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Local Anesthetics Derived from Dialkylaminopropanediols. II. Esters of Piperidinopropanediol[1]

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In an earlier paper[2] one of us called attention to the fact that the phenyl carbamates of dialkylaminopropanediols were local anesthetics of merit. In a later publication[3] the same author pointed out that certain other phenyl carbamates were more active local anesthetics than the corresponding *p*-aminobenzoates at present on the market. During the pharmacological studies on the phenyl urethans of dialkylaminopropanediols[4] it was found that the corresponding aminobenzoates were inferior as local anesthetics (unpublished).

On the basis of further pharmacological and clinical study, the hydrochloride of piperidinopropanediol diphenylurethane (Diothane) has been selected as the best anesthetic among those previously discussed.

As a part of the further investigation of the relationship of physiological activity to the structure of various esters of piperidinopropanediol, we have made esters with the following acids: benzoic,[5] *p*-aminobenzoic,[6] *p*-tolylcarbamic and α-naphthyl carbamic. The first two esters named have been previously prepared and anesthetic activity attributed to them but no definite pharmacological data was given. The two carbamates are new, and in so far as the authors are aware, these acids have never been used in preparing local anesthetics.

Experimental

Piperidinopropanediol Di-α-naphthylurethan Hydrochloride.—A solution of 15.9 g. of piperidinopropanediol in 100 cc. of dry benzene was heated to the boiling point and a solution of 34 g. of α-naphthyl isocyanate in 50 cc. of dry benzene was slowly added. The mixture was heated for thirty minutes to complete the reaction, then cooled, filtered and a cold saturated solution of hydrogen chloride gas in dry benzene was added during stirring. The mixture was cooled overnight, the precipitate filtered off, washed with acetone, dissolved in a small volume of methyl alcohol and poured into acetone, precipitating 34 g. of piperidinopropanediol di-α-naphthylurethan hydrochloride; melting point 202–203°.

Anal. Calcd. for $C_{30}H_{31}O_4N_3 \cdot HCl$: Cl, 6.65. Found: Cl, 6.66, 6.72.

Piperidinopropanediol Di-*p*-tolylurethan Hydrochloride.—Following the above procedure, 40 g. of piperidinopropanediol and 77 g. of *p*-tolyl isocyanate were caused to

(1) A preliminary report of this research was made before the Medicinal Section of the American Chemical Society, New Orleans, March, 1932.

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

(3) Rider, *ibid.*, **52**, 2583 (1930).

(4) Rider, *J. Pharmacol.*, **39**, 457 (1930)

(5) Pyman, *J. Chem. Soc.*, **93**, 1793 (1908).

(6) Einhorn, Fiedler, Ladisch and Uhlfelder, *Ann.*, **371**, 142 (1909).

react and the hydrochloride of the resulting ester precipitated and purified, yielding 70 g. of piperidinopropanediol di-*p*-tolylurethan hydrochloride; melting point 223–225°.

Anal. Calcd. for $C_{24}H_{31}O_4N_3 \cdot HCl$: Cl, 7.68. Found: Cl, 7.74, 7.72.

Pharmacological.—All compounds were tested by Topical application to the cornea of the rabbit and by intradermal injection into the human forearm, following previously described techniques.[4] Toxicity determinations were made by subcutaneous injection into guinea pigs. The data on the different esters are summarized in Table I.

TABLE I

$ACOOCH_2CH(OCOA) \cdot CH_2NC_5H_{10} \cdot HCl$ COMPOUNDS

ACOOH	Concentration, molar	Duration of anesthesia (minutes) Rabbit cornea	Intradermal wheal	Toxicity to guinea pigs LD_{50} Mg./Kg.
Phenylcarbamic acid	0.00575	28	55	400
Tolylcarbamic acid	.00575	50	42	250
Naphthylcarbamic acid	.00575	103	32	300
p-Aminobenzoic acid	.00575	Incomplete	23	150
Benzoic acid	.00575	Incomplete	12	>600

The phenyl carbamate derivative was the most powerful anesthetic for injection and was only exceeded in its activity on the cornea by the two other urethans, both of which were decidedly irritating. Only the benzoate was less toxic than the phenyl urethan and the anesthetic activity of this compound was very low.

Summary

In a series of local anesthetics prepared from piperidinopropanediol, the di-phenyl carbamate is better than the di-α-naphthyl carbamate, the di-*p*-tolyl carbamate, the di-benzoate or the di-*p*-aminobenzoates.

CINCINNATI, OHIO RECEIVED AUGUST 13, 1932
PUBLISHED FEBRUARY 9, 1933