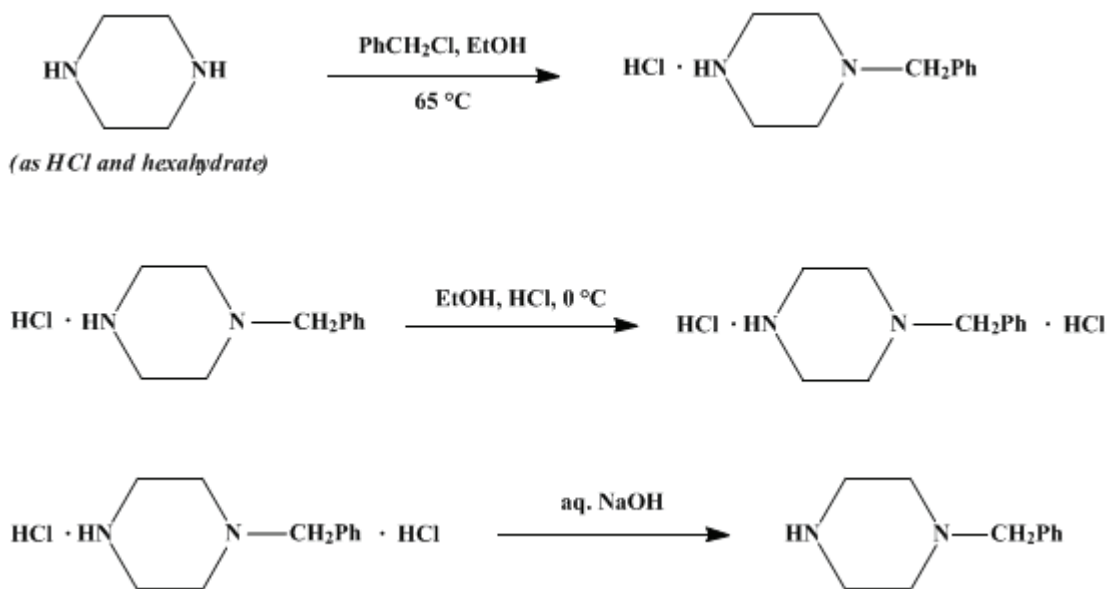


1-BENZYLPIPERAZINE

[Piperazine, 1-benzyl-]



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Checked by James Cason and Taysir Jaouni.

1. Procedure

A solution of 24.3 g. (0.125 mole) of [piperazine hexahydrate](#) in 50 ml. of absolute [ethanol](#), contained in a 250-ml. Erlenmeyer flask, is warmed in a bath at 65° as there is dissolved in the solution, by swirling, 22.1 g. (0.125 mole) of [piperazine dihydrochloride monohydrate](#) ([Note 1](#)). As warming in the bath at 65° is continued, there is added during 5 minutes, with vigorous swirling or stirring, 15.8 g. (14.3 ml., 0.125 mole) of recently distilled [benzyl chloride](#). The separation of white needles commences almost immediately. After the solution has been stirred for an additional 25 minutes at 65°, it is cooled, and the unstirred solution is kept in an ice bath for about 30 minutes. The crystals of [piperazine dihydrochloride monohydrate](#) are collected by suction filtration, washed with three 10-ml. portions of ice-cold absolute [ethanol](#), and then dried. Recovery of the dihydrochloride is 21.5–22.0 g. (97–99%) ([Note 2](#)).

The combined filtrate and washings from the [piperazine dihydrochloride](#) are cooled in an ice bath and treated with 25 ml. of absolute [ethanol](#) saturated at 0° with dry [hydrogen chloride](#) ([Note 3](#)). After the solution has been well mixed, it is cooled for 10–15 minutes in an ice bath. The precipitated white plates of [1-benzylpiperazine dihydrochloride](#) are collected by suction filtration, washed with dry [benzene](#), and dried. The product, which melts at about 280° with decomposition, after sintering at about 254° ([Note 4](#)), amounts to 29.0–29.5 g. (93–95%). A solution of this salt in 50 ml. of water is made alkaline (pH > 12) with about 60 ml. of 5*N* [sodium hydroxide](#), then extracted twelve times with 20-ml. portions ([Note 5](#)) of [chloroform](#). The combined extracts are dried over anhydrous [sodium sulfate](#), and the pale-brown oil ([Note 6](#)) remaining after removal of solvent is distilled at reduced pressure in a Claisen flask. The yield of pure [1-benzylpiperazine](#), b.p. 122–124°/2.5 mm., n_D^{25} 1.5440–1.5450, is 14.3–16.5 g. (65–75%).

2. Notes

1. [Piperazine dihydrochloride monohydrate](#), which is recovered almost quantitatively in this procedure, may be purchased from K and K Laboratories, Jamaica 33, New York, or from L. Light and Co., Ltd.,

Poyle, Colnbrook, Bucks, England. It may be readily prepared in essentially quantitative yield from the free base by the following procedure.

A brisk stream of [hydrogen chloride](#) gas is passed for 5–8 minutes into a solution of 24.3 g. (0.125 mole) of [piperazine hexahydrate](#) in 50 ml. of absolute [ethanol](#) contained in a 250-ml. Erlenmeyer flask. A wide gas-inlet tube (about 10 mm.) is used to avoid clogging, and the flask is cooled in an ice bath to keep the temperature at about 25°. After the gas stream has been discontinued, the contents of the flask are cooled to about 0°, and the crystalline product is collected by suction filtration and washed with two 25-ml. portions of ice-cold absolute [ethanol](#). The yield is about 22 g. (0.125 mole).

2. If the filtrate from this isolation is evaporated to dryness at reduced pressure, crude [1-benzyl-4-piperazinium chloride](#) is left as a residue. For removal of any [piperazine dihydrochloride](#), the chloride may be crystallized after rapidly filtering a hot solution in about 50 ml. of absolute [ethanol](#). Concentration of the filtrate, followed by cooling, gives 12.4 g. (84%) of [1-benzyl-4-piperazinium chloride](#) as prismatic plates, m.p. 167–168°. This salt may be converted to the dihydrochloride by treatment with ethanolic [hydrogen chloride](#).

3. When absolute [ethanol](#) is saturated with [hydrogen chloride](#) at 0°, the resultant solution is about 10.5*N* in [hydrogen chloride](#).

4. The melting point has been reported as 253° by Baltzly and co-workers.²

5. The checkers found continuous extraction with [chloroform](#) to be convenient.

6. The free base rapidly absorbs [carbon dioxide](#) on exposure to air and should therefore be protected during both manipulation and storage. The undistilled oil may be converted in good yield to [1-benzoyl-4-benzylpiperazine hydrochloride](#), m.p. 245–245.5°, by treatment with [benzoyl chloride](#) in [benzene](#) solution.

3. Discussion

[1-Benzylpiperazine](#) has been prepared^{2,3} by the reaction of [piperazine](#) and [benzyl chloride](#), followed by fractionation of [piperazine](#), and the mono- and dibenzyl derivatives. It has also been obtained⁴ by alkaline hydrolysis of [1-benzyl-4-carbethoxypiperazine](#). The present method, which is a modification of that first reported by Cymerman Craig, Rogers, and Tate,⁵ is simple and yields an easily purified product.

4. Merits of Preparation

The benzyl group, easily removed by hydrogenolysis, is an ideal blocking group for the preparation of 1-monosubstituted, and of 1,4-unsymmetrically disubstituted, piperazines.

Published methods for preparation of [1-benzylpiperazine](#) involve either fractionation of mixtures of [piperazine](#) and its 1-benzyl- and 1,4-dibenzyl derivatives or the use of [1-carbethoxypiperazine](#) as an intermediate. The procedure here described is simple; it yields, in 30 minutes, pure [1-benzylpiperazine dihydrochloride](#), stable to storage, from readily available starting materials, and free of any disubstituted compound.

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 5, 904](#)

References and Notes

1. Department of Chemistry, University of Sydney, Sydney, Australia.
 2. R. Baltzly, J. S. Buck, E. Lorz, and W. Schon, *J. Am. Chem. Soc.*, **66**, 263 (1944).
 3. R. E. Lutz and N. H. Shearer, *J. Org. Chem.*, **12**, 771 (1947).
 4. B. W. Horrom, M. Freifelder, and G. R. Stone, *J. Am. Chem. Soc.*, **77**, 753 (1955).
 5. J. Cymerman Craig, W. P. Rogers, and M. E. Tate, *Australian J. Chem.*, **9**, 397 (1956).
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

ethanol (64-17-5)

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

carbon dioxide (124-38-9)

benzoyl chloride (98-88-4)

benzyl chloride (100-44-7)

1-Benzylpiperazine,
Piperazine, 1-benzyl- (2759-28-6)

piperazine hexahydrate (142-63-2)

piperazine dihydrochloride monohydrate

piperazine dihydrochloride (142-64-3)

1-benzylpiperazine dihydrochloride

1-benzyl-4-piperazinium chloride

1-benzoyl-4-benzylpiperazine hydrochloride

piperazine (110-85-0)

1-benzyl-4-carbethoxypiperazine

1-carbethoxypiperazine (120-43-4)