1-Benzyl-4-chloromethylpiperidine: A Building Block in the Synthesis of Compounds of Pharmacological Interest

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Abstract: The first synthesis of 1-benzyl-4-(chloromethyl)piperidine (**1**) is described, together with its application in the synthesis of potential pharmaceuticals. Reaction of **1** with several purines in basic medium proceed through the initial formation of 1-benzyl-1-azoniabicyclo[2.2.1]heptane system, which then undergoes nucleophilic attack at two different carbons, yielding *N*-benzylpiperidine and *N*-benzylpyrrolidine derivatives.

Key words: *N*-benzylpiperidines, *N*-benzylpyrrolidines, purines, alkylations, rearrangements

The *N*-benzylpiperidine moiety is present in a wide variety of bioactive compounds, e.g. acetylcholinesterase inhibitors,[2,3] sigma receptor ligands,[4] dopamine and *N*-methyl-D-aspartate receptor antagonists,[5,6] dopamine and serotonin transporter analogs,[7,8] etc. On other hand, the purine ring is one of the most ubiquitous heterocycles in nature and its derivatives possess also a range of pharmacological activities, such antiviral,[9] anticancer,[10] hypoglycemic,[11] and memory-enhancing[12] profiles. In continuation of our work on the cholinergic agents of potential application in Alzheimer's disease, that either activate the neurotransmitter receptors (e.g. postsynaptic M_1 muscarinic agonists[13]) or increase acetylcholine level in the synaptic cleft (AChE inhibitors[14]), we are now interested in the synthesis of new compounds derived from *N*-benzylpiperidine and purines as potential acetylcholinesterase inhibitors (Figure).

Although the well known Mitsunobu reaction[15] has been successfully applied both to purines[16] and (hydroxymethyl)piperidines,[17] and we have previous experience in this type of transformations,[18] all our efforts to react several purines (namely, theophylline and 6-methylsulfanylpurine) and 1-benzyl-4-(hydroxymethyl)piperidine, in the presence of DEAD (diethyl azodicarboxylate) or DIAD (diisopropyl azodicarboxylate) and triphenylphosphine, failed. Then, we envisaged to use 1-benzyl-4-halomethylpiperidines as precursors (cf. Figure), and a bibliographic search showed that, despite their simple structure, they have not been described in the literature. In this paper we wish to describe the synthesis of 1-benzyl-4-(chloromethyl)piperidine (**1**) and its application as intermediate in the synthesis of pharmaceuticals, exemplified by its reactions with several purines in basic conditions.

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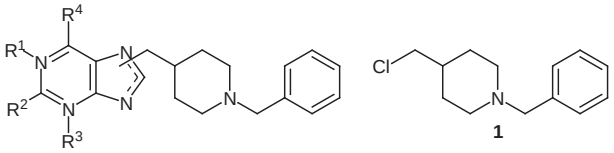
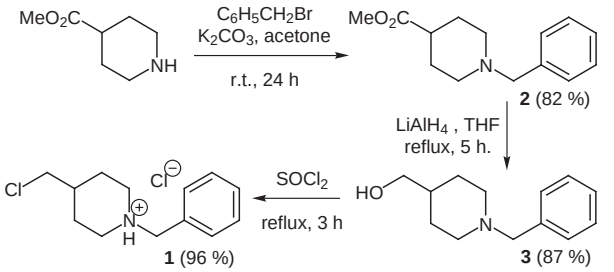


Figure The structures of purine-based compounds of pharmacological interest and 1-benzyl-4-chloromethylpiperidine (**1**).

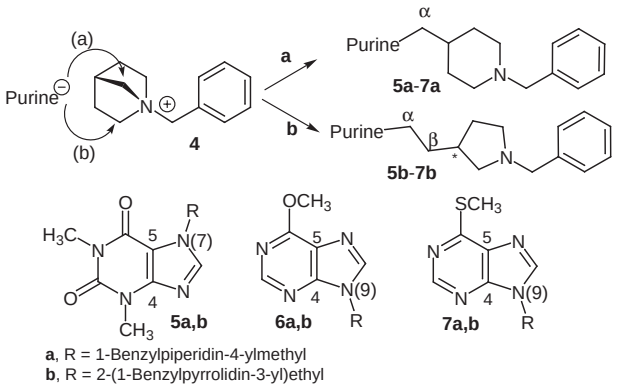
As shown in Scheme 1, 1-benzyl-4-(chloromethyl)piperidine (**1**) was prepared starting from commercially available methyl piperidine-4-carboxylate (methyl isonipecotinate). Treatment of **1** with benzyl bromide under basic conditions afforded the compound **2**, which after $LiAlH_4$ reduction produced the primary alcohol **3** in 71% yield. Compound **3** was then treated with thionyl chloride under reflux for 3 hours to give the desired chloromethyl derivative **1** as the hydrochloride, which was isolated as a stable white solid of (mp 139–140 °C).



Scheme 1

The reaction of several purines with the chloro derivative **1**, using sodium hydride as base and dimethoxyethane as solvent, afforded in all cases a mixture of two products that showed the same molecular peak in mass spectrometry, after their chromatographic separation. In the ^1H NMR spectrum of the first eluted product **5a**–**7a**, a symmetric subspectrum due to the nine protons of the piperidine moiety could be recognized, distributed in five separate signals (2,6-H_{eq}, 2,6-H_{ax}, 4-H, 3,5-H_{eq}, 3,5-H_{ax}). In contrast, the aliphatic subspectrum of the second product **5b**–**7b** did not resemble that of the 1,4-disubstituted piperidine moiety: the analogous nine protons appeared under eight signals, pointing out that it was a non-symmetric structure and suggesting that during the reaction a skeletal rearrangement could have occurred. Firstly in the basic medium the chloro derivative **1** could suffer an internal quaternization through a nucleophilic attack of the

basic nitrogen atom to the chlorine-bearing carbon,[19] yielding 1-benzyl-1-azoniabicyclo[2.2.1]heptane chloride **4** as intermediate (Scheme 2). Then, the nucleophilic attack of the sodium salt of the corresponding purine to this intermediate could follow two different ways. Ring opening through path **a** affords compounds derived from benzylpiperidine **5a**–**7a**, while pathway **b** yields benzylpyrrolidine derivatives **5b**–**7b**. Both of them were obtained as a mixture of stereoisomers due to the nonsymmetric structure of the 1,3-disubstituted pyrrolidine. Both benzylpiperidine and benzylpyrrolidine derivatives were isolated in moderate yields, probably due the stability of the quaternary ammonium intermediate **4**, according to a previous work concerning the reactivity of benzylquinuclidinium bromide towards nitrogen-containing heterocycles.[20] In addition, we isolated the stable intermediate **4** (see experimental part), that showed spectroscopic data in accordance with a related bicyclic structure previously described.[21]



a, R = 1-Benzylpiperidin-4-ylmethyl
b, R = 2-(1-Benzylpyrrolidin-3-yl)ethyl

Scheme 2

All new compounds showed combustion analyses and spectroscopic data in agreement with their structures. Although theoretically the purine ring can be alkylated at two different positions, N-7 or N-9, in these experimental conditions only one purine isomer could be isolated, according to the nature of the heterocyclic system. In each final product the position of alkylation was unequivocally established by NMR using a combination of bidimensional ^1H ^{13}C NMR experiments. Carbons attached to hydrogen atoms were easily assigned by HSQC experiments through their linkage to their respective hydrogens, and the carbons not containing hydrogens were elucidated with the use of HMBC experiments. Of paramount importance is the unambiguous assignment of carbons 4 and 5 of the purine heterocycle because they are the key to prove the position of the benzylpiperidine or benzylpyrrolidine fragment, knowing their linkage with the first methylene protons (α) (See Scheme 2).

Chemical shifts of purine carbons are summarized in Table 1. In theophylline derivatives **5a**,**b** the resonance at δ = 149.0 was assigned to carbon 4 since in the HMBC diagrams was the only signal that correlated simultaneously with the aromatic purine proton (8-H, at δ = 7.5) and a methyl group at δ = 3.5. Similarly, the resonance at δ = 107 that showed HMBC link with purine 8-H, but not with a methyl group, was attributed to carbon 5. In 6-methoxypurine and 6-methylthiopurine derivatives **6a**,**b** and **7a**,**b**, respectively, 4-C (δ = 150) was the only carbon that showed HMBC cross signals with both aromatic purine protons, δ(2-H) = 8.7 and δ(8-H) = 8.9, whereas 5-C (at δ = 121 in **6a**,**b** and at δ =131 in **7a**,**b**) only correlated with 8-H.

Table 1 ^{13}C NMR Chemical Shifts (δ) of the Purine Fragment of **5a**,**b**–**7a**,**b**

Product	2-C	4-C	5-C	6-C	8-C
5a	151.7	149.0	107.0	155.2	141.3
5b	151.6	148.9	106.9	155.1	140.7
6a	151.9	152.1	121.4	161.0	142.5
6b	152.0	152.0	121.5	161.1	141.9
7a	152.0	148.4	131.4	161.7	142.8
7b	151.8	148.2	131.3	161.5	142.3

In each final product the position of alkylation was established using the observed HMBC correlations between the α-methylene protons and purine 4-C or 5-C (Table 2). In theophylline derivatives **5a**,**b** the fact that the α methylene protons correlated with carbon 5, but not with carbon 4, demonstrated that alkylation occurred at nitrogen 7. Conversely, in 6-methoxypurine and 6-methylthiopurine compounds **6** and **7a**,**b**, the same methylene showed HMBC link with 4-C but not with 5-C, revealing that alkylation took place at 9-N.

Table 2 Key H-C Correlations (δ) of **5a**,**b**–**7a**,**b** by HMBC Experiments

		Purine Connected Carbons		
Product	α-CH_2	4-C	5-C	8-C
5a	4.15	–	107.0	141.3
5b	4.24	–	106.9	140.7
6a	4.09	152.1	–	142.5
6b	4.20	152.0	–	141.9
7a	4.11	148.4	–	142.8
7b	4.20	148.2	–	142.3

In conclusion, we have described the first synthesis of 1-benzyl-4-(chloromethyl)piperidine (**1**) and its usefulness as building block in the synthesis of pharmaceuticals, exemplified in its reaction towards several purines, affording *N*-benzylpiperidine and *N*-benzylpyrrolidine derivatives.

Reagents and solvents were purchased from common commercial suppliers and were used without further purification. THF and dimethoxyethane (DME) were freshly distilled from $LiAlH_4$ prior their use. Chromatographic separations were performed on silica gel, using flash column chromatography (silica gel 60 Merck of 230–400 mesh), and compounds were detected with UV light (254 nm), iodine chamber, or ninhydrin.

Melting points were determined with a Reichert-Jung Thermovar apparatus. NMR spectra were recorded in $CDCl_3$ solutions, using Varian Unity-500 and Varian XL-300 spectrometers. Typical spectral parameters for ^{1}H NMR were: spectral width 10 ppm, pulse width 9 μs (57°), data size 32 K. The acquisition parameters in decoupled ^{13}C NMR spectra were: spectral width 16 kHz, acquisition time 0.99 s, pulse width 9 μs (57°), data size 32 K. Chemical shifts are reported in δ values (ppm) relative to internal Me_4Si and *J* values are reported in Hertz. Other experiments such HSQC (Heteronuclear Single-Quantum Coherence) and HMBC (Heteronuclear Multiple Bond Correlation) were obtained under standard conditions. Mass spectra (MS) were obtained by electronic impact (EI) at 70 eV in a Hewlett-Packard 5973 spectrometer (with direct insertion probe), by atmospheric pressure chemical ionization (APCI), or by electrospray ionization (ES) in a Hewlett-Packard MSD 1100 spectrometer. Elemental analyses were carried out in a Perkin-Elmer 240C equipment in the Centro de Química Organica 'Manuel Lora-Tamayo' (CSIC) and the results are within ± 0.4% of the theoretical values.

Methyl 1-Benzylpiperidine-4-carboxylate (2)

Compound **2** was obtained as a pure colorless syrup in 82% yield from methyl piperidine-4-carboxylate (Aldrich), benzyl bromide and K_2CO_3, following a described method.[22]

^{1}H NMR ($CDCl_3$): δ = 7.24 (s, 5 H), 3.60 (s, 3 H), 3.42 (s, 2 H), 2.78 (dt, 2 H, *J* = 11.6, 2.8 Hz), 2.22 (m, 1 H), 1.94 (dt, 2 H, *J* = 11.6, 2.8 Hz), 1.74 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 175.7, 138.3, 129.0, 128.2, 126.9, 63.2, 52.9, 51.6, 41.4, 28.2.

MS (EI): *m*/*z* (%) = 91 (100), 142 (65), 202 (15), 218 (16), 233 (26, $M^{+\cdot}$).

1-Benzyl-4-(hydroxymethyl)piperidine (3)

Following described methods, reduction of **2** with $LiAlH_4$ in THF at reflux for 5 h afforded alcohol **3**[23] in 87% yield as a syrup.

^{13}C NMR ($CDCl_3$): δ = 137.9, 129.3, 128.1, 127.0, 67.6, 63.5, 53.3, 38.4, 28.2.

1-Benzyl-4-chloromethylpiperidine Hydrochloride (1)

To the alcohol **3** (240 mg, 1.17 mmol) was added $SOCl_2$ (5 mL) dropwise with ice cooling, and then the mixture was refluxed for 3 h. $SOCl_2$ was evaporated to dryness, the residue was treated with Et_2O and the white precipitate collected by filtration; yield: 295 mg (96%); mp 139–140 °C.

^{1}H NMR ($CDCl_3$): δ = 12.3 (br, 1 H), 7.43 (m, 5 H), 4.10 (d, 2 H, *J* = 4.9 Hz), 3.36 (m, 4 H), 2.55 (m, 2 H), 2.06 (m, 4 H), 1.74 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 131.5, 130.2, 129.3, 127.8, 60.9, 51.9, 47.8, 37.1, 26.9.

MS (EI): *m*/*z* = 91 (100), 132 (49), 146 (48), 188 (18), 223 (43, $M^{+\cdot}$), 225 (14, M^+ + 2).

MS (APCI): *m*/*z* = 260 (M + H).

N-Alkylation of Purines; General Procedure

To a stirred suspension of NaH (3.5 equiv, oil free) in anhyd DME was added a solution of the appropriate purine (1 equiv) in DME under N_2, and the mixture was refluxed. After 30 min, a solution of **1** (1 equiv) in DME was slowly added and the mixture was refluxed under N_2 for an additional 72 h. The mixture was cooled to r.t. and H_2O was carefully added. The resulting mixture was treated with a 15% aq solution of NH_4Cl until pH 8 and evaporated to dryness. The residue was redissolved in CH_2Cl_2 (25 mL), washed with H_2O (3 × 25 mL), brine (25 mL), dried (Na_2SO_4) and evaporated to dryness, yielding syrups that were purified by flash chromatography on silica gel columns.

7-[(1-Benzylpiperidin-4-yl)methyl]-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurine (5a) and 7-[2-(1-Benzylpyrrolidin-3-yl)ethyl]-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurine (5b)

Following the general method, the reaction of theophylline (110 mg, 0.60 mmol), chloro derivative **1** (148 mg, 0.60 mmol) and NaH (101 mg, 2.10 mmol, oil free) in DME (20 mL) gave a mixture of two products, that were separated by flash chromatography on a silica gel column, using CH_2Cl_2–MeOH (20:1) as eluent. Fractions of R_f 0.7 (CH_2Cl_2–MeOH, 5:1) afforded unreacted starting theophylline (10 mg, 9%).

5a

Isolated as a syrup from the fractions with R_f 0.6 (CH_2Cl_2–MeOH, 5:1); yield: 18 mg (8%).

^{1}H NMR ($CDCl_3$): δ = 7.48 (s, 1 H), 7.29 (m, 5 H), 4.15 (d, 2 H, *J* = 7.1 Hz), 3.60 (s, 3 H), 3.59 (s, 2 H), 3.49 (s, 3 H), 2.90 (br d, 2 H, *J* = 11.5 Hz), 1.95 (dt, 2 H, *J* = 11.5, 2.2 Hz), 1.92 (m, 1 H), 1.58 (br d, 2 H, *J* = 11.5), 1.38 (dq, 2 H, *J* = 11.5, 3.5 Hz).

^{13}C NMR ($CDCl_3$): δ = 155.2, 151.7, 148.9, 141.3, 139.8, 129.2, 128.2, 127.1, 107.0, 63.0, 52.8, 52.6, 36.7, 29.7, 29.4, 28.0.

MS (EI): *m*/*z* (%) = 91 (100), 276 (75), 367 (25, $M^{+\cdot}$).

5b

Isolated as a colorless syrup from the fractions with R_f 0.5 (CH_2Cl_2-MeOH, 5:1); yield: 32 mg (16%).

^{1}H NMR ($CDCl_3$): δ = 7.49 (s, 1 H), 7.31 (m, 5 H), 4.26 (ddd, 1 H, *J* = 14.1, 7.8, 6.2 Hz), 4.21 (ddd, 1 H, *J* = 14.1, 7.8, 6.2 Hz), 3.66 (d, 1 H, *J* = 12.5 Hz), 3.62 (d, 1 H, *J* = 12.5 Hz), 3.56 (s, 3 H), 3.38 (s, 3 H), 2.82 (dd, 1 H, *J* = 8.7, 7.2 Hz), 2.70 (ddd, 1 H, *J* = 8.9, 7.8, 6.2 Hz), 2.57 (ddd, 1 H, *J* = 8.9, 8.4, 6.3 Hz), 2.21 (dd, 1 H, *J* = 8.7, 6.8 Hz), 2.15 (m,1 H), 2.04 (ddt, 1 H, *J* = 12.3, 7.8, 6.3 Hz), 1.96 (m, 2 H), 1.51 (ddt, 1 H, *J* = 12.3, 8.4, 6.2 Hz).

^{13}C NMR ($CDCl_3$): δ = 155.1, 151.6, 148.9, 140.7, 137.8, 128.9, 128.3, 127.3, 106.9, 60.2, 59.4, 53.5, 46.1, 36.5, 34.6, 30.2, 29.7, 27.9.

MS (EI): *m*/*z* (%) = 91 (100), 276 (57), 367 (44, $M^{+\cdot}$).

9-(1-Benzylpiperidin-4-ylmethyl)-6-methoxy-9*H*-purine (6a) and 9-[2-(1-Benzylpyrrolidin-3-yl)ethyl]-6-methoxy-9*H*-purine (6b)

Following the general method, alkylation of 6-methoxypurine (182.3 mg, 1.15 mmol) with the chloro derivative **1** (300.0 mg, 1.15 mmol) in DME (40 mL), in the presence of NaH (165.0 mg, 3.44 mmol, oil free), afforded a crude syrup that was purified on a silica gel column using CH_2Cl_2–MeOH (20:1) as eluent. From the fractions of R_f 0.6 (CH_2Cl_2–MeOH, 5:1) starting 6-methoxypurine was recovered (25 mg, 14%).

6a

Fractions of R_f 0.5 (CH_2Cl_2–MeOH, 5:1) yielded compound **6a** (20 mg, 5%) as a colorless syrup.

^{1}H NMR ($CDCl_3$): δ = 8.51 (s, 1 H), 7.85 (s, 1 H), 7.25 (m, 5 H), 4.15 (s, 3 H), 4.09 (d, 2 H, *J* = 7.3 Hz), 3.44 (s, 2 H), 2.85 (br d, 2 H, *J* = 11.8 Hz), 1.92 (m, 1 H), 1.89 (dt, 2 H, *J* = 11.8, 2.3 Hz), 1.53 (br d, 2 H, *J* = 12.2 Hz), 1.34 (dq, 2 H, *J* = 12.2, 3.6 Hz).

^{13}C NMR ($CDCl_3$): δ = 161.0, 152.1, 151.9, 142.5, 138.2, 129.0, 128.1, 126.9, 121.4, 63.0, 54.1, 52.8, 49.6, 36.3, 29.8.

MS (EI): *m*/*z* (%) = 91 (100), 246 (93), 337 (23, $M^{+\cdot}$).

6b

From the fractions of R_f 0.3 (CH_2Cl_2–MeOH, 5:1) compound **6b** was isolated (52 mg, 14%) as a pure syrup.

^{1}H NMR ($CDCl_3$): δ = 8.52 (s, 1 H), 7.87 (s, 1 H), 7.28 (m, 5 H), 4.21 (t, 2 H, *J* = 6.8), 4.18 (s, 3 H), 3.61 (d, 1 H, *J* = 12.9 Hz), 3.57 (d, 1 H, *J* = 12.9 Hz), 2.78 (dd, 1 H, *J* = 8.1, 7.2 Hz), 2.65 (ddd, 1 H, *J* = 8.7, 7.7, 6.6 Hz), 2.51 (ddd, 1 H, *J* = 8.7, 8.3, 6.2 Hz), 2.15 (dd, 1 H, *J* = 8.1, 7.0 Hz), 2.10 (m, 1 H), 2.05 (m, 1 H), 1.98 (m, 2 H), 1.46 (ddt, 1 H, *J* = 12.2, 8.1, 6.1 Hz).

^{13}C NMR ($CDCl_3$): δ = 161.1, 152.0, 141.9, 138.5, 128.8, 128.3, 127.0, 121.5, 60.4, 59.7, 54.2, 53.6, 43.0, 35.7, 34.7, 30.3.

MS (EI): *m*/*z* (%) = 91 (100), 246 (45), 337 (12, $M^{+\cdot}$).

9-(1-Benzylpiperidin-4-ylmethyl)-6-methylsulfanyl-9*H*-purine (7a) and 9-[2-(1-Benzylpyrrolidin-3-yl)ethyl]-6-methylsulfanyl-9*H*-purine (7b)

From 6-methylsulfanyl-9*H*-purine (98 mg, 0.59 mmol), chloro derivative **1** (200 mg, 0.76 mmol) and NaH (128 mg, 2.67 mmol), and following the general method, a syrup was obtained. Its purification on a silica gel column using CH_2Cl_2–MeOH (20:1) as eluent yielded derivatives **7a** and **7b**. From the fractions of R_f 0.7 (CH_2Cl_2–MeOH, 5:1) unreacted starting purine was isolated (10 mg, 10%).

7a

Fractions of R_f 0.6 (CH_2Cl_2–MeOH, 5:1) afforded compound **7a** (29 mg, 13%) as a pure syrup.

^{1}H NMR ($CDCl_3$): δ = 8.71 (s, 1 H), 7.88 (s, 1 H), 7.26 (m, 5 H), 4.10 (d, 2 H, *J* = 7.2 Hz), 3.46 (s, 2 H), 2.86 (br d, 2 H, *J* = 11.6 Hz), 2.71 (s, 3 H), 1.92 (m, 1 H), 1.90 (dt, 2 H, *J* = 11.6, 2.2 Hz), 1.55 (br d, 2 H, *J* = 12.0 Hz), 1.35 (dq, 2 H, *J* = 12.0, 3.6 Hz).

^{13}C NMR ($CDCl_3$): δ = 161.7, 152.0, 148.4, 142.8, 138.1, 131.4, 129.1, 128.2, 127.0, 63.1, 52.8, 49.5, 36.4, 29.8, 11.7.

MS (EI): *m*/*z* (%) = 91 (100), 262 (25), 353 (5, $M^{+\cdot}$).

7b

Fractions of R_f 0.4 (CH_2Cl_2–MeOH, 5:1) yielded **7b** (60 mg, 29%) as a colorless syrup.

^{1}H NMR ($CDCl_3$): δ = 8.70 (s, 1 H), 7.90 (s, 1 H), 7.27 (m, 5 H), 4.20 (t, 2 H, *J* = 7.3), 3.59 (d, 1 H, *J* = 12.8 Hz), 3.56 (d, 1 H, *J* = 12.8 Hz), 2.74 (dd, 1 H, *J* = 8.7, 7.2 Hz), 2.71 (s, 3 H), 2.61 (ddd, 1 H, *J* = 8.8, 8.3, 6.0 Hz), 2.50 (ddd, 1 H, *J* = 8.8, 8.4, 6.1 Hz), 2.17 (dd, 1 H, *J* = 8.7, 6.5 Hz), 2.10 (m, 1 H), 2.04 (ddt, 1 H, *J* = 12.0, 8.3, 6.1 Hz), 1.97 (m, 2 H), 1.47 (ddt, 1 H, *J* = 12.0, 8.4, 6.0 Hz).

^{13}C NMR ($CDCl_3$): δ = 161.5, 151.8, 148.2, 142.3, 138.7, 131.3, 128.7, 128.2, 127.0, 60.3, 59.6, 53.6, 42.8, 35.6, 34.6, 30.3, 11.7.

MS (EI): *m*/*z* (%) = 91 (100), 262 (38), 353 (13, $M^{+\cdot}$).

1-Benzyl-1-azoniabicyclo[2.2.1]heptane Chloride (4)

A solution of **1** (50 mg, 0.19 mmol) in anhyd toluene (5 mL) was refluxed under N_2 for 24 h. The reaction mixture was cooled, the solvent evaporated to dryness and the residual brown syrup suspended in a mixture of CH_2Cl_2–Et_2O (ca. 1:1). Insoluble brown syrup was discarded and the supernatant liquid was evaporated to dryness in vacuo to afford the bicyclic compound **4** as a colorless syrup (25 mg, 58%).

^{1}H NMR ($CDCl_3$): δ = 7.58 (m, 2 H), 7.36 (m, 3 H), 5.12 (s, 2 H), 3.95 (m, 2 H), 3.67 (s, 2 H), 3.45 (m, 2 H), 2.84 (br s, 1 H), 2.20 (m, 2 H), 1.70 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 132.1, 130.3, 129.2, 128.9, 65.4, 60.3, 59.7, 35.1, 28.8.

MS (EI): *m*/*z* (%) = 91 (100), 97 (35), 188 (15, $M^{+\cdot}$).

MS (ES, positive mode): *m*/*z* = 188 (100%, $M^{+\cdot}$).

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