Ester Bio-isosteres: Synthesis of Oxadiazolyl-1-azabicyclo[2.2.1]heptanes as Muscarinic Agonists

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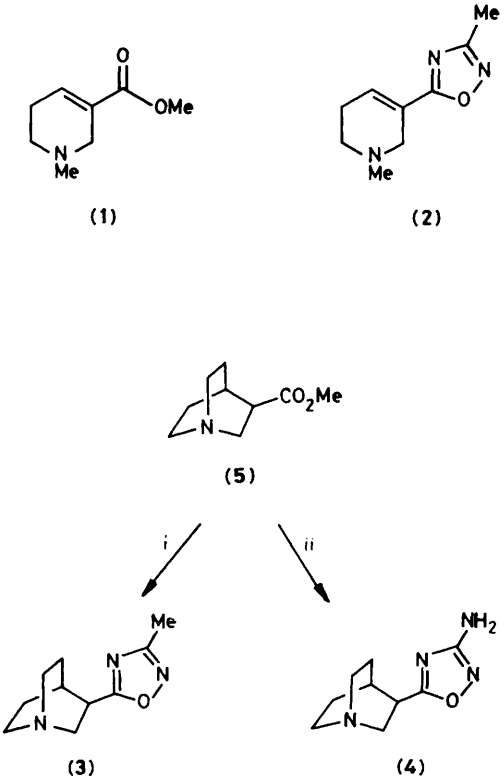
The methyl ester functionality in arecoline and related esters has been replaced by 1,2,4-oxadiazole to generate the most potent and efficacious muscarinic agonists known.

The cholinergic hypothesis of Alzheimer's disease[1] (also known as senile dementia of the Alzheimer type) has led to the belief that enhancement of muscarinic cholinergic transmission at cerebral cortical sites would be beneficial for treatment of the disease. As part of a study aimed at improving the clinical profile of the muscarinic agonist, arecoline (**1**),[2,3] the metabolically-labile methyl ester functionality[4] was replaced by methyloxadiazole. In addition, it was anticipated that this change would also improve the efficacy[5] of (**1**) which behaves as only a weak partial agonist in cerebral cortex compared to the endogenous transmitter (acetylcholine).[6] The value of this replacement is demonstrated in this report since it led to the discovery of the most potent and efficacious muscarinic agonist known in spite of lacking a quaternary entity normally assumed[7] to be obligatory for full agonist behaviour.

The arecoline-derived methyloxadiazole (**2**)† was available directly from (**1**) in 65% yield by treatment in refluxing tetrahydrofuran (THF) with 1.5 equiv. of the sodium salt of acetamide oxime (using NaH). The compound proved to be more potent than (**1**) itself but had marginally less efficacy as assessed by a two-stage binding assay designed to measure both parameters.[8] However the activity was sufficiently interesting to warrant the synthesis of related molecules bearing functionality predicted by *ab initio* Gaussian-80 calculations‡ to potentiate interactions between agonist and receptor (see below). Thus both methyl- and amino-oxadiazoles in the quinuclidine series were prepared [(**3**) and (**4**) respectively, Scheme 1] starting from methyl quinuclidine-3-carboxylate (**5**)[9] and these compounds showed a marked increase in activity over (**1**).



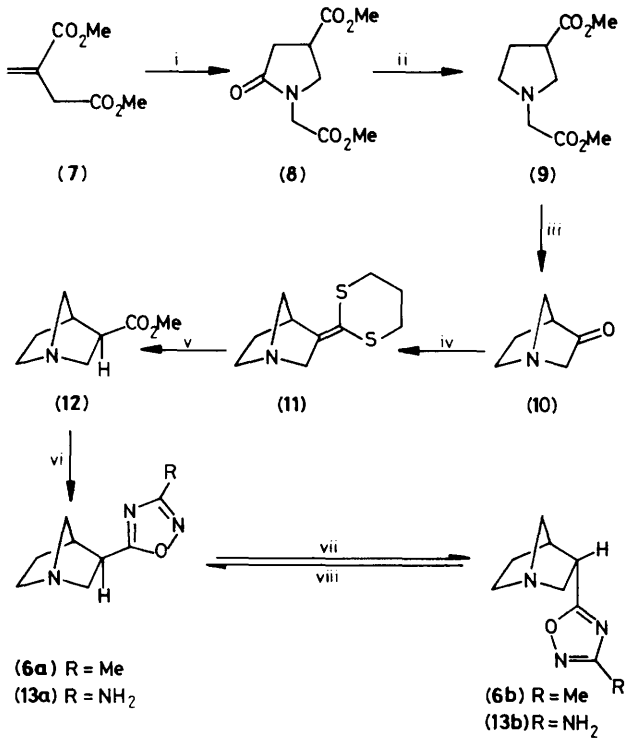
Scheme 1. *Reagents*: i, $MeC(=NOH)NH_2$, NaH, THF, molecular sieve, reflux, 4 h (82%); ii, $[NH_2C(=NOH)NH_2]_2 \cdot H_2SO_4$, NaOEt, EtOH, molecular sieve, reflux, 4 h (50%).

Introduction of further asymmetry into the molecule in order to probe stereochemical features of the agonist binding site was achieved using the 1-azabiyclo[2.2.1]heptane ring system in place of quinuclidine. A stereoselective route to both diastereoisomers of the methyloxadiazole (**6a—b**) has thus been developed (Scheme 2). Reaction of dimethyl itaconate (**7**) with methyl glycinate in refluxing methanol gave (**8**) which was reduced with diborane in THF to give the pyrrolidine (**9**) in 40% overall yield. The Dieckmann cyclisation was achieved using potassium t-butoxide in toluene and subsequent hydrolysis and decarboxylation afforded the azabicyclic ketone (**10**) in high yield (65%) given the strained nature of the product. This represents a considerable improvement over the only reported[10] synthesis of (**10**) which involved the thermal cyclisation of 3-hydroxy-4-hydroxymethylpiperidine. Treatment of (**10**) in THF with 2-trimethylsilyl-2-lithio-1,3-dithiane gave the ketene dithioacetal (**11**) as a stable crystalline solid in quantitative yield. Acidic methanolysis of (**11**) generated (**12**)§ as the thermodynamically favoured '*exo*' diastereoisomer (as shown) by equilibration of the protonated intermediate. Oxadiazole formation under the basic conditions described above gave a 9 : 1 mixture of (**6a**) and (**6b**) from which (**6a**)§ was readily isolated in 50% yield by column chromatography on alumina. It was later shown in epimerisation studies under basic conditions on (**6b**) that the stereochemical integrity of the ester (**12**) was of little consequence since the ratio of oxadiazole products represents the thermodynamic mixture of diastereoisomers. However, the anion generated from (**6a**) with lithium di-isopropylamide (LDA) in THF at −78 °C could be transformed into (**6b**) as the major

† This and all new compounds described have been fully characterised and assessed for purity by ^1H n.m.r. spectroscopy at 360 MHz, mass spectrometry, elemental analysis (C, H, N), and chromatography (t.l.c., h.p.l.c., and g.c. where possible).

‡ Molecules were constructed from *X*-ray crystal data or using the OPTIMOL procedure (Dr. T. Halgren, Rahway) within the Merck Molecular Modelling System. Gaussian-80 (QCPE 446) and Denpot (QCPE 483) electrostatic potential calculations were performed using the CHEMQM interface within the CHEMX program supplied by Chemical Design Ltd., Oxford.

§ The relative stereochemistry in these molecules was assigned by ^1H n.m.r. COSY and nuclear Overhauser enhancement experiments (with Dr. R. Herbert).



Scheme 2. *Reagents*: i, NaOMe, MeOH, $NH_2CH_2CO_2Me.HCl$, reflux, 16 h; ii, BH_3·THF, THF, reflux, 1 h, then K_2CO_3 soln., reflux, 1 h; iii, Bu^tOK, PhMe, 140 °C, 4 h, then reflux conc. HCl, 16 h; iv, Bu^nLi, 2-trimethylsilyl-1,3-dithiane, −35 to 20 °C; v, MeOH, HCl (gas), 55 °C, 4 h; vi, NaH, $MeC(=NOH)NH_2$, THF, powdered molecular sieve, reflux, 1.5 h; vii, LDA, THF, −78 °C, then HOAc, THF, −78 °C; viii, NaOMe, MeOH, 20 °C.

diastereoisomer (ratio 3:1) by kinetic proton capture, at −78 °C, at the less hindered face of the azabicycle. Similar chemistry also provided the amino-oxadiazoles (**13a**, **b**).

The amino-oxadiazole (**13a**) proved to be the most potent and most efficacious muscarinic agonist known, being 200-fold more potent than (**1**) and displaying efficacy at cortical muscarinic receptors greater than even acetylcholine itself. In general, it was discovered that affinity for the site of the receptor labelled by [^{3}H]oxotremorine-M (the 'agonist' binding site) was markedly dependent on the nature of the oxadiazole 3-substituent. For optimum binding to this site it was argued that the correct alignment and strength of two hydrogen bonding interactions (normally associated with the ester oxygens of acetylcholine) between receptor and ligand are vital. Indeed it was shown that affinity for the agonist binding site correlated directly with the magnitude of the negative potential in the vicinity of the oxadiazole ring nitrogens. Substituents such as amino which are capable of enhancing the hydrogen bond acceptor properties of the oxadiazole ring nitrogen atoms are therefore beneficial. Thus, by careful consideration of the nature of the oxadiazole substituent and its influence on the binding characteristics of the resulting molecules, it has been possible to design ligands which maximise available interactions with the receptor.

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