thiadiazol-5-yl)pyridine (6a)[12] and 3-(1,2,4-Oxadiazol-5-yl)pyridine (10). Thionicotinamide (7.8 g, 56.5 mmol) suspended in CH_2Cl_2 (200 mL) was stirred with dimethylformamide dimethyl acetal (20 mL) for 2 days. The solvent was evaporated and the residue was treated with HOSA (9.6 g, 85 mmol) in MeOH (125 mL) for 15 h in the presence of pyridine (9 mL, 113 mmol). After evaporation, aqueous K_2CO_3 was added and the mixture was extracted with CH_2Cl_2. The extracts were dried and evaporated to give a residue which was chromatographed on silica (Lobar) to give the first-eluting compound **10** (370 mg, 4%): mp 83 °C; MS m/z 148 (CI^+, $[M + 1]^+$); ^1H NMR ($CDCl_3$) δ 7.51 (1 H, dd, J = 5 and 8 Hz, 5-CH), 8.43 (1 H, dt, J = 8 and 2 Hz, 4-CH), 8.55 (1 H, s, 3'-CH), 8.84 (1 H, d, J = 5 Hz, 6-CH), and 9.40 (1 H, s, 2-CH). Anal. ($C_7H_5N_3O$) C, H, N.

Further elution gave mixed fractions and then **6a** (370 mg). Crystallization of the mixed fractions from Et_2O/hexane gave an additional 460 mg of pure **6a** (total 730 mg, 8%): mp 83–84 °C; MS m/z 163 (M^+); ^1H NMR ($CDCl_3$) δ 7.48 (1 H, ddd, J = 0.7, 4.9, and 7.9 Hz, 5-CH), 8.29 (1 H, dt, J = 2.0 and 7.9 Hz, 4-CH), 8.68–8.72 (2 H, m, 6-CH and 3'-CH), and 9.21 (1 H, d, J = 2.0 Hz, 2-CH). Anal. ($C_7H_5N_3S$) C, H, N.

Compound **6b** was prepared by the same method.[12] The structure of **10** was confirmed by repeating the reaction above starting from nicotinamide to give the same compound in 13% yield.

1-Methyl-3-(1,2,4-thiadiazol-5-yl)-1,2,5,6-tetrahydropyridine Hydrochloride (11a). Compound **6a** (310 mg, 1.96 mmol) in acetone (4 mL) was stirred with MeI (0.25 mL, 4.0 mmol) for 3 days. The reaction mixture was diluted with Et_2O (20 mL) and filtered to give a yellow solid which was dissolved in EtOH (5 mL) and water (5 mL). $NaBH_4$ (85 mg, 2.24 mmol) was added in portions over 15 min while the mixture was cooled at 0 °C. After further stirring for 1 h, the reaction was extracted four times with Et_2O, and the combined extracts were dried and evaporated. The residue was treated with ethereal HCl, evaporated, and then recrystallized from MeOH/Et_2O to give **11a** (125 mg, 29%); mp 134 °C; MS m/z 181 (M^+ of free base); ^1H NMR (D_2O) δ 2.77–2.84 (2 H, m, 5-CH_2), 3.09 (3 H, s, NCH_3), 3.42–3.62 (2 H, br s, 6-CH_2), 4.19–4.38 (2 H, br s, 2-CH_2), 7.11–7.15 (1 H, m, 4-CH), and 8.73 (1 H, s, 3'-CH). Anal. ($C_8H_{11}N_3S$·HCl) C, H, N.

11b was prepared by a similar reaction sequence, mp 182 °C. Anal. ($C_9H_{13}N_3S$·HCl·0.33H_2O) C, H, N.

3-(1,2,4-Thiadiazol-5-yl)-1,2,5,6-tetrahydropyridine Hydrochloride (12a). Compound **11a** (95 mg, 0.52 mmol) was heated under reflux for 2 h with vinyl chloroformate (0.065 mL, 0.75 mmol) in CH_2ClCH_2Cl (2 mL). After cooling, water (5 mL) and 2 N HCl (0.5 mL) were added, and the mixture was extracted three times with Et_2O. The combined extracts, dried and evaporated, gave an oil which was treated with methanolic HCl for 2 h. The solvent was evaporated and the residue was crystallized from MeOH/Et_2O to give **12a** (23 mg, 15%): mp 237 °C dec; MS m/z 167 (M^+ of free base); ^1H NMR (D_2O) δ 2.69–2.75 (2 H, m, 5-CH_2), 3.47 (2 H, t, J = 6.2 Hz, 6-CH_2), 4.23 (2 H, d, J = 2 Hz, 2-CH_2), 7.12–7.16 (1 H, m, 4-CH), and 8.72 (1 H, s, 3'-CH). Anal. ($C_7H_9N_3S$·HCl·0.25H_2O) C, H, N.

12b was obtained by the same method, mp 177 °C dec. Anal. ($C_8H_{11}N_3S$·1.5HCl) C, H, N.

1-Methyl-3-(1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine Hydrochloride (14). To a solution of **12** (256 mg, 1.7 mmol) in acetone (2 mL) was added MeI (0.25 mL, 4.0 mmol). The mixture was stirred for 24 h then diluted with Et_2O and filtered to give a yellow solid which was suspended in H_2O (5 mL) and EtOH (5 mL) at 0 °C. $NaBH_4$ (70 mg, 1.8 mmol) was added and the mixture was stirred for 1 h then diluted with H_2O and extracted with Et_2O (4×). The combined extracts were dried and evaporated, and the residue was purified by chromatography on alumina. The major product, treated with ethereal HCl, gave **14** (54 mg, 16%): mp 146–147 °C; MS m/z 166 (CI^+, $[M + 1]^+$ of free base); ^1H NMR (D_2O) δ 2.80–2.88 (2 H, m, 5-CH_2), 3.08 (3 H, s, NCH_3), 3.44–3.60 (2 H, br m, 6-CH_2), 4.20–4.32 (2 H, br m, 2-CH_2), 7.38–7.40 (1 H, m, 4-CH), and 8.72 (1 H, s, 3'-CH). Anal. ($C_8H_{11}N_3O$·HCl) C, H, N.

1-*tert*-[(Butyloxy)carbonyl]-3-(methoxycarbonyl)-pyrrolidine (16). To a solution of 3-(methoxycarbonyl)-pyrrolidine (10 g, 77 mmol) in CH_2Cl_2 (50 mL) at 4 °C was added dropwise a solution of $(BOC)_2O$ (16.9 g, 77 mmol) in CH_2Cl_2 (50 mL). The reaction was stirred at 20 °C for 16 h and then evaporated and chromatographed on silica to give a colorless oil (12.9 g, 73%): MS m/z 230 $(M + 1)^+$; ^1H NMR ($CDCl_3$) δ 1.46 (9 H, s, ^{t}Bu), 2.10–2.15 (2 H, m, 4-CH_2), 3.00–3.10 (1 H, m) with 3.25–3.40 (1 H, m) and 3.44–3.68 (3 H, m) (2-CH_2, 3-CH, and 5-CH_2), and 3.71 (3 H, s, OCH_3). Anal. ($C_{11}H_{19}NO_4$·0.25H_2O) C, H, N.

1-*tert*-[(Butyloxy)carbonyl]-3-carbamoylpyrrolidine (17). Ester **16** from above (8.2 g, 36 mmol) in MeOH (20 mL) was stirred with H_2O (20 mL) containing NaOH (1.7 g, 43.2 mmol) for 15 min. The MeOH was removed and the remaining solution was acidified with AcOH, extracted (6×) with CH_2Cl_2, dried, and evaporated to yield a white solid. This was dissolved in CH_2Cl_2 (40 mL) containing Et_3N (1.96 g, 19 mmol) and cooled to 0 °C. Ethyl chloroformate (2.12 g, 19 mmol) was added and the solution was allowed to warm to room temperature before bubbling NH_3 through until the solution was basic. The reaction mixture was poured onto H_2O and extracted with CH_2Cl_2 (6×). The extracts were dried to yield **17** as a white solid (3.7 g, 48%): mp 111–113 °C; MS m/z 213 (CI^-, $[M - 1]^-$); IR (Nujol) 3350, 3175, 1695, 1665, and 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (9 H, s, $C(CH_3)_3$), 2.07–2.16 (2 H, m, 4-CH_2), 2.88–3.00 and 3.28–3.38 (each 1 H, each m, 5-CH_2), 3.44–3.68 (3 H, m, 2-CH_2 and 3-CH), and 5.82–6.04 (2 H, br d, NH_2). Anal. ($C_{10}H_{18}N_2O_3$) C, H, N.

1-*tert*-[(Butyloxy)carbonyl]-3-(thiocarbamoyl)pyrrolidine (18). A solution of **17** (214 mg, 1 mmol) in benzene (10 mL) was heated with Lawesson's reagent (202 mg, 0.5 mmol) for 2 h. The cooled mixture was chromatographed on silica eluting with MeOH/CH_2Cl_2 (1:20) to yield **18** as a white solid (103 mg, 45%); mp 131–133 °C; MS m/z 229 (CI^-, $[M - 1]^-$; IR (Nujol) 3300, 3180, 1670, 1650, 1165, and 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (9 H, s, $C(CH_3)_3$), 2.14–2.22 (2 H, m, 4-CH_2), 3.27–3.37 (2 H, m, 5-CH_2), 3.54–3.70 (3 H, m, 2-CH_2 and 3-CH), and 8.06–8.20 (2 H, br s, NH_2). Anal. ($C_{10}H_{18}N_2O_2S$) C, H, N.

1-*tert*-[(Butyloxy)carbonyl]-3-[(*N*,*N*-dimethylacetamidino)thiocarbonyl]pyrrolidine (19). A solution of **18** (230 mg, 1 mmol) in CH_2Cl_2 (10 mL) was treated with dimethylacetamide dimethyl acetal (287 mg, 2.4 mmol) for 16 h. The mixture was chromatographed on silica eluting with MeOH/CH_2Cl_2 (1:20) to give **19** as a colorless oil (30.0 mg, 100%): MS m/z 300 (CI^+, $[M + 1]^+$); ^1H NMR ($CDCl_3$) δ 1.45 (9 H, s, $C(CH_3)_3$), 2.13–2.27 (2 H, m, 4-CH_2), 2.42 and 2.43 (3 H, 2 × s, N=CCH_3 *E* and *Z* isomers), 3.10 and 3.12 (3 H, 2 × s) and 3.20 and 3.21 (3 H, 2 × s, $N(CH_3)_2$), and 3.25–3.36 (1 H, m) and 3.42–3.66 (4 H, m) (2-CH_2, 3-CH, and 5-CH_2).

3-(3-Methyl-1,2,4-thiadiazol-5-yl)pyrrolidine Hydrochloride (20). A solution of **19** (2.8 g, 9.4 mmol) in EtOH (50 mL) was treated with pyridine (1.5 g, 18.8 mmol) and HOSA (1.3 g, 11.2 mmol) in MeOH (10 mL) for 2 h. The solvents were removed, and the residue was taken up in H_2O and CH_2Cl_2. The CH_2Cl_2 extract was dried and evaporated and then dissolved in

EtOH (50 mL) and 2 N HCl (20 mL, 40 mmol) and heated under reflux for 20 min. The EtOH was evaporated, H_2O (10 mL) was added, and the mixture was extracted with CH_2Cl_2. The aqueous solution was made basic to pH 10 (Na_2CO_3), extracted with CH_2Cl_2 (4×), dried, and evaporated. The residue in Et_2O was treated with ethereal HCl, from which **20** precipitated as a white solid (670 mg, 35%): mp 135–137 °C; MS m/z 170 (CI^+, $[M + 1]^+$); ^1H NMR (D_2O) δ 2.25–3.39 (1 H, m) and 2.63–2.70 (1 H, m, 4-CH_2), 2.62 (3 H, s, CH_3), 3.47–3.64 (3 H, m, one of 2-CH_2 and 5-CH_2), 3.85 (1 H, dd, J = 7 and 9.5 Hz, one of 2-CH_2), and 4.24 (1 H, quin, J = 7 Hz). Anal. ($C_7H_{11}N_3S$·HCl·0.25H_2O) C, H, N.

1-Methyl-3-(3-methyl-1,2,4-thiadiazol-5-yl)pyrrolidine Hydrochloride (21). A solution of **20** (169 mg, 1 mmol) in formic acid (3 mL) containing formaldehyde (3 mL of a 40% solution in water) was heated under reflux for 15 min. The mixture was evaporated to dryness under reduced pressure and the residue was partitioned between aqueous K_2CO_3 solution and CH_2Cl_2. The CH_2Cl_2 extract was dried and evaporated and the residue was purified by column chromatography on silica eluting with MeOH/CH_2Cl_2 (1:10). The oil thus obtained was treated with oxalic acid and triturated with Et_2O to give **21** (125 mg, 45%): mp 105–107 °C; MS m/z 184 (CI^+, $[M + 1]^+$); ^1H NMR (D_2O) δ 2.28–2.39, 2.44–2.50, 2.65–2.72, and 2.79–2.84 (each 0.5 H, each m, 4-CH_2), 2.61 and 2.62 (each 1.5 H, each s, CH_3), 3.03 and 3.05 (each 1.5 H, each s, NCH_3), 3.29–3.46 (1.5 H, m) with 3.65 (0.5 H, dd, J = 9 and 12 Hz), 3.83–3.98 (1.5 H, m) and 4.18 (0.5 H, dd, J = 7.5 and 12 Hz) (2-CH_2 and 5-CH_2), 4.28 (0.5 H, quin, J = 8.5 Hz, 0.5 (3-CH)), and 4.44 (0.5 H, quin, J = 7 Hz, 0.5 (3-CH)). Anal. ($C_8H_{13}N_3S$·$(COOH)_2$·0.25H_2O) C, H, N.

General Procedure for the Preparation of Quinuclidinylthiadiazoles (25a–i). 3-(3-Benzyl-1,2,4-thiadiazol-5-yl)quinuclidine Hydrogen Oxalate (25i). A solution of 3-(methoxycarbonyl)quinuclidine (**22**; 1.69 g, 10 mmol) in THF (20 mL) was treated with LDA (freshly prepared from diisoprylamine (700 mg, 15 mmol) and ^{n}BuLi (7.5 mL, 2 M)) in THF (50 mL) at −78 °C under N_2 for 1 h. 3-Benzyl-5-chloro-1,2,4-thiadiazole (3.15 g, 15 mmol) was added and the reaction was allowed to warm slowly to room temperature. The solvent was evaporated and the residue was stirred in MeOH (100 mL) and 2 N NaOH (10 mL) for 1 h. The MeOH was evaporated and the aqueous solution was extracted with EtOAc and then adjusted to pH 2 with concentrated HCl. After 3 h the solution was made basic and extracted with CH_2Cl_2. The combined CH_2Cl_2 solutions were dried and evaporated to give an oil which was treated with oxalic acid. Crystallization from MeOH/Et_2O gave **25i** (1.1 g, 29%): mp 88–90 °C; MS m/z 285 (M^+ of free base); ^1H NMR (D_2O) δ 1.76–1.98 and 2.08–2.26 (each 2 H, each m, 5-CH_2 and 8-CH_2), 2.46–2.52 (1 H, m, 4-CH), 3.29–3.50 (4 H, m, 6-CH_2 and 7-CH_2), 3.74–3.88 (2 H, m, 2-CH_2), 4.03–4.10 (1 H, m, 3-CH), 4.34 (2 H, s, C*H*$_2$Ph), and 7.23–7.43 (5 H, m, Ph). Anal. ($C_{16}H_{19}N_3S$·$(COOH)_2$·0.33H_2O) C, H, N.

3-(3-Methyl-1,2,4-thiadiazol-5-yl)-3-(methoxycarbonyl)quinuclidine Hydrochloride (24b). A solution of **22** (7.2 g, 42 mmol) in THF (400 mL) under N_2 was treated with LDA (40 mL of a 1.5 M solution in cyclohexane, 60 mmol) at −78 °C for 1 h. 5-Chloro-3-methyl-1,2,4-thiadiazole (7.0 g, 52 mmol) was added and the mixture was allowed to warm slowly to 20 °C. The solvent was evaporated then dilute HCl (300 mL) was added and washed twice with Et_2O. The aqueous solution was made basic with K_2CO_3 and extracted with Et_2O (3×). These latter extracts were dried and treated with ethereal HCl, and the precipitated salt was recrystallized to give **24b** (1.52 g, 13.5%): mp 142 °C (MeOH/EtOAc); MS m/z 267 (M^+ of free base); ^1H NMR (D_2O) δ 1.74–1.85 (1 H, m) and 1.91–2.14 (3 H, m) (5-CH_2 and 8-CH_2), 2.65 (3 H, s, CH_3), 2.90–2.92 (1 H, m, 4-CH), 3.28–3.46 (4 H, m, 6-CH_2 and 7-CH_2), 3.92 (3 H, s, OCH_3), 4.27 (1 H, d, J = 14 Hz, one of 2-CH_2), and 4.43 (1 H, dd, J = 14 and 2.5 Hz, one of 2-CH_2). Anal. ($C_{12}H_{18}N_3O_2S$·HCl) C, H, N.

α-(Tetrahydropyranyloxy)phenylacetamidine Hydrochloride (28). To a solution of sodium (230 mg, 10 mmol) in dry EtOH was added α-(tetrahydropyranyloxy)benzyl cyanide (21.7 g, 100 mmol). After stirring for 16 h, the reaction was cooled to −50 °C and dry NH_3 (50 mL) was condensed into the solution. Dry NH_4Cl (5.3 g, 100 mmol) was added and the reaction was allowed to warm to 25 °C overnight. After filtration and evaporation of the solvents, the residue was taken up into H_2O (200 mL), washed with CH_2Cl_2 (2 × 200 mL), and evaporated to give **28** as a white solid (22.9 g, 85%): mp 53–55 °C; MS m/z 235 (M + H)$^+$; ^1H NMR (D_2O) δ 1.50–1.86 (6 H, m, 3 × CH_2), 3.49–3.53, 3.60–3.69, and 3.91–3.96 (0.5 H, 1 H, and 0.5 H, respectively, CH_2O), 4.64 and 5.00 (each 0.5 H, each t, J = 7 Hz, CHO), 5.61 and 5.64 (each 0.5 H, each s, PhC*H*), and 7.47–7.61 (5 H, m, Ph).

3-[1-Phenyl-1-(tetrahydropyranyloxy)methyl]-5-chloro-1,2,4-thiadiazole (27). Compound **28** (22.8 g, 85 mmol) was dissolved in cold, aqueous NaOH solution (4.2 N, 120 mL, 0.5 mol) and a solution of perchloromethyl mercaptan (19.5 g, 110 mmol) in CH_2Cl_2 (120 mL) was added to the vigorously stirred reaction mixture over 1 h. After a further hour the organic layer was separated and the aqueous solution was reextracted with CH_2Cl_2 (3 × 100 mL) to give an oil which was purified by column chromatography on silica in hexane/Et_2O (1:1) to yield **27** as an oil (10.0 g, 36%): MS m/z 209 ($M - C_5H_9O_2$)$^+$; ^1H NMR ($CDCl_3$) δ 1.51–1.93 (6 H, m, 3 × CH_2), 3.46–3.54, 3.73–3.80, and 3.88–3.94 (1 H, 0.5 H and 0.5 H, respectively, each m, CH_2O), 4.69 and 4.84 (each 0.5 H, each s, PhC*H*), and 7.25–7.55 (5 H, m, Ph). Anal. ($C_{14}H_{15}ClN_2O_2S$) C, H, N.

3-[3-(1-Hydroxy-1-phenylmethyl)-1,2,4-thiadiazol-5-yl]quinuclidine Hydrogen Oxalate (29a). Reaction of 3-(methoxycarbonyl)quinuclidine (4.0 g, 24 mmol) with **27** (7.75 g, 24 mmol) by the general method described above gave **29a** as its free base (1.1 g, 15%) which was treated with oxalic acid to give the hydrogen oxalate salt: mp 61–62 °C; MS m/z 301 (M^+ of free base); ^1H NMR (D_2O) δ 1.70–1.90 and 2.06–2.25 (each 2 H, each m, 5-CH_2 and 8-CH_2), 1.45–1.52 (1 H, m, 4-CH), 3.24–3.47 (4 H, m, 6-CH_2 and 7-CH_2), 3.73–3.87 (2 H, m, 2-CH_2), 4.06–4.13 (1 H, m, 3-CH), 6.14 (1 H, s, C*H*OH), and 7.36–7.50 (5 H, m, Ph). Anal. ($C_{16}H_{19}N_3OS$·$(COOH)_2$·H_2O) C, H, N: calcd, 10.26; found, 9.78.

3-(3-Benzoyl-1,2,4-thiadiazol-5-yl)quinuclidine Hydrogen Oxalate (29b). Free base of compound **29a** (1.0 g, 3.3 mmol) in CH_2Cl_2 (50 mL) was stirred with activated MnO_2 (5 g). After 0.5 h, the reaction was filtered and the MnO_2 repeatedly washed with CH_2Cl_2. The combined extracts were evaporated to yield **29b** as its free base (1.0 g), from which the hydrogen oxalate salt was prepared: mp 95–97 °C dec; MS m/z 299 (M^+ of free base); ^1H NMR (D_2O) δ 1.92–1.98 and 2.16–2.34 (each 2 H, each m, 5-CH_2 and 8-CH_2), 2.58–2.62 (1 H, m, 4-CH), 3.36–3.58 (4 H, m, 6-CH_2 and 7-CH_2), 3.84–4.04 (2 H, m, 2-CH_2), 4.22–4.30 (1 H, m, 3-CH), 7.62 (2 H, t, J = 8 Hz, 3-H and 5-H of Ph), 7.79 (1 H, t, J = 8 Hz, 4-H of Ph), and 8.13 (2 H, d, J = 8 Hz, 2-H and 6-H of Ph). Anal. ($C_{16}H_{17}N_3OS$·$(COOH)_2$·0.67H_2O) C, H, N.

3-[3-(1,1-Diphenyl-1-hydroxymethyl)-1,2,4-thiadiazol-5-yl]quinuclidine Hemi(hydrogen oxalate) (25j). Free base of compound **29b** (0.92 g, 3.1 mmol) in dry THF (50 mL) under dry nitrogen was treated with phenylmagnesium bromide (3 mL of a 3 M solution in Et_2O) at 25 °C for 2 h. Saturated NH_4Cl was added and the mixture was partitioned between H_2O and CH_2Cl_2 (2 × 100 mL) to yield **25j** free base as an oil (633 mg, 54%), which was crystallized as the hemi hydrogen oxalate salt: mp 185–186 °C; MS m/z 377 (M^+ of free base); ^1H NMR (D_2O) δ 1.72–1.96 and 2.04–2.26 (each 2 H, each m, 5-CH_2 and 8-CH_2), 2.46–2.50 (1 H, m, 4-CH), 3.26–3.40 (4 H, m, 6-CH_2 and 7-CH_2), 3.73–3.83 (2 H, m, 2-CH_2), 4.10–4.15 (1 H, m, 3-CH), and 7.31–7.42 (10 H, m, 2 × Ph). Anal. ($C_{22}H_{23}N_3OS$·0.5$(COOH)_2$·1.5H_2O) C, H, N, S.

General Procedure for the Preparation of Azanorbornylthiadiazoles. (a) ***endo*-3-(1,2,4-Thiadiazol-5-yl)-1-azabicyclo[2.2.1]heptane Hydrogen Oxalate (33a).** To a solution of 3-(methoxycarbonyl)-1-azabicyclo[2.2.1]heptane (**30**; 1.05 g, 6.7 mmol) in THF (25 mL) under N_2 at −78 °C was added 1.5 M LDA·THF complex in cyclohexane (5 mL). The reaction was stirred at −78 °C for 1 h, then 5-chloro-1,2,4-thiadiazole (950 mg, 7.9 mmol) was added. After 30 min the reaction was allowed to warm slowly to room temperature and the solvent was evaporated. The residue was treated with MeOH (15 mL) and 2 N NaOH (15 mL) for 1.5 h, then the MeOH was evaporated and the remaining aqueous solution was extracted three times with EtOAc. The aqueous solution was adjusted to pH 1 with concentrated HCl and allowed to stand for 3 h, then aqueous K_2CO_3 was added and the solution was extracted five times with CH_2Cl_2. The combined extracts were dried and evaporated to give a yellow oil (720 mg, 59%) which was treated with oxalic acid (450 mg) in MeOH and evaporated. The residue was crystallized twice from MeOH/^{i}P-

rOH to give **33a** (200 mg, 11%): mp 140–141 °C; MS m/z 182 (CI^+, $[M + 1]^+$ of free base); ^1H NMR (D_2O) δ 1.62–1.71 (1 H, m, one of 5-CH_2), 1.97–2.08 (1 H, m, one of 5-CH_2), 3.34–3.60 (5 H, m, 4-CH, 6-CH_2, and 7-CH_2), 3.74 (1 H, ddd, J = 2.3, 6.0, and 12.2 Hz, endo-2-CH_2), 3.98 (1 H, dt, J = 3.0 and 12.2 Hz, exo-2-CH_2), 4.45–4.53 (1 H, m, 3-CH), and 8.75 (1 H, s, 3′-CH). Anal. ($C_8H_{11}N_3S\cdot(COOH)_2$) C, H, N.

(b) *exo*-3-(1,2,4-Thiadiazol-5-yl)-1-azabicyclo[2.2.1]heptane Hydrogen Oxalate (34a). The mother liquor from the crystallization of **33a** above was treated with NaOMe (1 g, 18.5 mmol) for 2 h then evaporated. Water was added and extracted five times with CH_2Cl_2. The combined extracts were dried and evaporated to give a yellow oil which was treated with oxalic acid (350 mg, 3.8 mmol) in MeOH and evaporated. The residue was crystallized twice from MeOH/Et_2O to give **34a** (435 mg, 38%): mp 121.5 °C; MS m/z 182 (CI^+, $[M + 1]^+$ of free base); ^1H NMR (D_2O) δ 1.98–2.08 (1 H, m, one of 5-CH_2), 2.22–2.33 (1 H, m, one of 5-CH_2), 3.25–3.32, 3.34–3.44, and 3.50–3.60 (2 H, 1 H and 2 H, respectively, each m, 4-CH, 6-CH_2, and 7-CH_2), 3.82 (1 H, ddd, J = 2.0, 8.6, and 12.1 Hz, one of 2-CH_2), 3.89 (1 H, ddd, J = 2.8, 5.4, and 12.1 Hz, one of 2-CH_2), 4.02–4.10 (1 H, m, 3-CH), and 8.72 (1 H, s, 3′-CH). Anal. ($C_8H_{11}N_3S\cdot(COOH)_2$) C, H, N.

The relative stereochemistry of compounds **34** were determined from a complete assignment of the COSY-45 NMR for **34b** in which additional crosspeaks were observed corresponding to ^4J coupling between transantiperiplanar protons as expected in a rigid bicyclic system of this type. These were found for H3/anti-H7, endo-H2/anti-H7, exo-H2/exo-H6, endo-H5/syn-H7, and endo-H6/syn-H7, conclusively proving the relative stereochemistry of these protons and thus that the thiadiazole moiety was exo (syn- and anti- for H7 refer to the disposition of these protons with respect to the bridge bearing the thiadiazole group). Similarly for **33b**, crosspeaks were observed for ^4J exo-H2/exo-H6 and ^4J endo-H2/anti-H7, thus defining the stereochemical relation of exo-H2 and endo-H2. Since ^3J exo-H2/H3 (11.5 Hz) > ^3J endo-H2/H3 (5.7 Hz), H3 was assigned as cis to exo-H2, making the thiadiazole substituent endo. This was confirmed by NOE experiments which demonstrated that H3 was on the same face of the molecule as exo-H2. These stereochemical assignments are consistent with the observed thermodynamic stabilities of the two isomers on base-catalyzed epimerization.

Molecular Modeling. 3,5-Dimethyl-1,2,4-oxadiazole and 3,5-dimethyl-1,2,4-thiadiazole were constructed with data from X-ray diffraction or microwave spectroscopy for the heterocyclic ring.[11] Ab initio molecular orbital calculations were carried out on these molecules with GAUSSIAN 80[9] at the STO-3G level. The wave functions obtained were used in DENPOT 80[8] to generate electrostatic potential maps using a 2-dimensional grid consisting of 900 calculation points (30 × 30) over the molecule and surrounding space, in the plane of the ring, from which the local minimum potentials adjacent to N2 and N4 were taken. Conformational analyses were carried out with the OPTIMOL program[21] within the Merck molecular modeling facility.[22] The energies of individual conformers were calculated at each 20° rotation around C3–C5′ after minimization with a molecular mechanics force field.[21] The S enantiomer was used in each case with the dihedral angle measured viewing down the C3–C5′ bond. Tables of these energies are available as supplementary material.

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Supplementary Material Available: Microanalysis data for the compounds synthesized and conformational analysis energies for **33b**, **34b**, **38**, and **39** (3 pages). Ordering information is given on any current masthead page.

(21) Halgren, T., unpublished. OPTIMOL is based on MM2 (Allinger, N. L. *J. Am. Chem. Soc.* 1977, *99*, 8127) and differs mainly in the use of partial charges on atoms, instead of bond dipoles, and in the absence of unshared pairs on certain nitrogen and oxygen atoms.

(22) (a) Gund, P.; Andose, J. D.; Rhodes, J. B.; Smith, G. M. *Science* 1980, *208*, 1425. (b) Smith, G. M.; Hangauer, D. G.; Andose, J. D.; Bush, B. L.; Fluder, E. M.; Gund, P.; McIntyre, E. F. *Drug Inf. J.* 1984, *18*, 167.

Book Reviews

One and Two Dimensional NMR Spectroscopy. By Atta-ur-Rahman. Elsevier Science Publishers B. V., Amsterdam, The Netherlands. 1989. xx + 578 pp. 17 × 24.5 cm. ISBN 0-444-87316-3. $186.75.

In ever increasing numbers medicinal chemists are turning to advanced NMR experiments to solve complex structural problems. These problems vary from structure elucidation of natural products to probing the 3-dimensional structure of ligand–receptor complexes. To date, few texts are available for the medicinal chemist, as well as organic chemist, to expand his or her knowledge of NMR without getting bogged down in the mathematics of matrix algebra. This book provides, in my opinion, an excellent forum for the chemist who is familiar with the fundamentals of NMR to develop an understanding of the more sophisticated 1D and 2D experiments in common use today. This book clearly and concisely presents 1D and 2D experiments in terms of pulse sequences and simple vector models with clear concise illustrations.

The book is separated into 14 chapters of varying detail, each concentrating on a different type of NMR experiment. Chapter 1 provides a clear introduction into the general principles of NMR. Topics covered in this chapter include probe tuning, shimming, dynamic range problems, quadrature phase detection in both dimensions, coherence transfer, phase cycling, composite pulses, and rotation of vectors. Chapter 2 gives an excellent explanation of spin-echo and polarization transfer experiments. In this chapter the various modifications of the 1D INEPT and DEPT experiments are given. In order to aid the reader in developing an understanding of the applications of material present in the chapter, a short problem set (with answers) is included at the end of the chapter. These problems involve the structure elucidation of several natural products. Chapter 3 covers in limited detail the 1D INADEQUATE experiment for the determination of carbon-carbon connectivities. Chapter 4 presents a very good discussion of the theory of the nuclear Overhauser effect, presenting the various relaxation pathways. The 1D NOE difference experiment is presented and discussed in detail. Chapter 4 also includes a problem set at the end of the chapter. Chapter 5 gives a good nonmathematical introduction to the principles of 2D NMR. Chapters 6 and 7 cover the infrequently used, but historically important, techniques of heteronuclear and homonuclear J-resolved spectroscopy. Both chapters give examples of many different types of experiments and have problem sets at the end. Chapter 8 gives a very good (89 pages) discussion of homonuclear shift correlation spectroscopy. Topics covered in this very well-written chapter include coupling constants from phase-sensitive COSY spectra, peak shape, shaping functions, coherence transfer pathways in COSY spectra, COSY-45, phase-sensitive COSY, relay COSY, and SECSY spectra. Chemical shift correlations through cross-relaxation and exchange processes are covered in chapter 9. Chapter 9 presents a very good discussion of various NOESY experiments including heterorelayed NOESY and homorelayed NOESY spectra. Rotating-frame NOE or ROESY spectra and heteronuclear NOE or HOESY spectra are also discussed in this chapter. As with several other chapters, a problem set is included. Chapter 10 presents a discussion of