[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Di-urethans as Local Anesthetics

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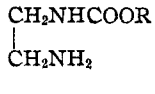
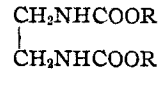
A study of a series of *p*-aminophenyl urethans of Formula I showed that such compounds produced local anesthesia, both subcutaneously and topically.[1] Although these compounds possessed low toxicities they were quite irritating to the tissues. This irritation was ascribed[1] to the presence of the *p*-phenylenediamine nucleus.

In order to establish this point it was desirable to study the pharmacological effect of urethans of Formulas II and III in which the *p*-phenylenediamine grouping is replaced by the ethylenediamine grouping. In compounds of these structures it might be possible to retain the high local anesthetic power, but eliminate the irritating effect.

I



II



III

Compounds with the structure II have not yet been prepared, but in the present work two compounds corresponding to structure III have been made as test compounds for that series. The ethyl and isoamyl ethylene di-urethans were readily prepared by the reaction between ethylenediamine and ethyl chloroformate and isoamyl chloroformate, respectively. The isoamyl derivative was chosen because in the previous studies on compounds of structure I, the maximum combined subcutaneous and surface anesthesia was exhibited by the isoamyl derivative.

Through the courtesy of the Lilly Research Laboratories the pharmacological effects of these two di-urethans were determined. Neither of the di-urethans was irritating to the rabbit's cornea or when injected under a guinea pig's skin. The toxicities were low, the lethal dose being greater than 300 mg./kg. in white rats. However, 1% solutions of these di-urethans caused no local anesthetic effect at all. When the ethyl derivative was dusted on the rabbit's cornea an anesthesia lasting four minutes was produced while the isoamyl compound caused an anesthesia for twenty-six minutes. These pharmacological data in conjunction with that previously reported[1] and the well-known irritation caused by *p*-phenylenediamine[2] itself confirms the suggestion that the irritating effects of *p*-aminophenyl urethans are due to the *p*-phenylenediamine grouping. The urethans generally have a low toxicity and possess the ability to cause surface anesthesia.

(1) Horne, Cox and Shriner, THIS JOURNAL, **55**, 3435 (1933).

Experimental

Ethyl Chloroformate and Isoamyl Chloroformate.—These esters were prepared from phosgene and the anhydrous alcohols according to the procedure of Adams, Kamm and Marvel.[3]

Ethyl Ethylene Di-urethan.—Twenty-one grams of ethyl chloroformate was added slowly to 12 g. of anhydrous ethylenediamine cooled to 0°. The reaction mass solidified and was decomposed with ice water. The di-urethan was filtered and recrystallized from 95% alcohol. It melted at 108–109°.

Anal. Calcd. for $C_8H_{16}N_2O_4$: N, 13.9; C, 47.05; H, 7.84. Found: N, 13.5; C, 46.92; H, 7.83.

Isoamyl Ethylene Di-urethan.—This urethan was prepared by the same method as above from isoamyl chloroformate and anhydrous ethylenediamine. It melted at 99–101°.

Anal. Calcd. for $C_{14}H_{28}N_2O_4$: N, 9.72. Found: N, 9.74.

Summary

Ethyl and isoamyl ethylene di-urethans have been prepared and found to be non-toxic and non-irritating. They exhibited local anesthetic action when dusted on the rabbit's cornea.

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(2) Hanzlik, *J. Indus. Hyg.*, **4**, 386, 448 (1923); Erdmann and Vahlen, *Arch. Expt. Path. Pharmacol.*, **53**, 402 (1905); Dubois and Vignon, *Compt. rend.*, **107**, 533 (1888); *Arch. de physiol.*, [4], **2**, 255 (1888); Meisner, *Arch. Expt. Path. Pharmacol.*, **84**, 181 (1918).

(3) Adams, Kamm and Marvel, "Org. Chem. Reagents I," Univ. of Ill., Bull., No. 43 (1919).