chlorobenzene does not give a condensation product, nor does triethanolamine condense with the nitro halides.

The presence of water or alkali determines the yield of each type of product.

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[CONTRIBUTION FROM THE LABORATORIES OF THE WM. S. MERRELL CO.]

A Further Note on the Purification of Piperidine

BY E. S. COOK[1]

In previous papers have been described in detail the purification of piperidine by a distillation process[2] and the effect of this purification upon the activity of derived local anesthetics,[3] especially Diothane (piperidinopropanediol diphenylurethan hydrochloride).[4] In these papers it was shown that piperidine fractions boiling both higher and lower than pure piperidine gave less active anesthetics and that this depression in activity is at least partially accounted for by a physiological antagonism between the individual compounds present in the anesthetics prepared from the impure fractions.

The piperidine used for the earlier studies was obtained by the electrolytic reduction of pyridine. There has now become available commercially a piperidine prepared by catalytic reduction[5] and it became desirable to repeat a part of our studies using the catalytically prepared piperidine.

Experimental Part

The piperidine prepared by electrolytic and catalytic reduction of pyridine had a reboiling range,[6] uncorrected, of 103–111° and 104.6–106°, respectively. These two varieties of piperidine were then purified by a single distillation through the 9-foot (2-meter) column previously described.[2] The low fraction of the electrolytic and catalytic varieties (15 and 12%) had a reboiling range of 96–106° and 97.6–105.8°, respectively. The middle fraction (50 and 85%) had a reboiling range of 105.4–106.2° and 105.4–106.1°, respectively. Of the catalytic variety only a 3% residue remained, which was not examined; the corresponding residue from the electrolytic variety (35%) had a reboiling range of 106–116°. Extensive drying removed some water from both low fractions, but in no case was the boiling point raised to that of pure piperidine, which was found to be 106.3° (corr.) at 751 mm.

Piperidinopropanediol diphenylurethan hydrochloride (diothane) was prepared from all piperidine fractions (except the residual high fraction from the catalytic piperidine) by a procedure essentially similar to that previously reported.[7] The various samples all melted within a few degrees of each other (between 199 and 205°, corr.) as would be expected from the previous work.

These samples in 0.125% solution were tested for local anesthetic activity on the rabbit cornea. The duration of anesthesia for the diothane prepared from the electrolytic and catalytic varieties of piperidine was as follows: the low fractions, 21 and 22 min., the middle fractions, thirty-six and one-half and thirty-four min., respectively; that of the high fraction of the electrolytic, 26 min.

Summary

Piperidine prepared by the catalytic reduction of pyridine is of higher purity than that prepared by electrolytic reduction. Both, however, contain impurities which lower the local anesthetic activity of piperidinopropanediol diphenylurethan hydrochloride and which can be removed by distillation through a proper column. The piperidine prepared by catalytic reduction is particularly free from high boiling impurities.

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(1) Present address: Institutum Divi Thomae, Cincinnati, Ohio.

(2) E. S. Cook and T. H. Rider, THIS JOURNAL, **59**, 1739 (1937).

(3) T. H. Rider and E. S. Cook, *ibid.*, **59**, 1741 (1937).

(4) T. H. Rider and E. S. Cook, *J. Pharmacol.*, in press.

(5) Piperidine prepared by both processes was furnished by the Monsanto Chemical Co.

(6) For determination of reboiling range, see ref. 2.

(7) T. H. Rider, THIS JOURNAL, **52**, 2115 (1930).