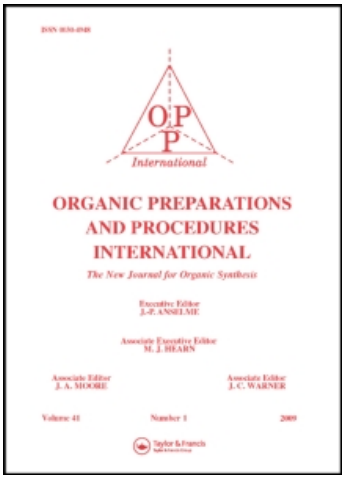

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ONE-POT SYNTHESIS OF 4-[2-(3, 4-DICHLOROPHENOXY)ETHYL]-1-PENTYLPIPERIDINE HYDROCHLORIDE (SB 201823-A)

Oskar Axelsson[a]; Dan Peters[a]
[a] NeuroSearch A/S, Glostrup, DENMARK

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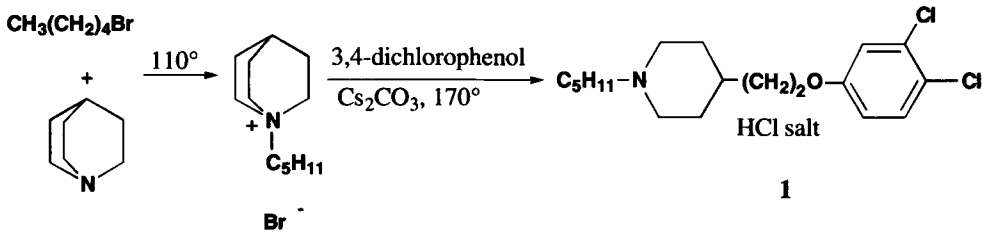
ONE-POT SYNTHESIS OF 4-[2-(3,4-DICHLOROPHENOXY)ETHYL]-1-PENTYLPIPERIDINE HYDROCHLORIDE (SB 201823-A)

Submitted by Oskar Axelsson* and Dan Peters
(02/13/95)

NeuroSearch A/S, 26B Smedeland
DK-2600 Glostrup, DENMARK

The experimental drug 4-[2-(3,4-dichlorophenoxy)ethyl]-1-pentylpiperidine (**1**, SB 201823-A) has been shown to protect against neuronal damage after brain ischemia in rats and to be a blocker of neuronal calcium channels.[1] We needed a sample of this compound for pharmacological evaluation but the published synthesis[2] used 4-(2-hydroxyethyl)piperidine, which is no longer commercially available, as the starting material. To overcome this problem, we devised a very convenient one-pot, two-step synthesis of **1** in 79% yield starting with quinuclidine, as outlined below.



EXPERIMENTAL SECTION

The NMR spectrum was recorded on a Bruker AM 500 MHz spectrometer with DMSO-d_6 as the solvent and chemical shifts are reported as ppm downfield from TMS. The mass spectrum was obtained on a JEOL JMS AX-505W double focusing mass spectrometer. The IR spectrum was recorded on a Perkin Elmer 1310 IR-spectrometer. Only the most prominent MS and IR peaks are reported. The melting point was determined with a Griffin melting point apparatus which was calibrated using the Aldrich Melting point standards kit.

Procedure.- Quinuclidine (1.11 g, 10 mmol) was quaternized by stirring with 1-bromopentane (1.51 g, 10 mmol) without solvent for 1 hr at 110°. To this salt was then added 3,4-dichlorophenol (2.44 g, 15 mmol) and cesium carbonate[3] (3.26 g, 10 mmol). The flask was flushed with nitrogen and the mixture was stirred at 170° (bath temperature) for 15 hrs. After cooling to room temperature, the solid was partitioned in a mixture of ether (50 mL) and water (50 mL). The phases were separated and the aqueous layer was extracted with another 50 mL portion of ether. The combined organic phases were dried over magnesium sulfate. The hydrochloride of **1** (3.0 g, 79%), pure according to TLC (CH_2Cl_2/EtOH, 9:1), could then be precipitated by the addition of methanolic HCl (2.5 mL of a 4.3 M solution), mp. 177-178°, lit.[2] 177-178°.
IR: 2940, 2500, 1470, 1360 cm^{-1}.

^{1}H NMR: δ 7.51 (d, J = 8.7 Hz, 1), 7.25 (d, J = 3.7 Hz, 1), 6.95 (dd, J_1 = 8.7 Hz, J_2 =3 .7 Hz, 1), 4.05 (t, J = 7.0 Hz, 2), 3.43 (d, J = 14.0 Hz, 2), 2.94 (m, 2), 2.83 (dd, J_1 = 12.9 Hz, J_2 = 10.7 Hz, 2), 1.88 (d, J = 13.5 Hz, 2), 1.75-1.60 (m, 5), 1.1.49-1.60 (m, 2), 1.35-1.25 (m, 4), 0.89 (t, 6.7 Hz, 3). EI MS: m/z = 343 (5%, molecular ion), m/z = 286 (base peak).

Anal. Calcd for $C_{18}H_{28}Cl_3NO$: C, 56.77; H, 7.41; N, 3.68. Found: C, 56.80; H, 7.63; N, 3.64

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2. T. H. Brown and D. G. Cooper, World Patent WO 92/02502; *Chem. Abs.*, **116**, 235459 (1992).

3. Cesium carbonate proved to be a much more efficient base than potassium carbonate. With the latter, only a 3% yield of **1** was obtained after 15 hrs at 195°. The crude product from this reaction was of much lower purity and required chromatographic purification.

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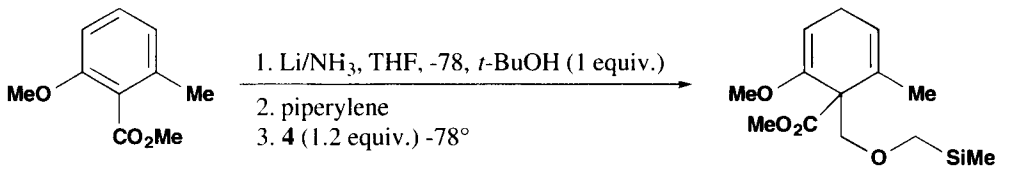
THE SYNTHESIS OF TRIMETHYLSILYLMETHOXYMETHYL CHLORIDE

Submitted by Arthur G. Schultz* and Yongwen Wang
(02/13/95)

Department of Chemistry
Rensselaer Polytechnic Institute
Troy, NY 12180-3590

The direct oxidation of aliphatic ethers is difficult because of their high oxidation potential (≥ 2.5 V vs. Ag/AgCl).[1] Substitution of a silyl group for a hydrogen atom at the α-position of ethers results in a significant decrease in oxidation potentials (1.6 to 1.7 V).[2] In connection with a study of photoinduced single electron transfer (SET) reactions in the 2,5-cyclohexadien-1-one series, we desired a practical synthesis of 1,4-cyclohexadiene **2** from methyl 2-methoxy-6-methylbenzoate (**1**).



1 **2**