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.

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

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

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

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.

uncorr.). This compound was also prepared from Eastman Kodak Co. piperidine and melted at 190–192°, corr.

γ-(2-Methylpiperidino)-propanol was prepared from 2-methylpiperidine (reboiling range 117–119°[2]) and trimethylene bromohydrin in the presence of anhydrous potassium carbonate by heating on the steam-bath for three hours and then in the oil-bath at 135–145° for three hours because of the low reactivity of 2-substituted piperidines.[3] Water white liquid, b. p. 110–112° at 10 mm. **γ-(2-Methylpiperidino)-propanol phenylurethan hydrochloride** prepared in previously described manner,[5] m. p. 218.5–219.5°, corr. *Anal.* Calcd. for $C_{10}H_{23}O_2N_2Cl$: Cl, 11.35. Found: Cl, 11.55.

Pharmacological Studies

Anesthetic activities determined by the rabbit cornea[8] and intradermal wheal methods are reported in Table I.

TABLE I

EFFECT OF PURITY OF INTERMEDIATE PIPERIDINE ON LOCAL ANESTHETIC ACTIVITY OF DIOTHANE (0.25% SOLUTION)

Piperidine[a]	Duration of Anesthesia, min. Rabbit cornea	Wheal, human forearm
Pure	67.5	74
Eastman Kodak	40.5	50
Low fraction	36.5	..
High fraction	45	..

[a] See Experimental Part for boiling ranges.

This shows that an increase of activity of about 50% is obtained by using specially purified piperidine. Table II compares the local anesthetic activity of three pairs of piperidino and 2-methylpiperidino anesthetics by the rabbit cornea method.

TABLE II

LOCAL ANESTHETIC ACTIVITY OF PIPERIDINO- AND 2-METHYLPIPERIDINO ANESTHETICS

Compound, hydrochloride of	Concentration, %	Duration, minutes, rabbit cornea
Piperidinopropanediol diphenylurethan	0.125	36.5
	.25	67.5
(2-Methylpiperidino)-propanediol diphenylurethan	.125	22
	.25	54
γ-Piperidinopropyl benzoate from pure piperidine	2	11[a]
γ-Piperidinopropyl benzoate from Eastman piperidine	2	6.75
γ-(2-Methylpiperidino)-propyl benzoate	2	14[b]
γ-Piperidinopropyl phenylurethan	1	17
γ-(2-Methylpiperidino)-propyl phenylurethan	1	12.5

[a] McElvain, Ref. 3, gives 0.
[b] McElvain, Ref. 3, gives 15.

(8) T. H. Rider, *J. Pharmacol.*, **39**, 1329 (1930).

It is of interest to note that in all series the phenylurethans are more active than the benzoates.[9] The piperidino derivatives are more active than their methylpiperidino homologs in the case of the phenylurethans. While 2-methylpiperidinopropyl benzoate is more active than piperidinopropyl benzoate, this difference is much less significant than previously reported. It may be assumed that the lower anesthetic activity of earlier samples of this piperidino derivative was due to the use of a somewhat impure piperidine and this seems to be borne out by the sample prepared from Eastman piperidine.

Discussion

As pointed out in our previous paper, the significance of these results is their indication that the physiologic activity of pure piperidine derivatives may differ widely from those prepared from less pure piperidine. Stress upon the purity of the piperidine used would, perhaps, be less indicated were it not for the fact that purification of the resultant anesthetics to apparent chemical purity does not give an end-product of maximum physiologic activity. It must be pointed out that the probable percentage impurity of such compounds is incapable of explaining the great variation in activity. We believe that a paper to be published elsewhere will provide an adequate explanation.

Summary

The use of piperidine of increased purity in the production of Diothane has for several years consistently given a product having considerably greater anesthetic activity than that shown by the original laboratory samples.

One of the contaminants in piperidine is 2-methylpiperidine. Its effect has been demonstrated in three pairs of local anesthetics containing piperidine and 2-methylpiperidine, respectively. The unmethylated homologs are more active in the phenylurethan series but the reverse is true in the benzoate series. The greater topical anesthetic activities of phenylurethans as compared to benzoates are again apparent in these series.

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(9) For comparison of benzoate to phenylurethan in the propanediol series, *cf.* E. W. Scott and T. H. Rider, THIS JOURNAL, **55**, 804 (1933).