THE SYNTHESIS, TOXICITY AND ANAESTHETIC POTENCY OF TWO NEW LOCAL ANAESTHETICS

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Einhorn in 1899 demonstrated the production of local anaesthesia by esters of *p*-aminobenzoic acid and in 1905 introduced *p*-aminobenzoyldiethylaminoethanol (procaine) as a local anaesthetic. Since then an enormous number of compounds chemically related to procaine have been prepared and many of them have proved useful for the production of local anaesthesia in one or another of several fields. On the other hand, comparatively few studies on the local anaesthetic properties of esters of phenylcarbamic acid (II) have been made, although chemically they are closely related to esters of *p*-aminobenzoic acid (I) as shown below:

The object of the present paper is to report our studies upon the synthesis, toxicity, and local anaesthetic activity of two new esters of phenylcarbamic acid, viz., sym. bis-(diethylamino)isopropyl phenylurethane dihydrochloride (III) and sym. dipiperidino-isopropyl phenylurethane dihydrochloride (IV).

EXPERIMENTAL

Sym. bis-(diethylamino)isopropylalcohol.—A mixture of sym. dichloroisopropylalcohol (10 g.) and diethylamine (22.6 g.) was refluxed for sixteen hours. It was then acidified with dilute hydrochloric acid (30 ml.) and washed with ether so as to remove any unchanged sym. dichloroisopropylalcohol. The addition of solid sodium hydroxide (15 g.) to the aqueous solution precipitated an oil which was taken up in ether. The ethereal extract was dried over potassium carbonate and then distilled to remove the solvent and excess diethylamine. The residue upon further distillation gave 11.0 g. (or 70% of the theoretical yield) of pure sym. bis-(diethylamino)isopropyl alcohol, b.p. 93°/6.2 mm. or 230–232°/769 mm. Berend (1884) obtained the same compound by a different process and gave its boiling point as 234.5°.

Sym. bis-(diethylamino)isopropyl phenylurethane dihydrochloride (III).—Sym. bis-(diethylamino)isopropylalcohol (4 g.) previously cooled to 0° was mixed thoroughly with phenyl-isocyanate (2.63 g.) and allowed to stand at 0° for one hour and then at room

temperature overnight. Since the phenylurethane thus formed failed to solidify upon cooling to -12° , it was treated with 40 ml. 10% hydrochloric acid. The resulting solution, after being freed from oily impurities by means of animal charcoal and dried *in vacuo* over sulphuric acid and solid sodium hydroxide, gave 7.1 g. of almost pure sym. bis-(diethylamino)isopropyl phenylurethane dihydrochloride, m.p. $205-210^{\circ}$. It crystallized from absolute alcohol in colourless crystals, extremely soluble in water, m.p. $210-211^{\circ}$ (bath preheated to 200°).

Found: C, 54.93; H, 8.42; N, 10.48. $C_{18}H_{33}O_2N_3Cl_2$ requires: C, 54.80; H, 8.44; N, 10.66%.

Sym. dipiperidino-isopropylalcohol.—Sym. dichloro-isopropylalcohol (6 g.) and piperidine (16 g.) were mixed and allowed to stand at 0° for one hour and then at room temperature for twenty hours. The mixture was then heated at $60-70^{\circ}$ for six hours and finally on a boiling water bath for five minutes. The mixture was diluted with water (20 ml.) and extracted several times with ether. The ethereal extract was dried over potassium carbonate, evaporated on the water bath and filtered to remove solid impurities. Pure sym. dipiperidino-isopropylalcohol distilled at $144-145^{\circ}/6.5$ mm.; yield, 6.9 g., or 66% of the theoretical. Vassiliadès (1937) gave $172-173^{\circ}/12$ mm. as the boiling point of the compound.

Found: C, 69.29; H, 11.39. Calcd. for $C_{13}H_{26}ON_2$: C, 68.96; H, 11.58%.

The 3,5-dinitrobenzoate was prepared, which crystallized from petroleum ether (b.p. $30-50^{\circ}$) in yellowish plates, m.p. $98-100^{\circ}$.

Found: C, 57.21; H, 6.73. Calcd. for $C_{20}H_{23}O_6N_4$: C, 57.11; H, 6.71%.

Sym. dipiperidino-isopropyl phenylurethane.—Sym. dipiperidino-isopropylalcohol (4 g.) and phenylisocyanate (2.72 g.) were mixed at 0° ; the reaction took place immediately with evolution of heat. After being kept in ice for a half-hour the mixture was allowed to stand at room temperature for sixteen hours. The resulting product, sym. dipiperidino-isopropyl phenylurethane, was extracted with petroleum ether (b.p. $40-60^{\circ}$) in a Soxhlet apparatus. It crystallized in colourless prisms, melting at $106-107^{\circ}$. Yield, 5.3 g., or 87% of the theory.

Found: C, 69.60; H, 8.87; N, 11.91. $C_{20}H_{31}O_2N_3$ requires: C, 69.51; H, 9.05; N, 12.17%.

Sym. dipiperidino-isopropyl phenylurethane dihydrochloride (IV).—The hydrochloride was prepared by dissolving the phenylurethane (1.5 g.) in ice-cold 5% hydrochloric acid (30 ml.) and evaporating the solution *in vacuo* over sulphuric acid and solid sodium hydroxide. The hydrochloride melted at $242-243^{\circ}$ (bath previously heated to 230°) and crystallized from warm dilute hydrochloric acid in colourless needles, readily soluble in water. The yield was quantitative.

Found: C, 57.15; H, 7.95; N, 9.75. $C_{20}H_{33}O_2N_3Cl_2$ requires: C, 57.39; H, 7.95; N, 10.05%.

TOXICITY

The determination of the LD50 of sym. dipiperidino-isopropyl phenylurethane dihydrochloride (hereafter referred to as PP) and sym. bis-(diethylamino)-isopropyl phenylurethane dihydrochloride (hereafter referred to as DP) was carried out on mice according to Kärber's method. For the purpose of comparison, the LD50s of cocaine and procaine were also determined. All drugs were given intraperitoneally. Table I shows that PP and DP are about as toxic as cocaine but several times more toxic than procaine.

TABLE I
THE LD50 OF PP, DP, COCAINE, AND PROCAINE

Drug	Dose, mg./kg.	Proportion killed	LD50, mg./kg.
PP	50	0/10	108
	70	2/10	
	90	3/10	
	110	7/10	
	130	10/10	
DP	90	0/10	151
	110	1/10	
	130	3/10	
	150	7/10	
	170	10/10	
Cocaine	60	0/12	91
	70	1/12	
	80	4/12	
	90	6/12	
	100	12/12	
Procaine	300	0/10	564
	400	2/10	
	500	5/10	
	600	7/10	
	700	10/10	

In order to compare the toxic action of the above drugs upon respiration and circulation, experiments were made on etherized cats, and the doses of the drugs which caused an appreciable depression of blood pressure and respiration were determined. The drugs were injected intravenously. The average results obtained on six cats are shown in Table II. These results show that PP and DP have an action on blood pressure and respiration more or less similar to that of cocaine but stronger than that of procaine.

TABLE II
DOSAGE OF PP, DP, COCAINE, AND PROCAINE REQUIRED TO PRODUCE AN APPRECIABLE DEPRESSION OF BLOOD PRESSURE AND RESPIRATION

Drug	Dose, mg./kg.	
	Circulation	Respiration
PP	1.0	1.8
DP	1.1	2.2
Cocaine	1.0	1.7
Procaine	6.0	7.0

ANAESTHETIC POTENCY

The anaesthetic potencies of PP and DP were compared with those of cocaine and procaine by the rabbit's cornea method and the intradermal weal method.

These methods were chosen because they resemble more closely the clinical methods of applying local anaesthetics and also because they appear to give more reliable results than other methods (Sinha, 1936).

Rabbit's cornea method.—In this method the cornea was flooded with the drug solution and washed thoroughly with saline solution at the end of five minutes. The winking reflex was tested from time to time until it was completely restored to normal. Since there was marked individual variation in the sensitivity of the rabbit's eye toward anaesthetics and in some animals the sensitivity varied from time to time, comparisons with cocaine were made by applying the drug to be tested alternately to the same eye of a rabbit whose sensitivity showed little or no variation with time. In order to provide time for the recovery of the eyes, an interval of six to seven days was allowed between tests. Rider (1930) and Sinha (1936) have both asserted that repeated applications of cocaine render a cornea less sensitive to the drug. On the other hand, the writers found more often a slight increase rather than a decrease in the sensitivity of the rabbit's eye when cocaine was applied to it every six to seven days. Table III shows the anaesthetic potency of PP and DP and cocaine as determined by the rabbit's cornea method. The results are the average of two or three more or less consistent determinations, discordant results being discarded. It will be seen from Table III that while PP is about twice as potent as cocaine, DP is only one half as potent. Since the toxicity of these agents is about equal to that of cocaine, these results would warrant a clinical trial of these drugs as local anaesthetics for the production of surface anaesthesia.

TABLE III
THE ANAESTHETIC POTENCY OF PP AND DP AS DETERMINED BY THE
RABBIT'S CORNEA METHOD

Drug	Duration of anaesthesia in minutes in rabbits numbered 1 to 9										Efficiency ratio
	1	2	3	4	5	6	7	8	9	Mean	
PP 0.25%	10	11	23	14	19	17	—	—	—	16	2
DP 1%	14	—	—	—	17	16	17	19	15	16	1/2
Cocaine 0.5% ..	10	10	23	13	15	17	17	21	18	15	1

Intradermal weal method.—The method used was to inject 0.1 ml. of a sterilized solution intracutaneously on the flexor surface of the forearm. The duration of anaesthesia was determined by the time during which there was a loss of sensation of the injected area to pin pricks. Table IV shows the results obtained on three subjects; it will be seen that PP and DP were 12.5 and 5 times as potent as procaine respectively. Since the toxicities of PP and DP are

about six and four times that of procaine respectively, these results indicate that PP and DP may be of clinical value as local anaesthetics for the production of conduction anaesthesia.

TABLE IV
THE ANAESTHETIC POTENCY OF PP AND DP AS DETERMINED
BY THE INTRADERMAL METHOD

Drug	Duration of anaesthesia in minutes in different subjects				Efficiency ratio
	Ho	Fan	Hsia	Mean	
PP 0.02%	11	12	14	12.7	12.5
DP 0.05%	13	11	10	11.3	5.0
Procaine 0.25% ..	10	11	9	10.0	1.0

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SUMMARY

Two new phenyl urethanes, namely sym. bis-(diethylamino)isopropyl phenylurethane and sym. dipiperidino-isopropyl phenylurethane, were prepared. The dihydrochlorides of both exhibited marked local anaesthetic activity when tested by the rabbit's cornea and the human intradermal weal methods. In view of their activities and toxicities relative to cocaine and procaine they are considered worthy of clinical trial.

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