Synthesis of a New Series of *N*-Substituted-3-[1-alkyl(aryl)-4-piperidyl]azetidin-2-ones as Possible Muscarinic Agents

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Dedicated to the memory of Dr. Roland K. Robins

A new series of *N*-substituted-3-[1-alkyl(aryl)-4-piperidyl]azetidin-2-ones **2a-j** structurally related to the previously reported 2,7-diazaspiro[3.5]nonan-1-ones **1** have been synthesized and tested for their activity as muscarinic agents, both *in vitro* and *in vivo*. Preliminary pharmacological results showed that compounds **2** are devoid of significant cholinergic properties.

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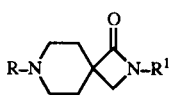
The muscarinic agonist RS-86 has been used in the treatment of Alzheimer's disease starting from 1982 [1] and since then a great effort has been made to derive new derivatives, possibly provided with higher potency and selectivity at the muscarinic receptors [2-6].

In a previous paper [7] we reported the synthesis of a series of substituted 2,7-diazaspiro[3.5]nonan-1-ones **1**, structurally related to RS-86. Though none of the compounds **1** was found to possess muscarinic affinity comparable to that of the model, some of them displayed weak cholinergic properties. To further define the structural requirements for optimum activity of this class, we have now synthesized a new series of *N*-substituted-3-(1-alkyl(aryl)-4-piperidyl)azetidin-2-ones **2**, formally derived from **1** by connecting the azetidinone ring to the piperidine moiety through a covalent bond.

We describe in this paper the synthesis of compounds **2a-j** (see Scheme 1 for symbols).



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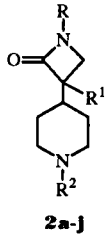
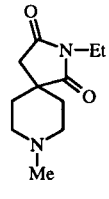


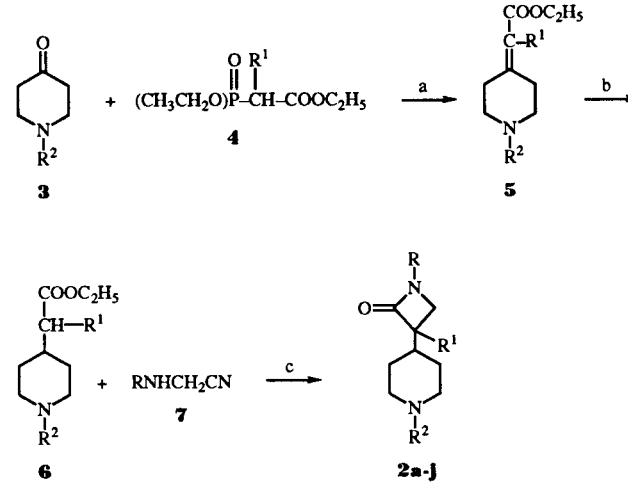
2a-j



RS-86

As shown in Scheme 1, compounds **2** were prepared starting from the appropriate *N*-substituted piperidones **3** which were condensed with the required ethyl phosphonate **4** to give the unsaturated esters **5**. Catalytic reduction of **5** in the presence of 10% Pd/C or PtO_2, depending on the *N*-substituent, gave the corresponding esters **6**, which were cyclized to the desired **2** by treatment at $-70°$ with the appropriate *N*-cyanomethylamines **7** and lithium diisopropylamide (LDA), generated *in situ* from diisopropylamine and buthyllithium. The thus obtained **2a-j** were then purified by silica gel chromatography, followed by distillation under vacuum or crystallization. The required *N*-cyanomethylamines **7** were in turn prepared from the corresponding amines by treatment with potassium cyan-

Scheme 1

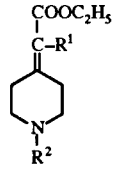


a) NaH/C_6H_6 b) 10% Pd/C or PtO_2/H_2/EtOH c) LDA/THF/-70°C

Compound	R	R^1	R^2
2a	C_2H_5	CH_3	$CH_2C_6H_5$
2b	C_6H_5	H	$CH_2C_6H_5$
2c	$CH_2C_6H_5$	H	CH_3
2d	C_6H_5	H	CH_3
2e	$CH_2C_6H_5$	H	$CH_2C_6H_5$
2f	C_6H_5	CH_3	$CH_2C_6H_5$
2g	C_2H_5	H	$CH_2C_6H_5$
2h	C_2H_5	H	C_2H_5
2i	C_2H_5	H	CH_3
2j	C_6H_5	CH_3	CH_3

Table I

Physical Properties of Compounds **5**, **6**



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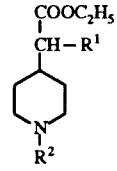

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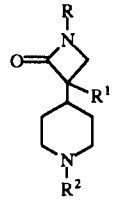
Compound	R^1	R^2	Yield %	bp C/mm HG	IR cm^{-1}	^{1}H-nmr δ (ppr)
5a	CH_3	$CH_2C_6H_5$	95	150/0.5	1710	1.2 (t, 3H), 1.9 (s, 3H), 2.1-2.7 (m, 8H), 3.5 (s, 2H), 4.2 (q, 2H), 7.4 (s, 5H)
5b	H	$CH_2C_6H_5$	72	oil [a,b]	1710	1.2 (t, 3H), 2.1-2.6 (m, 6H), 2.9-3.1 (m, 2H), 3.5 (s, 2H), 4.2 (q, 2H), 5.6 (s, 1H), 7.4 (s, 5H)
5c	H	CH_3	83	60/0.1	1710	1.3 (s, 3H), 2.2-2.6 (m, 9H), 2.9-3.1 (m, 2H), 4.2 (q, 2H), 5.7 (s, 1H)
5h	H	C_2H_5	90	76/0.01	1710	1.0-1.9 (m, 6H), 2.2-2.7 (m, 8H), 2.9-3.1 (m, 2H), 4.2 (q, 2H), 5.7 (s. 1H)
5j	CH_3	CH_3	94	129/20	1710	1.3 (t, 3H), 1.9 (s, 3H), 2.3 (s, 3H), 2.4-2.7 (m, 8H), 4.2 (q, 2H)
6a	CH_3	$CH_2C_6H_5$	80	150/0.5	1720	1.1-2.0 (m, 14H), 2.8-3.1 (m, 2H), 3.5 (s, 2H), 4.2 (q, 2H), 7.3 (s, 5H)
6b	H	$CH_2C_6H_5$	94	140/0.4	1720	1.3 (t, 3H), 1.5-2.2 (m, 9H), 2.6-3.1 (m, 2H), 3.5 (s, 2H), 4.1 (q, 2H), 7.3 (s, 5H)
6c	H	CH_3	90	16	1720	1.3 (t, 3H), 1.9-2.4 (m, 9H), 2.9 (s, 3H), 3.4-3.6 (m, 2H), 4.2 (q, 2H)
6h	H	C_2H_5	87	16	1730	1.0-1.4 (m, 6H), 1.5-2.4 (m, 9H), 2.7-3.1 (m, 4H), 4.2 (q, 2H)
6j	CH_3	CH_3	92	oil [a,c]	1730	1.3 (t, 6H), 1.4-2.0 (m, 8H), 2.3 (s, 3H), 2.8-3.0 (m, 2H), 4.2 (q, 2H)

[a] Purified by silica gel chromatography. [b] Eluent chloroform/ethyl acetate 8/2. [c] Eluent chloroform/methanol 95/5.

Table II

Physical Properties of Compounds **2**



2a-j

Compound	R	R^1	R^2	Yield %	Mp °C or Bp °C/mmHg	Formula	^{1}H-nmr δ (ppm)
2a	C_2H_5	CH_3	$CH_2C_6H_5$	42	168/0.04	$C_{18}H_{26}N_2O$	1.1 (t, 3H), 1.3 (s, 3H), 1.3-2.2 (m, 7H), 2.7-3.4 (m, 6H), 3.5 (s, 2H), 7.3 (s, 5H)
2b	C_6H_5	H	$CH_2C_6H_5$	48	126-128 [a]	$C_{21}H_{24}N_2O$	1.4-2.3 (m, 7H), 2.7-3.8 (m, 5H), 3.5 (s, 2H), 7.3 (s, 10H)
2c	$CH_2C_6H_5$	H	CH_3	39	150/0.03	$C_{16}H_{22}N_2O$	1.1-2.1 (m, 7H), 2.3 (s, 3H), 2.7-3.4 (m, 5H), 4.4 (s, 2H), 7.3 (s, 5H)
2d	C_6H_5	H	CH_3	41	69-71 [a]	$C_{15}H_{20}N_2O$	1.4-2.5 (m, 7H) 2.3 (s, 3H), 2.7-3.8 (m, 5H), 7.1-7.5 (m, 5H)
2e	$CH_2C_6H_5$	H	$CH_2C_6H_5$	25	190/0.04	$C_{22}H_{26}N_2O$	1.1-2.3 (m, 7H), 2.7-3.4 (m, 5H), 3.5 (s, 2H), 4.4 (d, 2H), 7.3 (s, 10H)
2f	C_6H_5	CH_3	$CH_2C_6H_5$	50	170/0.04	$C_{22}H_{26}N_2O$	1.1-2.2 (m, 7H), 1.4 (s, 3H), 2.8-3.8 (m, 6H), 7.3 (s, 10H)

2g	C_2H_5	H	$CH_2C_6H_5$	28	155/0.07	$C_{17}H_{24}N_2O$	1.1 (t, 3H), 1.3-2.3 (m, 7H), 2.7-3.4 (m, 7H). 3.5 (s, 2H), 7.3 (s, 5H)
2h	C_2H_5	H	C_2H_5	25	100/0.03	$C_{12}H_{22}N_2O$	0.9-1.3 (m, 6H), 1.3-2.2 (m, 7H), 2.4 (q, 2H), 2.8-3.5 (m, 7H)
2i	C_2H_5	H	CH_3	28	100/0.04	$C_{11}H_{20}N_2O$	1.1 (t, 3H), 1.3-2.2 (m, 7H), 2.2 (s, 3H), 2.7-3.5 (m, 7H)
2j	C_6H_5	CH_3	CH_3	40	150/0.04	$C_{16}H_{22}N_2O$	1.4 (s, 3H), 1.6-2.0 (m, 7H), 2.3 (s, 3H), 2.8-3.1 (m, 2H), 3.5 (q, 2H), 7.4 (s, 5H)

[a] Crystallized from cyclohexane.

Table III

Elemental Analyses

Compound	M.W.	Calcd./Found % C	H	N
2a	286.4	75.48	9.15	9.78
		75.53	9.06	9.73
2b	320.4	78.72	7.55	8.74
		79.03	7.60	9.14
2c	258.3	74.38	8.58	10.84
		74.08	8.75	10.70
2d	244.3	73.74	8.25	11.46
		73.53	8.26	11.29
2e	334.4	79.01	7.84	8.38
		78.86	7.81	8.41
2f	334.4	79.01	7.84	8.38
		79.17	7.92	8.28
2g	272.4	74.96	8.88	10.28
		74.66	8.90	9.89

ide and aqueous formaldehyde, according to Overman [8]. Only the *N*-phenylcyanomethylamine (**7d**) was obtained by directly condensing aniline with chloroacetonitrile in the presence of triethylamine [9].

Compounds **2a-j** have been tested both *in vitro* and *in vivo* for their cholinergic properties. None of them showed significant activity when compared to the model RS-86.

EXPERIMENTAL

Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. The ir spectra were recorded 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.

General Procedure for the Synthesis of Esters **6**.

a) To a suspension of 80% sodium hydride (0.26 mole) in anhydrous benzene (100 ml) the required ethyl phosphonate **4** (0.26 mole) was added under nitrogen at such a rate to keep the temperature below 30°. The mixture was further stirred at room temperature for 1 hour and then a solution of the appropriate piperidone **3** (0.26 mole) in anhydrous benzene (50 ml) was added. After stirring for additional 15 minutes water (100 ml) was added, the organic layer separated and the aqueous phase extracted with benzene. The reunited organic layers were dried over sodium sulfate, the solvent evaporated and the unsaturated ester **5** purified by silica gel chromatography or distillation under vaccum (see Table I for data).

b) A mixture of the required **5** and 10% Pd/C (10/1 w/w) in ethanol was hydrogenated at room temperature. The catalyst was filtered off, the solvent evaporated and the residue purified by distillation under vacuum. When starting from *N*-benzyl-substituted **5**, PtO_2 was used as catalyst (see Table I for data).

N-(Cyanomethyl)ethylamine **7a**.

To a solution of sodium bisulfite in water (40 g) 37% formaldehyde (17.0 g, 0.22 mole) and ethylamine (10.0 g, 0.22 mole) were added, followed by a solution of KCN (14.4 g, 0.22 mole) in water (20 ml). The mixture was stirred for 15 minutes, treated with a saturated solution of sodium chloride (20 ml) and then extracted with ether. After evaporation of the solvent, **7a** was obtained by distillation (49%), bp 90°/25 mm Hg [10]; ir: (oil) 3340 (NH), 2240 (C≡N) cm^{-1}; ^1H nmr: δ 1.1 (t, 3H), 1.4 (s, 1H), 2.8 (q, 2H), 3.6 (s, 2H).

N-(Cyanomethyl)benzylamine **7b**.

Compound **7b** was prepared as above reported for **7a**, starting from benzylamine, yield 83%, bp 100°/0.7 mm Hg [11]; ir: (oil) 3340 (NH), 2240 (C≡N) cm^{-1}; ^1H nmr: δ 1.8 (s, 1H), 3.6 (s, 2H), 4.0 (s, 2H), 7.5 (s, 5H).

N-(Cyanomethyl)-*p*-methoxybenzylamine **7c**.

Compound **7c** was prepared as above reported for **7a**, starting from *p*-methoxybenzylamine, but it was purified by silica gel chromatography (eluent cyclohexane/ethyl acetate 7/3), yield 58% ir: (oil) 3340 (NH), 2240 (C≡N) cm^{-1}; ^1H nmr: δ 1.6 (s, 1H), 3.5 (s, 2H), 3.7 (s, 3H), 3.8 (s, 2H), 6.8 (d, 2H), 7.3 (d, 2H).

N-(Cyanomethyl)phenylamine **7d**.

A mixture of aniline (15.7 g, 0.17 mole), triethylamine (23.4 ml, 0.17 mole) and chloroacetonitrile (10 ml, 0.17 mole) in ethanol (100 ml) was refluxed for 4 hours. After evaporation of the ethanol, the residue was treated with ethyl acetate and the precipitate which formed filtered off. The organic layer was washed with water, the solvent evaporated and the residue distilled under vacuum to give in the order the unreacted aniline and **7d**, yield 22%, bp 150°/0.6 mm Hg [9]; ir: (oil) 3400 (NH), 2250 (C≡N) cm^{-1}; ^1H nmr: δ 3.6 (s, 1H), 3.7 (s, 2H), 6.2-7.1 (m, 5H).

General Procedure for the Synthesis of *N*-Substituted-3-(1-alkyl-(aryl)-4-piperidyl)azetidin-2-ones **2**.

To a solution of diisopropylamine (7.1 ml, 0.05 mole) in anhydrous THF (190 ml) cooled at −70° and under nitrogen, a 2.5 *M* solution of *n*-butyllithium (20 ml; 0.05 mole) was added dropwise. After stirring for 30 minutes, a solution of the appropriate ester **6** (0.047 mole) in anhydrous THF (50 ml) was added. Stirring was continued for 1 hour at −70° and then a solution of the required *N*-cyanomethylamine (**7**, 0.024 mole) in THF was added. After 1 hour, cooling was interrupted and the mixture stirred for further 20 hours. A solution of ammonium chloride (18.0 g, 0.36 mole) in water (120 ml) was then added and the mixture extracted with chloroform. After evaporation of the solvent the residue was purified by silica gel chromatography (chloroform/methanol 9/1) to give the desired **2** (see Table II for data).

Pharmacology.

All compounds have been tested according to reported procedures [12-15]. 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 ^{3}H-QNB as ligand.

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* To whom correspondance should be addressed.

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