Brit. J. Pharmacol. (1948), **3**, 297.

PHENYLTHIOURETHANES AS LOCAL ANAESTHETICS

BY

YAO-TSENG HUANG, YU-WEN YIEH,* AND I. CHANG

From the Institute of Chemistry, Academia Sinica, and the Department of Pharmacology, National Medical College of Shanghai, Shanghai, China

(Received May 5, 1948)

Huang, Lu, and Chang (1946) found that the hydrochlorides of sym. bis(diethylamino)*iso*propyl phenylurethane and sym. dipiperidino-*iso*propyl phenylurethane exhibited marked local anaesthetic potency and relatively low toxicity. In view of these results and the similarity between the chemical behaviour of oxygen and sulphur, the hydrochlorides of two new phenylthiourethanes, viz. diethylaminoethyl phenylthiourethane (SD) and sym. dipiperidino-*iso*propyl phenylthiourethane (SPP), have been prepared and tested for toxicity and local anaesthetic activity. The formulae of these two compounds are given below.

(SD) $C_6H_5NH.CS.OCH_2CH_2N(C_2H_5)_2,HCl$

(SPP) $C_6H_5NH.CS.OCH(CH_2NC_5H_{10})_2,2HCl$

EXPERIMENTAL

Diethylaminoethyl phenylthiourethane hydrochloride was made by allowing sodium diethylaminoethoxide (prepared from diethylaminoethanol (2.35 g.) and powdered sodium (0.45 g.) in xylene (6 c.c.) on a steam-bath) to stand overnight with phenyl *iso*thiocyanate (3 g.). The product was acidified and the xylene removed in ether. The free base was an oil, but the hydrochloride crystallized from ethanol-ether; m.p. 121–122° C.; yield, 4.3 g. (Found: C, 54.0; H, 7.4; N, 10.0. $C_{13}H_{21}OSN_2Cl$ requires: C, 54.0; H, 7.3; N, 9.7 per cent.)

Sym. dipiperidino-isopropyl phenylthiourethane was prepared similarly from dipiperidino-*iso*propanol and phenyl *iso*thiocyanate. The free base crystallized from 90 per cent alcohol; m.p. 125–126° C. (Found: C, 66.6; H, 8.6; N, 11.7. $C_{20}H_{31}OSN_3$ requires: C, 66.5; H, 8.7; N, 11.6 per cent.) The hydrochloride crystallized when the free base was dissolved in warm 3*N* hydrochloric acid; needles, turning red at 200°, m.p. 235–236° C. (Found: N, 10.0. $C_{20}H_{33}OSN_3Cl_2$ requires: N, 9.7 per cent.)

Toxicity and anaesthetic potency

The experimental methods used were similar to those described previously (Huang *et al.*, 1946) except that guinea-pigs were used instead of human subjects for the intradermal weal tests. The results are collected in the Table. It will be seen that SD was about two-thirds as toxic as cocaine and SPP about equal in toxicity to cocaine. SD was about two-thirds and SPP about five times as potent as cocaine when tested on the rabbit cornea. When compared with procaine by the intradermal weal method, SD and SPP were about two and thirteen times as potent respectively.

TABLE

TOXICITIES AND ANAESTHETIC POTENCIES

Drug	LD50 in mice (Karber's method) mg./kg.	Anaesthetic potency (efficiency ratio, average of 7 experiments)	
		Rabbit's cornea	Intradermal weal (guinea-pig)
SD ..	165 (50)†	2/3	2
SPP ..	97 (50)†	5	13
Cocaine	102 (50)†	1	—
Procaine	—	—	1

† Total number of mice in parentheses.

The practical value of a local anaesthetic depends among other things upon its being non-irritant and stable to sterilization by heat. It was observed that both SD and SPP produced congestion of the conjunctiva in the rabbit's cornea tests and necrosis of the skin in the intradermal weal tests in concentrations at which local anaesthesia was achieved.

When solutions of SPP and SD were sterilized at 100° C. for one hour, the anaesthetic activity of the former was completely lost but that of the latter remained unchanged.

SUMMARY

The hydrochlorides of diethylaminoethyl phenylthiourethane and sym. dipiperidino-*iso*propyl phenylthiourethane have been synthesized. Both exhibited marked local anaesthetic activity in the rabbit cornea and intradermal weal (guinea-pig) tests, but they are regarded as unsuitable for clinical application because they were found to be irritant. They had toxicities in mice of the same order as cocaine.

REFERENCE

Huang, Y.-T., Lu, M.-C., and Chang, I. (1946). *Brit. J. Pharmacol.*, **1**, 273.

* Present address: National Hsiang-Ya Medical College, Changsha, China.