sponding unsaturated ketones with traces of a halogen acid, preferably hydrobromic.

The low molecular weight ketols are reduced readily to the corresponding glycols electrolytically at a mercury cathode in a permanently bicarbonate solution.

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

# Para-Aminophenyl Urethans as Local Anesthetics

BY W. H. HORNE, R. F. B. COX AND R. L. SHRINER

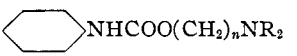
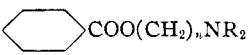
A comparison of the structures for compounds of the novocaine type (VIII) with those for *p*-aminophenyl urethans (III) shows that the transposition of the nitrogen atom results in an isomeric substance whose local anesthetic properties should be very interesting to study.

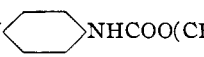
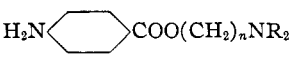
CHART I

Urethans Benzoates

(I) $H_2N—COOR$

(II)  (VI) 

(III)  (IV)  (VII) 

(V)  (VIII) 

The parallelism is quite interesting for (VIII) is an ester of *p*-aminophenylformic acid whereas (III) is an ester of *p*-aminophenylcarbamic acid. The simple phenyl urethans (II) which are isomeric with alkyl *p*-aminobenzoates (VI) and with benzoates of amino alcohols (VII) are known to possess local anesthetic action. Since urethans[1] (I) cause general anesthesia and phenyl urethans[2] (II and IV) are known to possess local anesthetizing power, the introduction of an amino group first into the benzene ring (III) and then into the side chain (V), thus making the urethan more like novocaine, should produce interesting variations of these molecules and at the same time complete a logical series of structural changes from urethan to novocaine as indicated in Chart I. An excellent review of the relationship between local anesthetic activity and structure in compounds of types IV, VI, VII and VIII has been prepared by Hirschfelder and Bieter.[3]

The purpose of the present communication is to describe the preparation

(1) Dixon, "Manual of Pharmacology," Arnold, London, 1908, p. 68.

(2) Fromherz, *Arch. exp. Path. Pharm.*, **76**, 257 (1914); Rider, *J. Pharmacol.*, **39**, 457 (1930); THIS JOURNAL, **52**, 2115 (1930).

(3) Hirschfelder and Bieter, *Physiol. Rev.*, **12**, 190 (1932).

and local anesthetic action of *p*-aminophenyl urethans of type III and V. Their preparation was accomplished according to the following scheme: alcohol plus *p*-nitrophenyl isocyanate ⟶ *p*-nitrophenyl urethan ⟶ *p*-aminophenyl urethan ⟶ *p*-aminophenyl urethan hydrochloride. The *p*-aminophenyl urethans of the amino alcohols were isolated as the free bases, the others as hydrochlorides.

## Experimental

***p*-Nitrophenyl Urethans.**—A benzene solution of *p*-nitrophenyl isocyanate[4] was treated with a slight excess of the alcohol. The spontaneous reaction was complete in a few minutes. The solution was filtered to remove bis-*p*-nitrophenyl urea which was formed due to any moisture present. The benzene was distilled and the residue recrystallized from carbon tetrachloride, xylene or petroleum ether. If the urethan was an oil it was converted to the hydrochloride or nitrate. The *p*-nitrophenyl urethans of the simple alcohols have been previously described.[4] The *p*-nitrophenyl urethans of the amino alcohols and their salts which are new are summarized in Table I.

TABLE I

*p*-NITROPHENYL URETHANS OF AMINO ALCOHOLS

| Amino alcohol | M. p., °C. | Molecular formula | Analyses, % Calcd. | Found | Remarks |
|---|---|---|---|---|---|
| $(C_2H_5)_2NCH_2CH_2OH$ | 59–60 | $C_{13}H_{19}O_4N_3$ | N, 14.95 | 14.66 | Pet. ether |
| | 212[a] | $C_{13}H_{19}O_4N_3 \cdot HCl$ | Cl, 11.17 | 11.12 | (insol. |
| | 192–193 | $C_{13}H_{19}O_4N_3 \cdot HNO_3$ | N, 16.28 | 16.35 | Water- |
| (*iso*-$C_5H_{11})_2NCH_2CH_2OH$ | 70–71 | $C_{19}H_{31}O_4N_3$ | N, 11.51 | 11.67 | (insol. |
| | 129–130 | $C_{19}H_{31}O_4N_3 \cdot HCl$ | Cl, 8.83 | 8.90 | Acetone |
| (*n*-$C_5H_{11})_2NCH_2CH_2CH_2OH$ | Oil | $C_{20}H_{33}O_4N_3$ | | | (and $CHCl_3$ |
| | 153–154 | $C_{20}H_{33}O_4N_3 \cdot HCl$ | Cl, 8.53 | 8.69 | (sol. |
| (*iso*-$C_5H_{11})_2NCH_2CH_2CH_2OH$ | Oil | $C_{20}H_{33}O_4N_3$ | | | |
| | 150–151 | $C_{20}H_{33}O_4N_3 \cdot HCl$ | Cl, 8.53 | 8.36 | $(AcO)_2O$ sol. |
| | 111–112 | $C_{20}H_{33}O_4N_3 \cdot HNO_3$ | N, 12.67 | 12.50 | Water insol. |

[a] Bloc Maquenne.

***p*-Aminophenyl Urethans of Aliphatic Alcohols.**—The reduction of 8 g. of the *p*-nitrophenyl urethans of the simple alcohols in 100 cc. glacial acetic acid was completed in fifteen minutes using 0.2 g. of platinum oxide platinum black.[5] The catalyst was removed by filtration, the filtrate cooled in an ice-bath and neutralized with cold 10% sodium hydroxide. The free base was extracted with ether, and the ether solution dried and saturated with dry hydrogen chloride, which precipitated the hydrochloride. Their properties and analyses are given in Table II.

***p*-Aminophenyl Urethans of Dialkylamino Alcohols.**—The *p*-nitrophenyl urethans or their hydrochlorides shown in Table I were reduced catalytically in glacial acetic acid,[6] as before, or in methyl alcohol. The latter procedure was found more convenient because reduction of the hydrochloride followed by evaporation of the solvent yielded the desired monohydrochloride directly. The free bases were non-crystallizable oils. The salts prepared, their physical properties and analyses are compiled in Table III.

(4) Shriner and Cox, THIS JOURNAL, **53**, 1601 (1931); Horne and Shriner, *ibid.*, **53**, 3186 (1931).

(5) Adams, Voorhees and Shriner, "Organic Syntheses," J. Wiley and Sons, N. Y., 1932, Coll. Vol. I, p. 452.

(6) Cox, Eckler and Shriner, THIS JOURNAL, **53**, 3498 (1931).

TABLE II

*p*-AMINOPHENYL URETHAN HYDROCHLORIDES OF ALIPHATIC ALCOHOLS

| Alcohol | M. p., °C. | Formula | Nitrogen analyses, % Calcd. | Found |
|---|---|---|---|---|
| Methyl | 238 | $C_8H_{10}O_2N_2HCl$ | 13.83 | 14.13 |
| Ethyl | 238 | $C_9H_{12}O_2N_2HCl$ | 12.92 | 13.15 |
| Propyl | 221 | $C_{10}H_{14}O_2N_2HCl$ | 12.14 | 11.05 |
| Isopropyl | 228 | $C_{10}H_{14}O_2N_2HCl$ | 12.14 | 12.10 |
| Butyl | 219 | $C_{11}H_{16}O_2N_2HCl$ | 11.48 | 11.05 |
| *Sec*-butyl | 225 | $C_{11}H_{16}O_2N_2HCl$ | 11.48 | 11.97 |
| Isobutyl | 241 | $C_{11}H_{16}O_2N_2HCl$ | 11.48 | 11.00 |
| Amyl | 215 | $C_{12}H_{18}O_2N_2HCl$ | 10.82 | 10.42 |
| Isoamyl | 230 | $C_{12}H_{18}O_2N_2HCl$ | 10.82 | 10.85 |
| Hexyl | 218 | $C_{13}H_{20}O_2N_2HCl$ | 10.28 | 10.00 |
| Heptyl | 210 | $C_{14}H_{22}O_2N_2HCl$ | 9.77 | 9.66 |
| *Sec*-octyl | 195 | $C_{15}H_{24}O_2N_2HCl$ | 9.34 | 10.08 |

TABLE III

SALTS OF *p*-AMINOPHENYL URETHANS OF DIALKYLAMINO ALCOHOLS

| Amino alcohol | Molecular formula | M. p., °C. | Analyses, % Calcd. | Found |
|---|---|---|---|---|
| $(C_2H_5)_2NCH_2CH_2OH$ | $C_{13}H_{21}O_2N_3\cdot HCl$ | Oil | ... | ... |
| | $C_{13}H_{21}O_2N_3\cdot 2HCl$ | 219–220 | Cl, 21.91 | 22.10 |
| | $C_{13}H_{21}O_2N_3\cdot 3H_3BO_3$ | 368 dec.[a] | N, 9.62 | 9.15 |
| $(iso\text{-}C_5H_{11})_2NCH_2CH_2OH$ | $C_{19}H_{33}O_2N_3\cdot HCl$ | Oil | ... | ... |
| | $C_{19}H_{33}O_2N_3\cdot 2HCl$ | 212–214 dec. | Cl, 17.40 | 17.59 |
| $(n\text{-}C_5H_{11})_2NCH_2CH_2CH_2OH$ | $C_{20}H_{35}O_2N_3\cdot HCl$ | 126 | Cl, 9.31 | 9.42 |
| $(iso\text{-}C_5H_{11})_2NCH_2CH_2CH_2OH$ | $C_{20}H_{35}O_2N_3\cdot HCl$ | Oil | Cl, 9.31 | 9.25 |

[a] Bloc Maquenne. The analysis shows that this borate is not composed of exactly one molecule of base and three of boric acid.

In general, precipitation of the free bases as hydrochlorides from anhydrous ether yielded a dark colored oil which in some cases solidified on standing in the cold. Precipitation from dry acetone was much more satisfactory since a white crystalline solid was obtained almost instantaneously. The nitrates were precipitated by the action of a few drops of concentrated nitric acid on dilute aqueous solutions of their hydrochlorides. Recrystallization was usually accomplished with ethyl alcohol. The solubilities observed were in accord with expectation except for a few anomalies pointed out in Table I. The color of the nitro compounds varied from lemon-yellow to very nearly white. All the urethans were noticeably photosensitive, especially the reduced forms.

**Pharmacological Action.**—Through the courtesy of The Lilly Research Laboratories the local anesthetic action of 1% solutions of the monohydrochlorides was determined. The data obtained are summarized in Table IV.

Consideration of the data in Table IV indicates several interesting relationships between physiological action and structure.

1. The most striking fact is that all the urethans possessed the ability to cause surface anesthesia. Novocaine is entirely lacking in this respect but the higher homologs such as butyn do cause surface anesthesia. The simple alkyl aminobenzoates (VII) are also effective in topical anesthesia.[7]

(7) Adams and others, THIS JOURNAL, **48**, 1758 (1926).

TABLE IV

LOCAL ANESTHETIC ACTION OF *p*-AMINOPHENYL URETHANS

| | Alkyl or dialkylaminoalkylene group | Tox. Rats (mg./kg.) | Intra-cutaneous anesthesia 1% soln., min. | Surface anesthesia 1% soln., min. | Irritation[a] Cornea (rabbit) | Skin (rabbit) |
|---|---|---|---|---|---|---|
| Type Formula III | | | | | | |
| 1 | Methyl | > 300 | 0 | 7 | − | − |
| 2 | Ethyl | > 300 | 0 | 13 | − | − |
| 3 | *n*-Propyl | 170 | 0 | 15 | − | − |
| 4 | *Sec*-propyl | 210 | 0 | 15 | − | − |
| 5 | *n*-Butyl | 60 | 12 | 16 | + | +++ |
| 6 | *Sec*-butyl | 110 | 5 | 10 | + | +++ |
| 7 | Isobutyl | 130 | 26 | 24 | + | +++ |
| 8 | *n*-Amyl | 40 | 38 | 45 | + | +++ |
| 9 | Isoamyl | 90 | 77 | 44 | + | +++ |
| 10 | *n*-Hexyl | 30 | 53 | 47 | +++ | +++ |
| 11 | *n*-Heptyl | 120 | 83 | 35 | +++ | +++ |
| 12 | *Sec*-octyl | 160 | 32 | 20 | +++ | +++ |
| Type Formula V | | | | | | |
| 13 | $(C_2H_5)_2NCH_2CH_2$- | 90 | 38 | 7.5 | ++ | ++ |
| 14 | $(Iso\text{-}C_5H_{11})_2NCH_2CH_2$- | 10 | 120 | 45 | + | − |
| 15 | $(n\text{-}C_5H_{11})_2N(CH_2)_3$- | 20 | 120 | 19 | +++ | +++ |
| 16 | $(Iso\text{-}C_5H_{11})_2N(CH_2)_3$- | 20 | 163 | 37 | + | ++ |
| 17 | Borate of No. 13 | 160 | 31 | 35 | ++ | ++ |
| 18 | Cocaine | 17.5 | 41 | 20 | − | − |
| 19 | Novocaine | 45 | 24 | None | − | − |

[a] A (−) indicates no irritation, one (+) slight, two (++) moderate and three (+++) severe irritation.

2. The urethans in which R contains less than four carbon atoms do not cause anesthesia by injection.

3. Among the simple urethans the surface anesthesia is proportional to the length of the side chain and reaches a maximum when R contains five or six carbon atoms. By comparison the maximum effect in the case of the alkyl aminobenzoates[7] occurs when R contains 4 carbons.

4. The duration of injection anesthesia appears to rise from the *n*-butyl derivative to a maximum at *n*-heptyl.

5. In the simple urethans the toxicity increases with the length of side chain in the normal series. This behavior is similar to that of the *p*-amino-benzoates of amino alcohols.[8] The toxicity becomes a maximum when R contains six carbon atoms, falling rapidly at greater lengths.

6. The branching of side chains in simple urethans is accompanied by an increase in both surface and injection anesthetic potency and a decrease in toxicity, indicating that iso compounds are more desirable than their straight chain isomers. The reverse is true in the surface effect of the alkyl aminobenzoates.[7]

(8) Schmitz and Loevenhart, *J. Pharmacol.*, **24**, 159 (1925).

7. Though less toxic, the urethans derived from secondary alcohols are inferior to the normal or iso compound.

8. An interesting feature of compounds Nos. 13, 14, 15 and 16 is that they produced hypnosis upon intravenous injection in rats.

9. The animals that died from lethal doses did not have convulsions—a fact which is in sharp contrast to the behavior of other local anesthetics such as cocaine and novocaine.

10. All of these *p*-aminophenyl urethans are irritating regardless of whether they are applied topically or injected. Since the simple urethans (1–12) were prepared and studied first, it was thought that the irritation might be due to the fact that the monohydrochlorides of these urethans are slightly acidic by hydrolysis. It was for this reason that a second basic group was introduced into the molecule by preparing the *p*-aminophenyl urethans of the amino alcohols (13–16). These particular amino alcohols were chosen because β-diethylaminoethanol is readily prepared[9] and hence represents the most economical one for use. The others contain the amyl radicals which appear to be the most active from the results on the simple urethans. However, the *p*-aminophenyl urethans of these amino alcohols were also irritating and more toxic although their anesthetic power is quite high. Another attempt to reduce irritation was the preparation of a borate (Compound 17). The irritation was diminished but did not disappear. Hence it seems probable that the irritation caused by these molecules is due to the *p*-phenylenediamine grouping present. Similar toxic and irritating effects have been noted in other derivatives of this compound.[10]

## Summary

The *p*-aminophenyl urethans of the simple alcohols and dialkylamino alcohols have been prepared and their toxicity, local anesthetic activity and irritation studied. The relationships between structure and pharmacological action are discussed.

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(9) Horne and Shriner, THIS JOURNAL, **54**, 2925 (1932).

(10) Hanzlik, *J. Ind. Hyg.*, **4**, 386, 448 (1923); Erdmann and Vahlen, *Arch. expt. Path. Pharmakol.*, **53**, 402 (1905).