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The Purification of Piperidine and its Physiologic Significance[1]

BY E. S. COOK AND T. H. RIDER

The large scale manufacture of Diothane (piperidino-propanediol diphenylurethan hydrochloride) led to a product having approximately 50% greater anesthetic activity, yet the same toxicity as the original[2] laboratory product. While this increased activity is not a matter of recent observation, it has taken some time to explain it sufficiently to warrant publication.

The increase in activity is now attributed almost solely to the intensive purification of the piperidine used in manufacture. Interestingly enough, extensive recrystallization of the finished anesthetic was incapable of completing this purification. The analysis and physical characteristics of the pure and impure salts are almost identical, indicating that the impurity is very closely related to Diothane itself. These characteristics are discussed in more detail in the succeeding paper.

The original samples of Diothane were prepared from the purest piperidine then available which was repurified by fractionation through small laboratory columns with the selection of a fraction boiling (during distillation) over a range of not more than 1°. It was found later that when the reboiling range[3] of such a fraction was taken there was a spread of as much as 4°.

This made necessary the preparation of piperidine of very high purity. The usual methods in the literature for accomplishing this involve chemical purification, for example, *via* nitroso[4] or benzoyl[5] piperidine. These methods are unsatisfactory on a large scale and caused us to return to distillation methods with the development of a column capable of giving sharp fractionation. The piperidine, in 30-lb. (13.6-kg.) charges, is fractionated through a 9-foot (2.7-meter) lagged iron column packed with 1200 ft. (366 meters) of No. 18 iron jack chain. The head is of Pyrex glass and is the total condensation, adjustable take-off type similar to that described by Whitmore and Lux.[6] The take-off is adjusted to 2 drops per second which returns a steady stream of liquid through the column, giving a very high reflux ratio. A high grade of commercial piperidine having a reboiling range of about 103 to 111° is used as a starting material and a fraction is cut which boils between 106.2 and 106.7° at 750 ± 1 mm. as recorded by a thermometer totally immersed in the vapor. This fraction shows a reboiling range of 105.4 to 106.2°, uncorr., with 75% boiling at 105.8°. The corrected boiling point determined by a totally immersed Bureau of Standards certified thermometer is 106.3° at 751 mm.[7] With the present grade of commercial piperidine approximately 50% yields of satisfactory distillate are obtained in one fractionation.

The piperidine used to date has been prepared by the electrolytic reduction of pyridine having a reboiling range of 112.5–115.5°, uncorr., at 750 mm. with about 75% boiling between 114 and 115°; $n^{21}D$ 1.4981. The relative purity of the pyridine makes the question of the origin of the piperidine impurities significant. While we are not, at present, prepared to discuss this point in detail, some of the impurities may well be by-products of the electrolytic reduction rather than reduction products of impurities in the original pyridine. For example, the possibility of ring rupture during reduction should be considered.[8] Partially reduced pyridine may also be found;[9] in fact, tetrahydropyridine has been isolated from the electrolytic reduction products of pyridine.[10]

The reboiling range data on various samples of supposedly "pure" piperidine and of our new fraction are shown in Fig. 1. That this fraction is amply pure for the preparation of Diothane has been demonstrated by refractionating it through the large column into three equal portions, the middle cut being again fractionated into three more cuts, giving piperidine which was assumed to be of maximum purity. This material had practically the same reboiling range as that obtained by one fractionation and when converted into Diothane gave a product of no greater physiological activity than our once fractionated material. These fractionation studies suggest that our piperidine fraction is largely a single compound whereas the older "pure" products were probably mixtures. Electrometric titrations indicate that only bases of approximately the same strength are present and are of significance for estimating the relative molecular weights of the samples. The molecular weight of pure piperidine calculated from these titrations is 84.5 (calcd., 85.09). However, if appreciable quantities of bases of considerably lower strength,

(1) Presented before the Division of Organic Chemistry at the Chapel Hill Meeting of the American Chemical Society, April 12-15, 1937.

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

(3) Reboiling ranges are determined by distilling 40-cc. samples from a long-neck 50-cc. distilling flask attached to a short Liebig condenser. The rate of distillation is one drop of distillate per second. Temperatures of the vapor are recorded beginning with the first drop of distillate and ending just as the flask goes dry. This method undoubtedly exaggerates the boiling range but it is useful in detecting traces of high and low boiling impurities.

(4) D. Vorländer and T. Wallis, *Ann.*, **345**, 277 (1906).

(5) J. Semb and S. McElvain, THIS JOURNAL, **53**, 690 (1931).

(6) F. C. Whitmore and A. R. Lux, *ibid.*, **54**, 3448 (1932). We acknowledge the assistance of A. R. Lux, during his employ in our Laboratory, in the construction of the first still and in early purification studies.

(7) Other values in the literature vary from 105 to 106.5°. Apparently the most recent reliable determination is 106.5° at 760 mm. [F. T. Riley and K. C. Bailey, *Proc. Roy. Irish Acad.*, **38B**, 450 (1929)].

(8) *Cf.* (a) A. Lipp, *Ann.*, **294**, 135 (1897); (b) P. Sabatier and A. Mailhe, *Compt. rend.*, **144**, 784 (1907).

(9) W. Koenigs, *Ber.*, **40**, 3199 (1907).

(10) C. Marie and G. Lejeune, *J. chim. phys.*, **22**, 59 (1925).

such as unreduced pyridine, had been present, they would have been evident from such titration curves.[11]

The high fraction, which constitutes approximately 35% of our present commercial piperidine, has an average reboiling range of about 106–116° with approximately 25% boiling between 112 and 116°. The high boiling impurity appears to be largely 2-methylpiperidine, a carefully fractionated sample having the constants and giving the derivatives listed at the end of the paper. Less pure piperidine samples gave definite flats in the boiling point

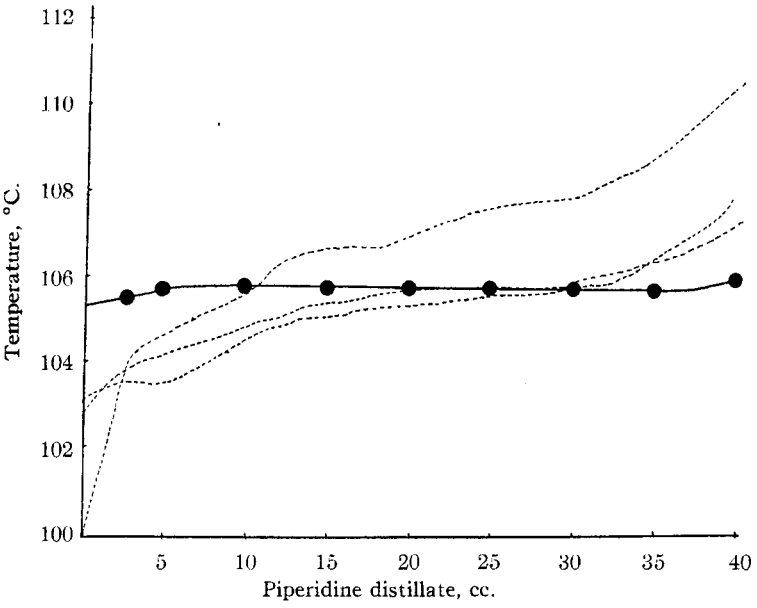

Fig. 1.—Solid line represents fraction described; dotted line various samples purchased as "pure" or "C. P."

curves indicative of the presence also of 3- and 4-methylpiperidines. Some viscous high boiling residue, constituting 3 to 4% of the piperidine, always remains after distillation. The possible presence of partially reduced pyridine in the high boiling fraction and especially in the residue receives some support from the marked ability of these fractions to decolorize potassium permanganate.[12] The importance of the elimination of such material was emphasized by the preparation of Diothane homologs from these fractions as well as from pure 2-methylpiperidine. In all cases these showed a lower local anesthetic activity than pure Diothane. These compounds and the pharmacological data will be reported in a subsequent paper.

For some time we assumed that the low boiling fraction (reboiling range 96–106°), which constitutes about 15% of the commercial piperidine, was merely wet piperidine and a certain amount of water was removable. Our failure, however, to "dry" this fraction completely led to further studies. Our pure piperidine was mixed with water and we found that this water could be removed completely by numerous drying agents. These agents, however, failed to raise the boiling point of the low fractions to that of pure piperidine. We also prepared a Diothane "homolog" from this dry, low boiling fraction and found its physiologic activity to be lower than that of pure Diothane. This suggests the presence of a low boiling impurity of unknown constitution. If, as mentioned above, ring rupture occurs during the reduction of pyridine, the chief product formed would be *n*-amylamine which boils at 103–104°. This amine has been isolated from the products of the mild catalytic reduction of pyridine.[8b] In apparent confirmation of this possibility is the fact that the low fraction gives a positive test for primary amines which, however, are present only in small amounts.

The absence of unreduced pyridine is indicated by the titration studies. The presence of unreduced pyridine or any partially reduced products in which the nitrogen has not acquired its hydrogen atom could not affect our work, however, since these compounds would not react (as secondary amine) in the preparation of piperidinopropanediol and would thus represent an impurity easily removed during the purification of the latter.

Piperidine, b. p. 106.3° corr. at 751 mm. (for reboiling range see text and Fig. 1), d^{25}_4 0.8671, $n^{20}D$ 1.4532.

Hydrochloride, m. p. 248.4–249.9° corr. (best previous m. p. is 245°, corr.[4]).

Piperidinoformanilide (from piperidine and phenylisocyanate), crystallized from alcohol, m. p. 172.6–173.6° corr. (previous m. p.'s are from 168 to 172°[13]).

2-Methylpiperidine, b. p. 117–119° uncorr. at 750 mm., d^{25}_4 0.8361, $n^{20}D$ 1.4473.

Hydrochloride, m. p. 216–217° corr. (best m. p. in literature is 210°[14]).

2-Methylpiperidinoformanilide (new compound), m. p. 127.9° corr. *Anal.* (micro) Calcd. for $C_{13}H_{18}ON_2$: N, 12.85. Found: N. 13.09, 13.10.

Discussion

The full significance of this work can only be appreciated when the physiologic properties of the piperidine derivatives are considered. In the specific case of Diothane and some related local anesthetics we have shown that the purification of piperidine here detailed has had a remarkable effect in increasing the local anesthetic activity. The details of this work constitute a succeeding paper. It is possible that other known physiologically active piperidine derivatives may have been prepared from impure piperidine. If this is the case, our experience would suggest the value of a pharmacologic restudy of such compounds after repreparation from pure piperidine.

Conclusion

Commercially available samples of "pure"

(11) A. Travers and Franquin, *Compt. rend.*, **191**, 1340 (1930).

(12) *Cf.* W. Koenigs and K. Bernhart, *Ber.*, **38**, 3042 (1905).

(13) W. Gebhardt, *ibid.*, **17**, 3040 (1884); O. Wallach and F. Lehrmann, *Ann.*, **237**, 250 (1887); Ruhemann, *J. Chem. Soc.*, **95**, 119 (1909).

(14) A. Lipp, *Ann.*, **289**, 211 (1896).

piperidine have been found to be quite impure. Intensive fractional distillation yields a pure product which is described. This pure product yields physiologically active derivatives of markedly different properties from those prepared from impure samples of piperidine.

CINCINNATI, OHIO RECEIVED JUNE 16, 1937

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The Effect of the Purification of Piperidine on the Activity of Derived Local Anesthetics[1]

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In a previous paper[2] it was mentioned that an apparent slight increase in the purity of piperidine caused a marked increase in the local anesthetic activity of Diothane (piperidinopropanediol diphenylurethan hydrochloride) and details of the purification of piperidine were given. The present paper reviews the chemical properties and preliminary pharmacological activities of a group of compounds of piperidine and 2-methylpiperidine, one of the contaminants present in commercial piperidine. We have found that there is little if any detectable chemical difference between the anesthetics prepared from the purest piperidine and those prepared from less pure fractions, but an as yet unexplained major difference in physiologic activity exists. The data show that much less active products are obtained when piperidine containing either high or low boiling material is used even though the end-products were recrystallized carefully and repeatedly. In the case of the pure 2-methylpiperidinopropanediol diphenylurethan hydrochloride a lower activity is also found.

These findings with the propanediols made it of interest to use our pure piperidine in preparing the corresponding homologs in two other series of local anesthetics, namely, the benzoates and phenylurethans of the γ-substituted propanols. Such a pair of benzoates had been prepared previously by McElvain,[3] who reported that the piperidino compound was inactive on the rabbit cornea, while the 2-methylpiperidino compound (metycaine) gave a fifteen-minute anesthesia in 2% concentration. Brill[4] had also prepared γ-piperidinopropyl benzoate and found it to have local anesthetic properties although no quantitative measurements were reported. On repreparing these compounds we found the piperidinopropyl benzoate made from our pure piperidine to be only slightly less active than the 2-methylpiperidino derivative. The γ-piperidinopropyl phenylurethan had been reported previously by us[5] but γ-(2-methylpiperidino)-propyl phenylurethan is a new compound. Here, as with the corresponding propanediol diphenylurethans, the unmethylated compound was the more active.

Experimental Part

Piperidinopropanediol diphenylurethan hydrochloride (Diothane) was prepared by a procedure essentially unchanged from that originally reported.[6] Samples were made from the previously reported specially pure piperidine fraction having a reboiling range of 105.4–106.2°, uncorr., 75% boiling at 105.8°,[7] as well as from Eastman Kodak Co. piperidine (reboiling range 103–107.6° and representative of the piperidine from which the early laboratory samples of Diothane were made), a low fraction (reboiling range 101–106°), and a high fraction (reboiling range 104.8–116°). The following comparison is found between the new Diothane and the old:[6] melting point (original) 201–202°, corr.; new 203.5–205°, corr. (capillary). *Anal.* Calcd. for $C_{22}H_{28}O_4N_3Cl$: C, 60.87; H, 6.51; N, 9.69; Cl, 8.17. Found: original sample, C, 60.99; H, 6.55; N, 9.44; Cl, 8.20; new sample, C, 60.76; H, 6.41; N, 9.37; Cl, 8.17. No solubility differences (solubility = 1.03% at 25°).

2-Methylpiperidinopropanediol diphenylurethan hydrochloride was prepared in the same manner. 2-Methylpiperidino-propanediol, m. p. 69–71°; 2-methylpiperidinopropanediol diphenylurethan hydrochloride, m. p. 192.2–194°, corr.; mixed m. p. with Diothane 199.4–201.4°, corr. *Anal.* Calcd. for $C_{23}H_{30}O_4N_3Cl$: Cl, 7.92. Found: Cl, 8.01, 8.01.

γ-Piperidinopropanol and phenylurethan hydrochloride prepared as previously reported.[5] Benzoate hydrochloride, m. p. 190.6–192.6°, corr., (McElvain[3] gives 186–188°

(1) Presented before the Division of Medicinal Chemistry at the Chapel Hill Meeting of the American Chemical Society, April 12–15, 1937.

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

(3) S. M. McElvain, *ibid.*, **49**, 2835 (1927).

(4) H. C. Brill, *ibid.*, **47**, 1134 (1925).

(5) E. S. Cook and T. H. Rider, *ibid.*, **58**, 1079 (1936).

(6) T. H. Rider, *ibid.*, **52**, 2115 (1930).

(7) See ref. 2. This compound represents the Diothane which has been on the market for some years in this degree of purity.