Synthesis of 1-Carbethoxy-4-cyano-4-phenylpiperidine

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Abstract □ 1-Carbethoxy-4-cyano-4-phenylpiperidine was synthesized as an intermediate for the preparation of meperidine. The intermediate product, in good yield, was obtained by selective carbanion formation of bis(β-chloroethyl)amine using dimethyl sulfoxide.

Keyphrases □ 1-Carbethoxy-4-cyano-4-phenylpiperidine—synthesized as intermediate for preparation of meperidine □ Meperidine—intermediate of 1-carbethoxy-4-cyano-4-phenylpiperidine synthesized

The objective of this work was to synthesize a new product, 1-carbethoxy-4-cyano-4-phenylpiperidine, as an intermediate for the preparation of meperidine hydrochloride (ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride[1]) in good yield. Eisleb (1, 2) synthesized several piperidine compounds; during the ring closure step of the synthesis, *i.e.*, the reaction of benzyl cyanide with benzylbis(β-chloroethyl)amine in the presence of sodium amide and toluene, he obtained approximately 60% yield of product. Blicke *et al.* (3) reported a 70% yield when a piperidine ring structure was formed through pyrolysis of α,α-di(β-dimethylaminoethyl)-α-phenylacetonitrile.

Kaiser and Hauser (4) indicated that the dialkylation of benzyl cyanide by alkyl halides in the presence of a strong base may take place *via* the stepwise formation of carbanions or by the formation of a dianion. Monoalkyl products formed in the reaction accounted for 60% of the yield.

Cram *et al.* (5–8) reported that dimethyl sulfoxide enhanced the rate of formation of carbanions and the rate of alkylation of these ions. This permitted the use of milder conditions and shorter reaction times, with resulting higher yields. Dimethyl sulfoxide, due to its solvating quality, increased the stability and useful lifetime of the charged, unstable carbanions by surrounding the carbanions with a protective solvate shell. Thus, it was hypothesized that the ring closure between benzyl cyanide and a bis(β-chloroethyl)amine derivative takes place by the stepwise formation of carbanions in the presence of two equivalents of strong base. Furthermore, by using dimethyl sulfoxide, the yield of the product could be increased. Ethyl bis(β-chloroethyl)carbamate was selected as the bis(β-chloroethyl)-amine derivative of choice to facilitate the *N*-substituent removal from the product, which is necessary in the ultimate synthesis of meperidine.

[1] The preferred USAN chemical name is ethyl 1-methyl-4-phenylisonipecotate hydrochloride.

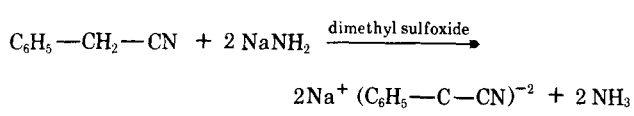
EXPERIMENTAL

Yields were determined on a gas chromatograph[2] equipped with a 1.83-m. (6-ft.) 3% SE-30 column, a flame-ionization detector, and an electronic integrator[3]. All solvents were analytical grade and were dried prior to use with a molecular sieve[4]. Dimethyl sulfoxide was stored over calcium hydride. IR spectra were obtained with a grating IR spectrograph[5]. Mass spectra were obtained on a high resolution mass spectrograph[6]. NMR spectra were obtained on a spectrograph[7] using deuterochloroform as a solvent and tetramethylsilane as the internal standard.

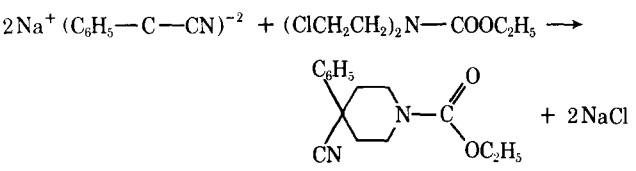
Ethyl Bis(β-chloroethyl)carbamate—Bis(β-chloroethyl)amino hydrochloride[8], 69.5 g. (0.5 mole), was slurried with 350 ml. methylene chloride in a 500-ml. three-necked, round-bottom flask. Triethylamine, 111.0 g. (1.1 moles), was added slowly to the stirred suspension from a dropping funnel connected to the neck of the flask. The slurry was cooled to −30° in a dry ice–acetone bath, and a solution of ethyl chloroformate, 59.7 g. (0.55 mole), in 100 ml. methylene chloride was slowly added to the cold slurry to minimize the internal temperature rise. After the chloroformate addition, the mixture was allowed to warm to room temperature with continuous stirring. The solvent was then evaporated under reduced pressure (water aspiration) to an oily slurry. The product was extracted with three 150-ml. aliquots of *n*-hexane. The extracts were combined, filtered, and evaporated; the residual oil was purified by vacuum distillation through a fractionating silverized Vigreaux column. The product obtained was a colorless, oily liquid, b.p. 78–79° (0.2 mm. Hg). The boiling point (0.3 mm. Hg) of ethyl bis(β-chloroethyl)carbamate is reported (9) to be 87°. Final identification was made by IR and NMR spectral analyses. The yield was 84.1 g., 74% of theoretical.

1-Carbethoxy-4-cyano-4-phenylpiperidine—A 50-ml. three-necked flask was equipped with magnetic stirrer, drying tube, and a flexible Teflon tube connected to a 10-ml. round-bottom flask for the purpose of controlled addition of solid sodium amide into the reaction flask. The apparatus was dried in an oven prior to use. Benzyl cyanide, 1.2 g. (0.01 mole), and ethyl bis(β-chloroethyl)carbamate, 2.4 g. (0.011 mole), were washed into the flask with 30 ml. of dry dimethyl sulfoxide. Sodium amide, 0.86 g. (0.022 mole), from a freshly opened bottle, was rapidly weighed, added to the 10-ml. flask, and connected to the 50-ml. flask *via* the Teflon tube. The solid sodium amide was added in small portions through the Teflon tube to the contents of the reaction vessel over a period of 30 min., causing the colorless solution to become green-brown in color. During addition, the internal temperature of the solution increased to 50° and ammonia was released.

[2] Model 320, Glowall Corp., Willow Grove, PA 19090
[3] Datex Scientific Instruments, Duarte, CA 91010
[4] Linde Division, Union Carbide, Moorestown, NJ 08057
[5] Perkin-Elmer Corp., Norwalk, Conn.
[6] Model 103-C, Consolidated Electrodynamics Corp., Monrovia, Calif.
[7] Model HA-100, Varian Associates, Palo Alto, Calif.
[8] Aldrich Chemical Co., Inc., Milwaukee, WI 53233



Scheme I



Scheme II

The solution was stirred for an additional 30 min., after which the contents of the flask were poured over 150 g. of ice, producing a milky emulsion. The emulsion was extracted with four 25-ml. aliquots of methylene chloride. The combined extracts were collected in a 100-ml. volumetric flask and adjusted to volume with methylene chloride. GC analysis of the solution disclosed a single high boiling component in the solution. The combined extracts were evaporated under vacuum. The distillate was collected at 145° (0.25 mm. Hg) and identified by IR, NMR, and mass spectroscopy as 1-carbethoxy-4-cyano-4-phenylpiperidine. The IR spectrum indicated absorption bands at 3.3–3.5 (CH_3CH_2—), 4.5 (C=N), and 5.9 (C=O) μ. The NMR spectrum consisted of: triplet, δ 1.27 (3H, CH_3CH_2O—, J = 7 Hz.); multiplet, δ 1.8–2.3 (4H, 3- and 5-CH_2, J_{gem} = 13 Hz.); triplet, each peak with further splitting, δ 3.25 (2H, axial 2- and 6-CH, $J_{gem} \sim J_{ax} \sim$ 12 Hz.); quartet, δ 4.15 (2H, CH_3CH_2O—, J = 7 Hz.); broad doublet, δ 4.35 (2H, equatorial 2- and 6-CH, $J_{gem} \sim$ 12 Hz.); and multiplet, δ 7.3–7.6 (5H, C_6H_5). The mass spectrum indicated a molecular ion at *m/e* 258. The yield ranged between 85 and 99% in six experiments when fresh sodium amide was used.

RESULTS AND DISCUSSION

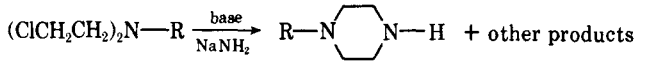
The resultant high yielding ring closure reaction between benzyl cyanide and ethyl bis(β-chloroethyl)carbamate is attributed to the solvating effect of dimethyl sulfoxide. The reaction probably takes place by a carbanion mechanism where the negatively charged benzyl cyanide species is enveloped by a protective solvate shell of dimethyl sulfoxide molecules, preventing side reactions and allowing the benzyl cyanide to proceed in a one-directional alkylating process. The probable reactions are shown in Schemes I and II. The importance of dimethyl sulfoxide in the reaction was apparent when earlier experiments using less polar solvents (such as diethyl ether, tetrahydrofuran, and benzene) resulted mainly in side products.

The selection of ethyl bis(β-chloroethyl)carbamate as a precursor for 1-carbethoxy-4-cyano-4-phenylpiperidine was based upon the following considerations:

1. The *N*-alkylated derivatives of bis(β-chloroethyl)amine show extreme reactivity in a basic medium (10, 11).

2. The basic amino group provides lability to the carbon–halogen bond by a neighboring group participating in the nucleophilic replacement of the halogen (12).

Therefore, *N*-alkylated bis(β-chloroethyl)amine, under strong basic conditions, would probably undergo undesirable side reactions as shown in Scheme III.



Scheme III

By decreasing the negative charge on the nitrogen of the amine, the lability of the carbon–halogen linkage should be decreased, thus decreasing undesirable side reactions. The carbonyl substitution of the amino group seemed feasible, especially in the form of a carbamate ester, because the removal of the carbethoxy group at a subsequent step in the meperidine synthesis was expected to occur with little or no difficulty.

Normeperidine was synthesized from 1-carbethoxy-4-cyano-4-phenylpiperidine by hydrolytic cleavage followed by esterification (1). Meperidine was prepared from normeperidine by methylation (1, 13).

CONCLUSION

A new product, 1-carbethoxy-4-cyano-4-phenylpiperidine, and its synthesis were devised to improve the ultimate synthesis of meperidine. The procedure improves the safety of earlier chemical synthesis while increasing the yield of meperidine.

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ACKNOWLEDGMENTS AND ADDRESSES

Received November 19, 1971, from the *School of Pharmacy, Temple University, Philadelphia, PA 19140*

Accepted for publication March 28, 1972.

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