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N-Benzylquinuclidinium bromide was ring opened by a series of heteronucleophiles, in the presence of cesium carbonate, to yield the corresponding *N*-benzyl-4-(2-hetero-ethyl)piperidines. The best yields were found with thiophenol (56%), phenol (55%), and benzimidazole (38%) as nucleophiles.

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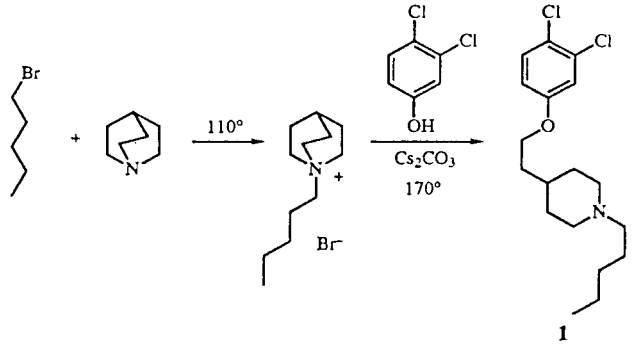
We recently described a convenient synthesis of the neuroprotective experimental drug 4-[2-(3,4-dichlorophenoxy)ethyl]-1-pentylpiperidine (**1**, SB 201823-A) [1,2]. The procedure, based on the nucleophilic ring-opening of an *N*-alkylquinuclidinium salt by a cesium phenolate [3], is outlined in Scheme 1. The satisfactory yield of **1** (79%), together with the fact that a number of biologically active compounds, potentially available by this type of reaction, have been described [4], prompted us to investigate the reactivity of a series of nucleophiles under these conditions.

Scheme 1



There is, to our knowledge, only one example of nucleophilic ring-opening of an alkylquinuclidinium salt in the literature and that is the thermal polymerization of a zwitterionic quinuclidinium salt [5]. A somewhat related example is the reaction of quinuclidine with phenylchloroformate to yield 1-phenoxycarbonyl-4-(2-chloroethyl)piperidine [6].

Results.

For this investigation benzylquinuclidinium bromide (**2**) was chosen as the common starting material instead of an alkyl salt as in the example in Scheme 1, since the benzyl group can be easily removed [7] after the ring-opening, making the synthetic sequence more general.

In Table 1 is shown the results of the reaction of a series of nucleophiles with **2**. Entries 1-3 show the results for three phenols. The unsubstituted phenol shows a selectivity for ring-opening over debenzylation that is very close to the 3:1 ratio expected from statistical considerations. However, the statistical ratio is not expected in the dealkylation of trialkyl benzyl quarternary ammonium salts since benzyl groups are generally cleaved off more easily than alkyl groups [8]. The relatively facile ring-opening is most likely an effect of the ring strain in the quinuclidine moiety where the three fused six-membered rings are in boat conformations. This strain is released in the ring-opened product but not in the debenzylated one.

Scheme 2

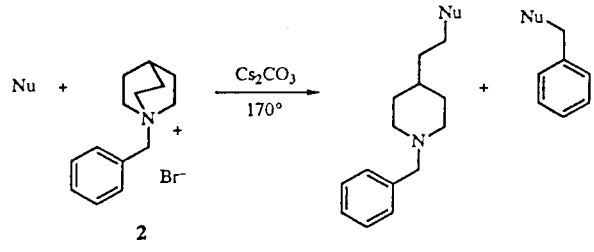


Table 1

Results from the Reaction of a Series of Nucleophiles with **2**

Entry	Nucleophile	Isolated yield (%)	Ratio [a]
1	Phenol	55	70/30
2	3-Aminophenol	15	64/36
3	4-Nitrophenol	33	79/21
4	Thiophenol	56	55/45
5	Benzoic acid	21	[b]
6	Diphenylamine	10	100/0
7	Benzimidazole	38	58/42
8	Indole	19	63/37
9	Melatonin	13	47/53 [c]

[a] Ratio of ring opening and debenzylation. Measured by gc/ms. [b] The products are not entirely stable to the reaction conditions. [c] Based on isolated yields.

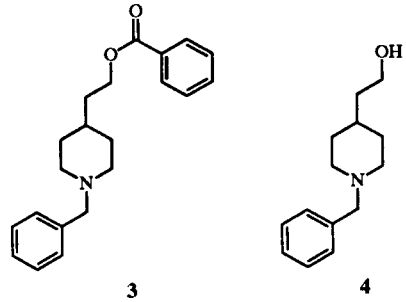
In entries 2 and 3 are found the electron rich 3-aminophenol and the electron poor 4-nitrophenol, respectively. They gave lower yields than phenol but showed similar selectivities for ring opening. No product where the 3-aminophenol had been alkylated on the amino group was found. The identity of the product was ascertained by acetylation of the amino group and the resulting amide proton could be readily detected by proton nmr. The ir absorption of the carbonyl group was found at 1660 cm^{-1}, typical of an amide.

Thiophenol (entry 4) reacted smoothly at a temperature as low as 100° but with more tendency towards

debenzylation than phenol. This is in line with the use of thiophenoxide for the removal of benzyl groups from quaternary ammonium salts [8].

Benzoic acid (entry 5) reacted quite smoothly but the expected product **3** was not entirely stable under the standard conditions. The main product was the alcohol **4**. Even under milder conditions a 69:31 mixture of **3** and **4**, respectively, was found.

Scheme 3



3 **4**

Among the nitrogen nucleophiles (entries 6-10), diphenylamine is outstanding in its selectivity for ring-opening. No debenzylation product could be detected but due to the slow rate of the reaction, only a low yield of the product was obtained.

Benzimidazole (entry 7) reacted with a low preference for ring-opening. Indole showed a similar reactivity but with slightly less debenzylation. Since there is a great interest in indole alkaloids we chose melatonin as an example of a more functionalized and sensitive nucleophile. The corresponding ring opened product was obtained in a yield of 13% after the reaction had run at 150° for 3 days. Melatonin was too sensitive to the reaction conditions to allow for the use of the standard 170°.

Conclusions.

The nucleophilic ring-opening of *N*-benzylquinuclidinium bromide is of practical value in several cases, most notably with phenols, thiophenols and nitrogen heterocycles as nucleophiles. The debenzylation reaction can in certain cases be a problem but due to the difference in basicity and polarity of the two different types of products, workup is generally convenient and chromatography is not always necessary.

EXPERIMENTAL

The ^{1}H-nmr spectra were recorded at 500 MHz and chemical shifts are reported as ppm downfield from TMS. The proton signals from the oxalic acid used to form crystalline salts of the compounds are usually broad and are not reported. The melting points were determined with a Griffin melting point apparatus which was calibrated using the Aldrich Melting point standards kit.

N-Benzylquinuclidinium Bromide (**2**).

Quinuclidine (10.0 g, 89.9 mmoles) and benzyl bromide (15.4 g, 89.9 mmoles) were refluxed in methanol (200 ml) for 1 hour. Evaporation and trituration with diethylether gave a crystalline residue of **2**, yield 23.5 g, 92%, mp 215-216°. The compound is known from the literature but no melting point is given [9].

Ring Opening: General Procedure.

To *N*-Benzylquinuclidinium bromide (**2**) (1.00 g, 3.54 mmoles) were added the appropriate nucleophile (3.54 mmoles) and cesium carbonate (1.15 g, 3.54 mmoles). The flask was flushed with nitrogen and the mixture was stirred at 170° (bath temperature) for 15 hours. After cooling to room temperature, the solid was dissolved in a mixture of ethyl acetate (50 ml) and aqueous sodium hydroxide (50 ml of a 1 *M* solution). The phases were separated and the aqueous layer was extracted with another 50 ml portion of ethyl acetate. The combined organic phases were dried over magnesium sulfate. Generally the compounds were purified by column chromatography on silica gel using appropriate mixtures of dichloromethane and methanol. The compounds were in most cases precipitated as their oxalates by treatment with 50 ml of a saturated solution of oxalic acid in ether. Analytical samples were recrystallized from water/ethanol (1:1). Where the preparations of individual compounds deviate from the general procedure this is described together with the analytical data.

4-(2-Phenoxyethyl)-1-benzylpiperidine Oxalic Acid Salt.

In this case diethyl ether was used instead of ethyl acetate and no chromatographic workup was necessary, mp 151-152°;.^{1}H-nmr (DMSO-d_6): 7.51-7.48 (m, 2H), 7.43-7.40 (m, 3H), 7.27 (t, J = 8.6 Hz, 2H), 6.93-6.91 (m, 3H), 4.09 (s, broad, 2H), 3.99 (t, J = 5.9 Hz, 2H), 3.26-3.20 (m, 2H), 2.83-2.78 (m, 2H), 1.87-1.81 (m, 2H), 1.75-1.62 (m, 3H), 1.51-1.45 (m, 2H).

Anal. Calcd. for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.21; H, 6.99; N, 3.60.

4-[2-(3-Aminophenoxy)ethyl]-1-benzylpiperidine.

This compound had ^{1}H-nmr (DMSO-d_6): 7.33-7.20 (m, 5H), 6.86 (t, J = 8.7 Hz, 1H), 6.11-6.09 (m, 2H), 6.05 (d, J = 8.7 Hz, 1H), 5.00 (s, broad, 2H), 3.87 (t, J = 7.2 Hz, 2H), 3.46-3.40 (m, 2H), 2.82-2.76 (m, 2H), 1.96-1.88 (m, 2H), 1.71-1.55 (m, 4H), 1.49-1.41 (m, 1H), 1.33-1.25 (m, 2H). The product above was obtained as an oil. Three equivalents of 3-aminophenol was used in this case. This compound was analyzed as the acetyl derivative by acetylation with acetic anhydride in dichloromethane. The crude acetyl derivative was crystallized from water/ethanol (1:1) to give 4-[2-(3-acetamido-phenyl)ethyl]-1-benzylpiperidine hydrate, mp 97-98°; ^{1}H-nmr (DMSO-d_6): (water peak not included) 9.88 (s, broad, 1H), 7.32-7.26 (m, 6H), 7.15 (t, J = 8.1 Hz, 1H), 7.23 (t, J = 8.1 Hz, 1H), 7.06 (d, J = 8.1Hz, 1H) 6.60 (d, J = 8.1 Hz, 1H), 3.96-3.92 (m, 2H), 3.42 (s, 2H), 2.77-2.73 (m, 2H), 2.01 (s, 3H), 1.91-1.87 (m, 2H), 1.68-1.61 (m, 4H), 1.47-1.41 (m, 1H), 1.22-1.16 (m, 2H).

Anal. Calcd. for $C_{22}H_{30}N_2O_3$: C, 71.32; H, 8.16; N, 7.56. Found: C, 71.12; H, 8.13; N, 7.54.

4-[2-(4-Nitrophenoxy)ethyl]-1-benzylpiperidine Oxalic Acid Salt.

This compound had mp 170-171°; ^{1}H-nmr (DMSO-d_6): 8.20 (d, J = 9.1 Hz, 2H), 7.47-7.42 (m, 5H), 7.14 (d, J = 9.1 Hz, 2H), 4.21-4.10 (m, 4H), 3.25-3.19 (m, 2H), 2.81-2.71 (m, 2H), 1.90-1.82 (m, 2H), 1.76-1.68 (m, 3H), 1.48-1.40 (m, 2).

Anal. Calcd. for $C_{22}H_{26}N_2O_7$: C, 61.38; H, 6.09; N, 6.41. Found: C, 61.48; H, 6.05; N, 6.41.

4-(2-Thiophenoxyethyl)-1-benzylpiperidine Oxalic Acid Salt.

In this case the reaction temperature was 100° instead of 170°. Diethyl ether was used instead of ethyl acetate and no chromatographic workup was necessary, mp 146-147°; ^{1}H-nmr (DMSO-d_6): 7.50-7.48 (m, 2H), 7.45-7.43 (m, 3H), 7.31 ("d", 4.6 Hz, 4H), 7.20-7.16 (m, 1H), 4.16 (s, broad, 2H), 3.19 (d, J = 14.4 Hz, 2H), 2.97 (t, J = 7.7 Hz, 2H), 2.77 (t, J = 12.0 Hz, 2H), 1.83-1.77 (m, 2H), 1.66-1.58 (m, 1H), 1.55-1.47 (m, 2H), 1.45-1.35 (m, 2).

Anal. Calcd. for $C_{22}H_{27}NO_4S$: C, 65.81; H, 6.78; N, 3.49. Found: C, 65.75; H, 6.81; N, 3.38.

4-(2-Benzoyloxyethyl)-1-benzylpiperidine Oxalic Acid Salt.

In this case the reaction was carried out at 150° in the presence of *N*-methylpyrrolidone (1 ml), mp 142-143°; ^{1}H-nmr (DMSO-d_6): 7.96 (d, J = 7.7 Hz, 2H), 7.65 (t, J = 7.7 Hz, 1H), 7.54 (t, J = 7.7 Hz, 2H), 7.47-7.41 (m, 5H), 4.34-4.30 (m, 2H), 4.12 (s, broad, 2H), 3.23-3.19 (m, 2H), 2.79-2.73 (m, 2H), 1.88-1.84 (m, 2H), 1.73-1.65 (m, 3) 1.46-1.40 (m, 2).

Anal. Calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.39. Found: C, 66.83; H, 6.58; N, 3.33.

4-[2-(Diphenylamino)ethyl]-1-benzylpiperidine Oxalic Acid Salt.

This compound had mp 150-151°; ^{1}H-nmr (DMSO-d_6): 7.49-7.42 (m, 4H), 7.28-7.24 (m, 4H), 6.96-6.90 (m, 7H), 4.20 (s, 2H), 3.72-3.68 (m, 2H), 3.26-3.20 (m, 2H), 2.84-2.78 (m, 2H), 1.84-1.80 (m, 2H), 1.58-1.49 (m, 3H), 1.43-1.37 (m, 2).

Anal. Calcd. for $C_{28}H_{32}N_2O_4$: C, 73.01; H, 7.00; N, 6.08. Found: C, 73.02; H, 7.01; N, 6.01.

4-[2-(1-Indolyl)ethyl]-1-benzylpiperidine Oxalic Acid Salt.

This compound had mp 187-189°; ^{1}H-nmr (DMSO-d_6): 7.53 (d, J = 7.5 Hz, 1H), 7.47-7.42 (m, 6H), 7.39 (d, J = 3.9 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 7.01 (t, J = 7.5 Hz, 1H), 6.41 (d, J = 3.9 Hz, 1H), 4.20 (t, J = 6.4 Hz, 2H), 4.13 (s, broad, 2H), 3.20 (d, broad, J = 11.0 Hz, 2H), 2.76-2.66 (m, 2H), 1.89-1.81 (m, 2H), 1.76-1.68 (m, 2H), 1.46-1.37 (m, 3).

Anal. Calcd. for $C_{24}H_{28}N_2O_4$: C, 70.56; H, 6.91; N, 6.86. Found: C, 70.13; H, 7.07; N, 6.72.

4-[2-(1-Benzimidazolyl)ethyl]-1-benzylpiperidine.

This compound had mp 109-110°; ^{1}H-nmr (deuteriochloroform): 7.87 (s, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.38 (d, J = 8.2 Hz, 1H), 7.35-7.26 (m, 7H), 4.20 (t, J = 7.3 Hz, 2H), 3.60-3.52 (m, 2H), 3.00-2.92 (m, 2H), 2.04-1.96 (m, 2H), 1.88-1.82 (m, 2H), 1.75-1.67 (m, 2H), 1.52-1.42 (m, 2H), 1.33-1.26 (m, 1).

Anal. Calcd. for $C_{21}H_{25}N_3$: C, 78.96; H, 7.89; N, 13.15. Found: C, 78.96; H, 7.65; N, 13.13.

1-{1-[3-(2-Acetamido-1-ethyl)-5-methoxyindolyl]}-2-[4-(1-benzyl)piperidyl]ethane.

This reaction carried out at 150° for three days, mp 94-96°; ^{1}H-nmr (deuteriochloroform): 7.38-7.29 (m, 5H), 7.17 (d, J = 8.8 Hz, 1H), 7.02 (d, J = 2.7 Hz, 1H), 6.90-6.86 (m, 2H), 5.52 (s, broad, 1H), 4.06 (t, J =7.5 Hz, 2H), 3.86 (s, 3H), 3.60-3.47 (m, 4H), 2.95-2.86 (m, 4H), 2.01-1.95 (m, 2H), 1.93 (s, 3H), 1.79-1.65 (m, 4H), 1.45-1.35 (m, 2H), 1.33-1.28 (m, 1).

Anal. Calcd. for $C_{27}H_{35}N_3O_2$: C, 74.79; H, 8.14; N, 9.69. Found: C, 74.53; H, 8.11; N, 9.58.

REFERENCES AND NOTES

[1] O. Axelsson and D. Peters, *Org. Prep. Proc. Int.*, **27**, 571 (1995).

[2] C. D. Benham, T. H. Brown, D. G. Cooper, M. L. Evans, M. H. Harries, H. J. Herdon, J. E. Meakin, K. L. Murkitt, S. R. Patel, J. C. Roberts, A. L. Rothaul, S. J. Smith, N. Wood and A. J. Hunter, *Neuropharmacol.*, **32**, 1249 (1993).

[3] The potassium phenolate gave, under otherwise identical conditions, a yield of only 3%.

[4a] H. Sugimoto, Y. Tsuchiya, H. Sugumi, K. Higurashi, N. Karibe, Y. Iimura, A. Sasaki, Y. Kawakami, T. Nakamura, S. Araki, Y. Yamanishi and K. Yamatsu, *J. Med. Chem.*, **33**, 1880 (1990); [b] P. J. Gilligan, G. A. Cain, T. E. Christos, L. Cook, S. Drummond, A. L. Johnson, A. A. Kergaye, J. F. McElroy, K. W. Rohrbach, W. K. Schmidt and S. W. Tam, *J. Med. Chem.*, **35**, 4344 (1992); [c] A. A. Nagel, D. R. Liston, S. Jung, M. Mahar, L. A. Vincent, D. Chapin,Y. L. Chen, S. Hubbarb, J. L. Ives, S. B. Jones, J. A. Nielsen, A. Ramirez, I. A. Shalaby, A. Villalobos and W. F. White, *J. Med. Chem.*, **38**, 1084 (1995).

[5] G. Odian and D. Cangiano, *Polymer Preprints*, **31**, 707 (1990).

[6] J. D. Hobson and J. G. McCluskey, *J. Chem. Soc. C*, 2016 (1967).

[7] T. W. Green and P. G. M. Wuts, Protective Groups in Organic Synthesis, 2nd Ed, John Wiley and Sons, 1991.

[8] T. Kametani, K. Kigasawa, M. Hiiragi, N. Wagatsuma and K. Wakisaka, *Tetrahedron Letters*, 635 (1969).

[9] E. W. Valyocsik, World Patent WO 95/11196, *Chem. Abstr.*, **123**, 174323 (1995).