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SHORT PAPER

Synthesis of the selective antimuscarinic agent 4-{[cyclohexylhydroxy(2-methoxyphenyl)silyl]-methyl}-1,1-dimethylpiperazinium methyl sulfate (*o*-methoxy-sila-hexocyclium methyl sulfate)

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The synthesis of the potent and highly selective silicon-containing antimuscarinic agent *o*-methoxy-sila-hexocyclium methyl sulfate and its corresponding tertiary amine (isolated as the dihydrochloride) is described. The quarternary compound is an *o*-methoxy derivative of sila-hexocyclium methyl sulfate, which represents one of the tools currently used in experimental pharmacology for the subclassification of muscarinic receptors. The *o*-methoxy derivative, the pharmacological profile of which differs substantially from that of the non-methoxy compound, is also recommended as a tool for the investigation of muscarinic receptor heterogeneity.

Keywords: *o*-methoxy-sila-hexocyclium, sila-hexocyclium, sila-drugs, antimuscarinics, muscarinic receptor subtypes

INTRODUCTION

Recently, we reported on the synthesis of the selective antimuscarinic agent sila-hexocyclium methyl sulfate (**1b**, Scheme 1).[1] This silanol, a silicon analogue of the spasmolytic and anti-ulcer agent hexocyclium methyl sulfate (**1a**, Scheme 1), has become an important tool in experimental pharmacology for the classification of subtypes of muscarinic receptors.[2,3] It shows approximately the same high affinity to muscarinic M1 receptors in neuronal tissues and to M2β receptors in smooth muscle organs and exocrine glands, whereas its antimuscarinic potency at cardiac M2α receptors is lower by more than one order of magnitude.

The corresponding *o*-methoxy derivative, *o*-methoxy-sila-hexocyclium methyl sulfate (**4**), was also found to be a potent and highly selective antimuscarinic agent. The pharmacological profile, however, differs substantially from that of sila-hexocyclium methyl sulfate (**1b**).[4] A 22-fold difference in the affinity was found for **4** on neuronal M1 receptors compared with the affinity to M2β receptors in smooth muscle. Additionally, the affinity found for this agent on cardiac M2α receptors was lower than on M2β receptors by a factor of 3.5. Thus, the difference in affinity for *o*-methoxy-sila-hexocyclium methyl sulfate (**4**) for M1 over M2α receptors is 78-fold. To the best of our knowledge, silanol **4** is the first quaternary ammonium compound with high M1 receptor selectivity.

Here we report on the synthesis of *o*-methoxy-sila-hexocyclium methyl sulfate (**4**). In addition, the synthesis of its corresponding tertiary amine (isolated as the dihydrochloride **5**) is described, the antimuscarinic properties of which are currently under investigation. This paper represents a further report on our systematic studies on sila-substituted drugs (for recent reviews on this subject, see Refs 5 and 6).

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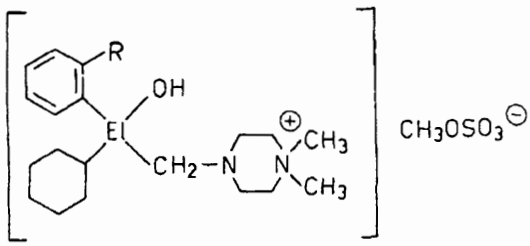


	El	R
1a	C	H
1b	Si	H
4	Si	OCH_3

Scheme 1

EXPERIMENTAL

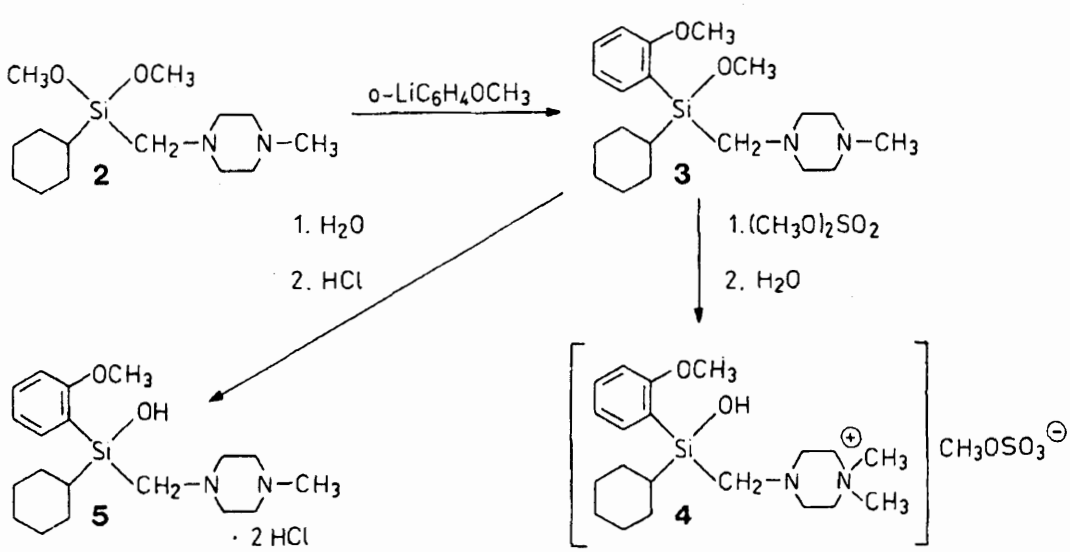
All synthetic procedures were performed under a nitrogen atmosphere and in dried solvents unless otherwise stated. Melting points were determined using a Kofler apparatus and are reported without correction. ^1H and ^{13}C NMR spectra were recorded on a Bruker WM-400 spectrometer operating at 400.1 and 100.6 MHz, respectively. Chemical shifts (ppm) were measured with respect to those of $(CH_3)_4Si$ (^1H, δ = 0) and $CDCl_3$ (^{13}C, δ = 77.05) as internal references. Assignment of the ^{13}C data was supported by DEPT (distortionless enhancement by polarization transfer) experiments. Mass spectra were obtained on a Finnigan-MAT-8430 mass spectrometer [EI MS: 70 eV; FAB MS: glycerol (liquid matrix), xenon (FAB source)]. The *m/z* values given are related to the isotopes ^1H, ^{12}C, ^{14}N, ^{16}O and ^{28}Si.

Cyclohexyldimethoxy[(1-methylpiperazin-4-yl)methyl]silane (2)

This compound (Scheme 2) was prepared according to Ref. 1.

Cyclohexylmethoxy(2-methoxyphenyl)-[(1-methylpiperazin-4-yl)methyl]silane (3)

A solution of n-butyllithium (60 mmol) in n-hexane (37.5 cm^3) was added dropwise at −30°C to a stirred solution of *o*-bromoanisole (11.2 g, 60 mmol) in diethyl ether (60 cm^3). After stirring for 2 h at −30°C, the reaction mixture was added dropwise within 20 min to a stirred solution of **2** (15.0 g, 52.4 mmol) in diethyl ether (200 cm^3) at 0°C. After stirring for 1 h at room temperature and heating at reflux for 3 h, the reaction mixture was cooled to room



Scheme 2

temperature. The insoluble material was filtered off and the filtrate was concentrated *in vacuo*. n-Hexane (200 cm^3) was added to the residue and the precipitate formed was filtered off. After concentrating the filtrate under reduced pressure, the remaining oily residue was distilled *in vacuo* (short Vigreux column) to give 12.9 g (yield 68%) of a colourless liquid, b.p. 164°C/0.005 Torr. ^1H NMR ($CDCl_3$): δ 1.0–1.3, 1.55–1.75 (m, 11H; SiC_6H_{11}), 2.20 (s, 3H; NCH_3), 2.25 and 2.34 (AB system, J_{AB} = 14.8 Hz, 2H; $SiCH_2N$), 2.15–2.6 (m, 8H; CCH_2N), 3.60 (s, 3H; $SiOCH_3$), 3.75 (s, 3H; $COCH_3$), 6.75–7.55 (m, 4H; aryl H). ^{13}C NMR ($CDCl_3$): δ 25.8 (C-1, SiC_6H_{11}), 26.8, 26.9 (2C), 27.9 and 28.0 (C-2–C-6, SiC_6H_{11}), 45.9 (NCH_3), 46.2 ($SiCH_2N$), 51.6 ($SiOCH_3$), 54.6 ($COCH_3$), 55.5 (2C) and 56.7 (2C) (CCH_2N), 109.3 (C-3, aryl C), 120.4 (C-5, aryl C), 123.2 (C-1, aryl C), 131.0 (C-4, aryl C), 136.0 (C-6, aryl C), 163.8 (C-2, aryl C). EI MS: *m/z* 362 (40%, M^+), 113 (100%, $C_6H_{13}N_2^+$). Calcd. for $C_{20}H_{34}N_2O_2Si$: C, 66.25; H, 9.45; N 7.73. Found: C, 66.1; H, 9.5; N, 7.8%.

4-{[Cyclohexylhydroxy-(2-methoxyphenyl)silyl]methyl}-1,1-dimethylpiperazinium methyl sulfate (*o*-methoxy-sila-hexocyclium methyl sulfate) (4)

Dimethyl sulfate (1.12 g, 8.88 mmol) was added dropwise at 0°C to a stirred solution of **3** (3.25 g, 8.96 mmol) in acetone (80 cm^3). After stirring for 12 h at 20°C, the solvent was removed *in vacuo* and diethyl ether (150 cm^3) was added to the residue. The solid material formed was separated by filtration, washed with diethyl ether (80 cm^3) and dried *in vacuo* at 50°C. The solid was dissolved in water (120 cm^3) and the resulting solution was stirred for 1 h at 50°C. After removing the water *in vacuo*, the solid residue was crystallized from acetone/diethyl ether (2:1, v/v) to give 2.7 g (yield 64%) of colourless crystals, m.p. 129°C. ^1H NMR ($CDCl_3$): δ 0.85–1.3, 1.5–1.8 (m, 11H; SiC_6H_{11}), 2.33 and 2.36 (AB system, J_{AB} = 14.7 Hz, 2H; $SiCH_2N$), 2.6–2.8 (m, 4H; CCH_2N), 3.21 (s, 6H; NCH_3, 3.35–3.5 (m, 4H; CCH_2N^+), 3.64 (s, 3H; $SOCH_3$), 3.80 (s, 3H; $COCH_3$), 4.1 ('s', broad, 1H; SiOH), 6.75–7.55 (m, 4H; aryl H). ^{13}C NMR ($CDCl_3$): δ 26.3 (C-1, SiC_6H_{11}), 26.8 (3C), 27.9 and 28.0 (C-2– C-6, SiC_6H_{11}), 46.3 ($SiCH_2N$), 50.1 (2C) (CCH_2N), 51.3 (2C) (NCH_3), 54.4 and 55.0 ($SOCH_3$, $COCH_3$), 62.0 (2C) (CCH_2N^+), 109.5 (C-3, aryl C), 120.9 (C-5, aryl C), 123.9 (C-1, aryl C), 131.4 (C-4, aryl C), 135.8 (C-6, aryl C), 163.6 (C-2, aryl C). FAB MS: *m/z* 363 (cation of **4**). Calcd. for $C_{21}H_{38}N_2O_6SSi$: C, 53.14; H, 8.07; N, 5.90. Found: C, 53.0; H, 8.1; N, 5.8%.

Cyclohexylmethoxy(2-methoxyphenyl)-[(1-methylpiperazin-4-yl)methyl]silanol dihydrochloride (5)

Water (1 cm^3) was added to a solution of **3** (1.00 g, 2.76 mmol) in diethyl ether (70 cm^3), and the resulting reaction mixture was stirred for 1 h at 20°C. The organic layer was quickly separated, dried over anhydrous Na_2SO_4 and cooled to 0°C. A 0.5 mol dm^{-3} solution of hydrogen chloride in diethyl ether (14 cm^3) was added and the reaction mixture was stirred for 5 min. The resulting precipitate was collected by filtration and crystallized from acetonitrile to give 0.9 g (yield 77%) of colourless crystals, m.p. 194–197°C. ^1H NMR ($CDCl_3$): δ 0.9–1.1, 1.1–1.4, 1.5–1.9 (m, 11H; SiC_6H_{11}), 2.87 (s, 3H; NCH_3), 2.9–3.0 (m, 2H; $SiCH_2N$), 3.15–4.0 (m, 8H; CCH_2N), 3.84 (s, 3H; OCH_3), 5.4 ('s', broad, 1H; SiOH), 6.85–7.65 (m, 4H; aryl H), 12.2 ('s', broad; NH), 13.4 ('s', broad; NH). ^{13}C NMR ($CDCl_3$): δ 25.7 (C-1, SiC_6H_{11}), 26.3, 26.4, 26.5, 27.5 and 27.6 (C-2–C-6, SiC_6H_{11}), 43.0 (NCH_3), 46.7 ($SiCH_2N$), 50.2, 50.3 and 52.7 (2C) (CCH_2N), 55.3 (OCH_3), 109.7 (C-3, aryl C), 121.0 (C-1, aryl C), 121.6 (C-5, aryl C), 132.8 (C-4, aryl C), 136.1 (C-6, aryl C), 163.0 (C-2, aryl C). FAB MS: *m/z* 349 (dication – H^+). Calcd. for $C_{19}H_{34}Cl_2N_2O_2Si$: C, 54.14; H, 8.13; Cl, 16.82; N, 6.65. Found: C, 54.5; H, 8.3; Cl, 16.6; N, 6.6%.

RESULTS AND DISCUSSION

The synthesis of *o*-methoxy-sila-hexocyclium methyl sulfate (**4**) is based on the approach developed for the preparation of the parent compound sila-hexocyclium methyl sulfate (**1b**) (see Ref. 1). Starting from readily available cyclohexyldimethoxy[(1-methylpiperazin-4-yl)methyl]silane[1] (**2**), **4** was prepared by a three-step synthesis with an overall yield of 44%. In the first

step, the *o*-methoxyphenyl group was introduced by reaction of **2** with *o*-methoxyphenyllithium in diethyl ether to give the corresponding arylsilane **3** (yield 68%). Reaction of **3** with one equivalent of dimethyl sulfate in acetone at 20°C resulted in a selective quaternization of the nitrogen atom of the nitrogen–methyl ($N-CH_3$) group. Because of crystallization problems, the respective ammonium derivative (characterized by ^1H NMR, ^{13}C NMR and FAB MS; data not given) could not be isolated as an analytically pure compound. Thus, after separation from the solvent and washing with diethyl ether, the quaternary product was hydrolyzed directly, without further purification, to give the silanol **4**, which was obtained (after recrystallization from acetone/diethyl ether) in the form of analytically pure crystals (yield 64%, based on **3**).

Hydrolysis of the methoxysilane **3** yielded the corresponding silanol which was not isolated and purified but converted directly into the dihydrochloride **5**. After recrystallization from acetonitrile, **5** was obtained as an analytically pure compound (yield 77%, based on **3**).

In the solid state, the silanols **4** and **5** are stable compounds which can be stored in closed flasks at room temperature without decomposition. In contrast, by analogy with other structurally related silanols, **4** and **5** can undergo a condensation reaction in solution to give the corresponding disiloxanes. However, the stability in diluted aqueous solution at room temperature was found to be sufficient to carry out the pharmacological experiments without special stability-related precautions.

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