Synthesis of a New Series of 8-Substituted-2,8-diazaspiro[4.5]decan-3-ones

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Dedicated to the memory of Dr. Roland K. Robins

A new series of 8-substituted-2,8-diazaspiro[4.5]decan-3-ones has been synthesized and tested in *in vitro* and *in vivo* assays predictive for cholinergic activity, in comparison with the muscarinic agent RS-86. Preliminary pharmacological data indicate that the compounds are devoid of significant cholinergic properties.

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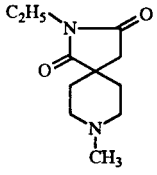
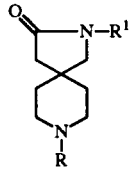
The deterioration in cognitive function which is a feature of the Alzheimer's disease (AD), is believed to be linked to the loss of cholinergic activity in the cortex and hippocampus [1]. This concept has recently led to a considerable effort in the development of cholinergic agonists or partial agonists for the treatment of AD [2].

As a part of our research in this area, we have synthesized a new series of compounds structurally related to the muscarinic agonist RS-86, in which the imidic ring has been substituted by an amidic function.

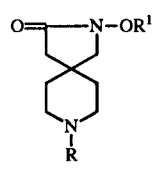
We describe in this paper the synthesis of compounds **4a-d** and **5a-e**, which can be formally derived from RS-86 by reduction of the α-carbonyl group, with respect to the piperidine ring.



RS-86



4a-d



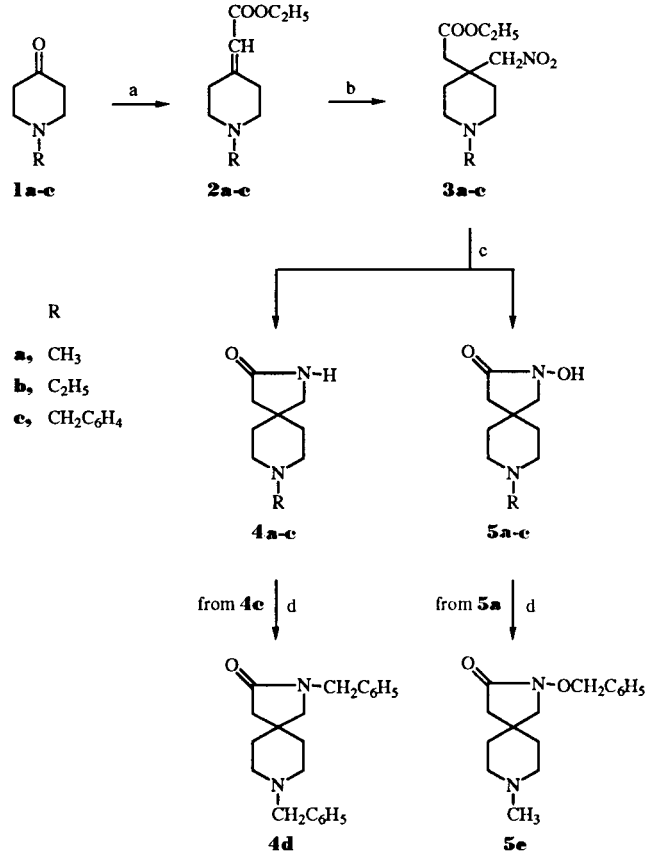
5a-e

Compounds **4,5**

For R^1 = H, R = CH_3 **a**, C_2H_5 **b**, $CH_2C_6H_5$ **c**
4d R = R^1 = $CH_2C_6H_5$
5e R = CH_3, R^1 = $CH_2C_6H_5$

As shown in Scheme 1, compounds **4a-c** and **5a-c** were prepared starting from the appropriate *N*-substituted piperidones **1**, which were condensed with triethylphosphone acetate to give the unsaturated esters **2a-c**, following a previously reported method [3]. Treatment of the latter with nitromethane in the presence of tetramethylguanidine (TMG) led to the corresponding nitromethyl derivatives **3a-c**. It is to be noted that when triton B was used instead of TMG, very poor yields were obtained. Catalytic reduction of **3a,b** in the presence of PtO_2 gave a 1:3 mixture of **4a,b** and **5a,b**. However, in the case of **3c** a 1:1 ratio of **4c** and **5c** was obtained. In contrast, when using Raney Ni as the catalyst, the main reaction product was

Scheme 1



1a-c **2a-c** **3a-c** **4a-c** **5a-c** **4d** **5e**

a) $(C_2H_5O)_2P(O)CH_2COOEt/NaH$, b) $CH_3NO_2/(CH_3)_2NC(=NH)N(CH_3)_2$, c) Ni/Raney or $PtO_2/H_2/EtOH$, d) $C_6H_5CH_2Cl/NaH/DMF$

Table I

Physical and Spectral Data of Compounds **3-5**

Compound	Yield %	Mp °C Bp °C/mm Hg	IR cm^{-1}	Formula	^1H-nmr δ (ppm)
3a	36	110/0.1	1720 (C=O) 1550, 1380 (NO_2)	$C_{11}H_{20}N_2O_4$	1.3 (s, 3H), 1.6-1.8 (m, 4H), 2.2-2.7 (m, 9H), 4.2 (q, 2H), 4.7 (s, 2H)
3b	25	90/0.1	1720 (C=O) 1550, 1380 (NO_2)	$C_{12}H_{22}N_2O_4$	1.0-1.4 (m, 6H), 1.6-1.9 (m, 4H), 2.3-2.6 (m, 8H), 4.2 (q, 2H), 4.7 (s, 2H),
3c	31	150/0.1	1720 (C=O) 1550, 1380 (NO_2)	$C_{17}H_{24}N_2O_4$	1.3 (s, 3H), 1.6-1.8 (m, 4H), 2.4-2.7 (m, 6H), 3.5 (s, 2H), 4.2 (m, 2H), 4.8 (s, 2H), 7.3 (s, 5H)
4a	60 [a]	88-90 [c]	3200 (NH) 1670 (C=O)	$C_9H_{16}N_2O$	1.6-1.9 (m, 5H), 2.2-2.5 (m, 8H), 3.2 (s, 2H), 5.9 (br s, 1H, exch with deuterium oxide)
4b	50 [a]	70-74 [c]	3200 (NH) 1680 (C=O)	$C_{10}H_{18}N_2O$	1.1 (s, 3H), 1.6-1.9 (m, 4H), 2.2 (s, 2H), 2.3-2.6 (m, 6H), 3.2 (s, 2H), 6.3 (br s, 1H, exch with deuterium oxide)
4c	25 [b]	150-152 [c]	3190 (NH) 1680 (C=O)	$C_{15}H_{20}N_2O$	1.6-1.8 (m, 4H), 2.2 (s, 2H), 2.3-2.5 (m, 4H), 3.2 (s, 2H), 3.5 (s, 2H), 5.8 (br s, 1H, exch with deuterium oxide), 7.4 (s, 5H)
5a	42 [b]	182-184 [c]	3400-3200 (OH) 1690 (C=O)	$C_9H_{16}N_2O_2$	1.6-1.8 (m, 4H), 2.1-2.6 (m, 9H), 3.4 (s, 2H), 8.1 (br s, 1H, exch with deuterium oxide)
5b	40 [b]	148-150 [c]	3400-3200 (OH) 1690 (C=O)	$C_{10}H_{18}N_2O_2$	1.2 (t, 3H), 1.6-1.8 (m, 4H), 2.2 (s, 2H), 2.3-2.6 (m, 6H), 3.5 (s, 2H), 6.4 (br s, 1H, exch with deuterium oxide)
5c	25 [b]	105-107 [c]	3400-3200 (OH) 1690 (CO)	$C_{15}H_{20}N_2O_2$	1.5-1.7 (m, 4H), 2.2 (s, 2H), 2.3-2.5 (m, 4H), 3.4 (s, 2H), 3.5 (s, 2H), 6.5 (br s, 1H, exch with deuterium oxide), 7.2 (s, 5H)

[a] Ni/Raney was used as catalyst. [b] PtO_2 was used as catalyst. [c] Crystallized from 2-butanone.

Table II

Elemental Analyses

Compound	MW	Calcd./Found C	H	N
4a	168.2	64.25 64.17	9.58 9.65	16.65 16.35
4b	182.3	65.90 65.76	9.95 10.04	15.37 15.11
4c	244.3	73.73 73.54	8.25 8.26	11.46 11.10
4d	334.5	79.00 79.13	7.83 7.97	8.38 8.21
5a	184.2	58.67 58.44	8.75 8.82	15.20 15.00
5b	198.3	60.58 60.33	9.15 9.18	14.13 13.96
5c	260.3	69.21 69.13	7.74 7.73	10.76 10.97
5e	274.4	70.04 70.30	8.08 8.13	10.21 10.15

always **4**. Nevertheless, it should be highlighted that in this case a partial concomitant debenzylation of **3c** occurred. Finally, alkylation of **4c** and **5a** with benzyl chloride in DMF/NaH brought about **4d**, respectively, **5e** in good yields.

EXPERIMENTAL

Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. The ir spectra were recorded in Nujol mulls on a Perkin-Elmer 1310 infrared spectrophotometer. The ^1H nmr spectra were recorded on a Hitachi-Perkin Elmer R 600 FR spectrometer; chemical shifts are reported as δ (ppm), relative to tetramethylsilane as internal standard. Deuteriochloroform was used as a solvent, unless otherwise noted. Analysis (tlc) on silica gel plates was used to check product purity. Silica gel 60 (Merck; 70-230 mesh) was used for column chromatography. The structures of all compounds were consistent with their analytical and spectroscopic data.

Esters **2a-c**.

Compounds **2a-c** were prepared by condensing the required piperidone **1** with triethylphosphone acetate, following a previously reported method [3]. See the same reference for physical and chemical data.

Ethyl (*N*-Substituted-4-nitromethyl)isonipecotate **3a-c**.

General Method.

A solution of the required ester **2** (0.025 mole), nitromethane (0.125 mole) and tetramethylguanidine (0.005 mole) was stirred at room temperature for 14 days and the end of the reaction was monitored by ir. The mixture was then treated with water and extracted with chloroform. After evaporation of the solvent, the residue was distilled under vacuum to give in the order the unreacted ester **2** and the desired **3**, which was further purified by silica gel chromatography, using chloroform/methanol 9/1 as eluent (see Table I for data).

N-Substituted-2,8-diazaspiro[4.5]decan-3-ones **4a-c**, **5a-c**.

General Method.

A solution of the required nitro derivative **3** in ethanol was

hydrogenated in the presence of PtO_2 (ratio 20/1 w/w). The catalyst was filtered off and the solvent evaporated to give a mixture of **4** and **5** in a ratio depending on the starting **3**. When only **4** was needed, Raney Ni was used as catalyst instead of PtO_2. Compounds **4** and **5** were separated by silica gel chromatography (eluent chloroform/methanol, 9/1) collecting as the first run **4**, immediately followed by **5**. All derivatives were then crystallized from methyl ethyl ketone (see Table I for data).

2,8-Dibenzyl-2,8-diazaspiro[4.5]decan-3-one **4d**.

To a solution of **4c** (0.44 g, 0.0018 mole) in DMF (10 ml), sodium hydride (0.05 g, 0.002 mole) was added and the mixture stirred for 30 minutes. Benzyl chloride (0.21 ml, 0.0018 mole) was then added and the mixture stirred overnight at room temperature. After cautiously treating with water, the mixture was extracted with chloroform and dried over sodium sulfate. After evaporation of the solvent, DMF was distilled under vacuum and the residue triturated with methyl ethyl ketone to give the desired **4d**, yield 80%, mp 61-63° (ethanol); ir: 1690 (CO) cm^{-1}; ^1H nmr: δ 1.5-1.7 (m, 4H), 2.2-2.6 (m, 6H), 3.0 (s, 2H), 3.5 (s, 2H), 4.5 (s, 2H), 7.4 (s, 10H).

2-Benzyloxy-8-methyl-2,8-diazaspiro[4.5]decan-3-one **5e**.

Compound **5e** was prepared as above described for **4d**, starting from **5a**, yield 83%, mp 62-63° (ethanol); ir: 1690 (CO) cm^{-1}; ^1H nmr: δ 1.4-1.6 (m, 4H), 2.1-2.3 (m, 9H), 30 (s, 2H), 5.0 (s, 2H), 7.3 (s, 5H).

Pharmacology.

All compounds have been tested according to reported procedures [4-7]. The following protocol has been used: Pharmacokinetics in anesthetized cat; nictitating membrane in anesthetized cat; bladder pressure in pithed rat; spontaneous motility and passive avoidance in rat; isolated ileum in guinea pig.

Mouse: Irwin's test, hypothermia, tremor induction, interaction with apomorphine and oxotremorine; rat cerebral cortex: binding studies, using ^3H-QNB as ligand.

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* To whom correspondance should be addressed.

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