[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY AND TOXICOLOGY, YALE UNIVERSITY MEDICAL SCHOOL]

# LOCAL ANESTHETICS DERIVED FROM DIALKYLAMINOPROPANEDIOLS. I. PHENYLURETHANS

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A great majority of the more recently synthesized local anesthetics are *p*-aminobenzoates of suitable alcohols. In view of the structural similarity between phenylcarbamic acid esters (I) and *p*-aminobenzoic acid esters (II), it is surprising that the field of the phenylurethans

(I) $C_6H_5NHCOO—$ (II) $NH_2C_6H_4COO—$

has not been more generally investigated from the standpoint of the determination of their local anesthetic properties. This is perhaps due to the rather unsatisfactory properties of the urethans studied by Fromherz[1] and Bonar and Sollman.[2] The only other references to this type of compound are found in patents[3] which give no data on pharmacological properties.

In a previous communication,[4] a general preparation of dialkylaminopropanediols ($R_2NCH_2CHOHCH_2OH$) was described and attention was called at that time to their probable usefulness in the synthesis of certain types of local anesthetics. This paper, the first of a series devoted to the preparation of anesthetics derived from these intermediates, deals specifically with the mono- and diphenylurethans, prepared by the action of phenyl isocyanate on the dialkylaminopropanediols

$$\begin{array}{l} R_2NCH_2 \\ | \\ CHOH \\ | \\ CH_2OH \end{array} + C_6H_5NCO \longrightarrow \begin{array}{l} R_2NCH_2 \\ | \\ CHOH \\ | \\ CH_2OCONHC_6H_5 \end{array} + C_6H_5NCO \longrightarrow \begin{array}{l} R_2NCH_2 \\ | \\ CHOCONHC_6H_5 \\ | \\ CH_2OCONHC_6H_5 \end{array}$$

The di-urethans are formed with comparative ease when the alcohols are reacted with two molecular proportions of phenyl isocyanate. The mono-urethans, however, are more difficult to obtain, since there is a decided tendency of the $\beta$-hydroxyl group of the dialkylaminopropanediols to react, even in the presence of an excess of the alcohol, yielding the di-urethans where the mono-urethans might be expected. In isolating the product from the reaction mixture, the obvious procedure would be to extract with dilute acid and liberate the free base by the addition of alkali. While it is possible to isolate the di-urethans in this manner, the mono-urethans are decomposed by alkali before they can be isolated. These considerations without doubt explain the error in German Patent 272,529,

[1] Fromherz, *Arch. Exptl. Path. Pharmakol.*, **76**, 257 (1914).

[2] Bonar and Sollman, *J. Pharmacol.*, **18**, 467 (1921).

[3] German Patents 272,529 and 364,038.

[4] Rider with Hill, THIS JOURNAL, **52**, 1528 (1930).

purporting to cover the mono-phenylurethan of diethylaminopropanediol. The free base only was prepared, and the preparation of this compound is poorly described by the patent. The only property given is the melting point, 106.5°, which is identical with that of the true diurethan as isolated by the writer. It seems certain, therefore, that this compound was isolated, rather than the one claimed.

In the preparation of these compounds the author has prepared for the first time di-*n*-butylaminopropanediol according to the procedure outlined in a previous paper.[4] In most cases the hydrochlorides of the urethans were prepared without isolating the free bases, and little consideration has been given to improving the yields, which range from 25–60%. Only those compounds whose pharmacological properties are satisfactory merit a more detailed study.

## Experimental

**Di-*n*-butylaminopropanediol.**—Equimolecular proportions of di-*n*-butylamine and glycidol were mixed and heated on a steam-bath for two hours. The reaction mixture was distilled under reduced pressure; di-*n*-butylaminopropanediol distils at 127° (3 mm.). The yield is 90% of the theoretical.

*Anal.* Calcd. for $C_{11}H_{25}O_2N$: N, 6.90. Found: N, 6.91, 6.93.

**Hydrochlorides of Mono-phenylurethans of Dialkylaminopropanediols.**—An ethereal solution of one mole of phenyl isocyanate is rapidly mixed with an ethereal solution of the dialkylaminopropanediol. The reaction mixture is refluxed until the characteristic odor of phenyl isocyanate disappears, this being taken as a criterion of the completion of the reaction. After cooling of the reaction mixture, the hydrochloride is precipitated, usually as an oil, by the addition of an ethereal solution of dry hydrogen chloride. The ether is decanted and the hydrochloride is recrystallized from acetone. The solubility of the urethans in acetone increases with the molecular weight, necessitating the use of a mixture of acetone and ethyl acetate for the recrystallization of the higher homologs. No difficulty is found in obtaining a crystalline solid when seed crystals are available, although the first isolation sometimes proves difficult. The urethan of the amyl homolog is exceedingly difficult to purify, since it must be thrown out of an ethyl acetate solution with ether, or recrystallized by evaporating a water solution. Either procedure gives a product of somewhat varying properties. The compounds prepared are as follows.

TABLE I

$C_6H_5NHCOOCH_2CHOHCH_2NR_2 \cdot HCl$ COMPOUNDS

| | | Nitrogen, % | | | Chlorine, % | | | |
|---|---|---|---|---|---|---|---|---|
| R | Formula | Calcd. | Found | | Calcd. | Found | | M. p., °C. |
| Methyl | $C_{12}H_{18}O_3N_2HCl$ | 10.2 | 10.1 | 10.0 | 12.9 | 12.8 | 13.0 | 138–140 |
| Ethyl | $C_{14}H_{22}O_3N_2HCl$ | 9.26 | 9.3 | 9.1 | 11.7 | 12.0 | 11.8 | 135 |
| *n*-Propyl | $C_{16}H_{26}O_3N_2HCl$ | 8.47 | 8.4 | 8.5 | 10.7 | 10.5 | 10.9 | 163–164 |
| Isobutyl | $C_{18}H_{30}O_3N_2HCl$ | 7.81 | 7.8 | 7.9 | 9.89 | 9.8 | 9.9 | 125–127 |
| *n*-Butyl | $C_{18}H_{30}O_3N_2HCl$ | 7.81 | 7.8 | 7.8 | 9.89 | 9.7 | 9.7 | 128–129 |
| *n*-Amyl | $C_{20}H_{34}O_3N_2HCl$ | 7.25 | 7.1 | 7.4 | 9.18 | 9.0 | 9.4 | 101–103 |
| Piperidino ($NR_2$) | $C_{15}H_{22}O_3N_2HCl$ | 8.90 | ... | ... | 11.3 | 11.3 | 11.8 | 176–177 |

**Hydrochlorides of Diphenylurethans of Dialkylaminopropanediols.**—The diphenylurethans are prepared in a manner entirely analogous to that of the mono-phenyl-

urethans by using two molecular proportions of phenyl isocyanate. The di-urethans are more soluble in acetone than the corresponding mono-urethans but are crystallized in the same manner. The following hydrochlorides of the di-phenylurethans of dialkylaminopropanediols have been prepared.[5]

TABLE II

$C_6H_5NHCOOCH_2CH(OCONHC_6H_5)CH_2NR_2 \cdot HCl$

| R | Formula | Nitrogen, % Calcd. | Found | | Chlorine, % Calcd. | Found | | M. p., °C. |
|---|---|---|---|---|---|---|---|---|
| Ethyl | $C_{21}H_{27}O_4N_3HCl$ | 9.96 | 10.1 | 9.8 | 8.4 | 7.9 | 8.3 | 109 |
| *n*-Propyl | $C_{23}H_{31}O_4N_3HCl$ | 9.36 | 9.4 | 9.2 | 7.9 | 8.1 | 8.0 | 183–188 |
| Isobutyl | $C_{25}H_{35}O_4N_3HCl$ | 8.80 | 8.75 | 8.85 | 7.4 | 7.5 | 7.4 | 116–118 |
| Piperidino ($NR_2$) | $C_{22}H_{27}O_4N_3HCl$ | 9.7 | ..... | | 8.2 | 8.1 | 8.2 | 197–198 |

**The Free Base of the Di-phenylurethan of Diethylaminopropanediol.**—The hydrochloride, prepared as above described, was dissolved in water, an excess of alkali added, the product separated by means of ether extraction, the ethereal solution dried over anhydrous sodium sulfate, filtered and evaporated. The residue was recrystallized from high-boiling petroleum ether, yielding crystals of the di-phenylurethan of diethylaminopropanediol; melting point 106.5°.

*Anal.* Calcd. for $C_{21}H_{27}O_4N_3$: N, 10.9. Found: N, 10.7, 10.9.

**Pharmacological Properties.**—The following table will serve roughly to evaluate the strength of the two series of compounds as local anesthetics. The tests were made with a 1% solution of the hydrochloride in distilled water. The time in minutes required for the production of sensory and motor anesthesia in the exposed sciatic nerve of the frog is given in the second and third columns. The fourth column gives the duration of anes-

TABLE III

ANESTHETIC PROPERTIES

| Compound | Time of onset of anesthesia, min. Sensory | Motor | Duration of anesthesia, min. Cornea |
|---|---|---|---|
| Cocaine | 4 | 14 | 26 |
| Mono-urethans | | | |
| R = methyl | 30 | 52 | Incomplete |
| R = ethyl | 25 | 49 | 15 |
| R = *n*-propyl | 14 | 31 | 26 |
| R = *n*-butyl | 6 | 23 | 42.5 |
| R = isobutyl | 8 | 26.5 | 50 |
| R = *n*-amyl | 6 | 13.5 | 65[a] |
| $NR_2$ = piperidino | 9.5 | 35 | Incomplete |
| Di-urethans | | | |
| R = ethyl | 18 | 47 | 30 |
| R = *n*-propyl | 16 | 55 | 42 |
| R = isobutyl | 10 | 36 | 41 |
| $NR_2$ = piperidino | 5 | 38 | 54 |

[a] Using a solution of 0.5 of 1%.

[5] The methyl and amyl homologs were also prepared, but not purified, the methyl compound being hygroscopic and the weakest anesthetic of the series, while the hydrochloride of the amyl compound is practically insoluble in water.

thesia after a one-minute application of the solution to the cornea of the rabbit.

From the table it may be seen that the compounds are comparatively much more effective on the cornea than on the exposed nerves. The isobutyl homolog of the series of mono-urethans, which is approximately twice as effective on the cornea as cocaine, has a much lower apparent toxicity, the minimum fatal dose for white mice, injected subcutaneously, being 1500 mg. per kilo.

Both the study of the production of anesthesia and that of the toxicity are complicated, more especially in the di-urethan series, by the tendency of the higher homologs to precipitate proteins. A further study of this feature, together with a more complete pharmacological report, will be published elsewhere.

Since these urethans show such promising local anesthetic properties, the author proposes to extend this field through the preparation of other urethan combinations of the dialkylaminopropanediols and the urethans of other amino alcohols.

## Summary

The mono- and di-phenylurethans of a number of dialkylaminopropanediols have been prepared and have been shown to have interesting local anesthetic properties.

Di-*n*-butylaminopropanediol has been prepared for the first time.

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# METHYL ISOPROPYL THIOINDIGOID DYES FROM PARACYMENE. I. DYES FROM AMINOCYMENE[1]

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## Introduction

The number of known sulfur-containing indigoid dyes is very great[2] and their commercial importance is steadily increasing, as shown by the introduction of new colors of this series into the industry. These dyes are of particular interest due to the great effect of substitution on the color. Whereas the derivatives of indigo do not differ greatly in color, those of thioindigo cover almost the entire range of the spectrum. A survey of the literature showed that practically all of the simple benzene derivatives

[1] This communication is an abstract of a portion of a thesis submitted by W. J. Cauwenberg in partial fulfilment of the requirements for the Degree of Doctor of Philosophy, to the Faculty of Pure Science of Columbia University.

[2] Truttwin, "Enzyklopadie der Kupenfarbstoffe," Springer, Berlin, 1920.