15 and 25°, $Na_2SO_4 \cdot 10H_2O$ appears, giving three stable phases. In Fig. 3, for the 25° isotherm, the curve a-b represents the solubility of $Na_2SO_4 \cdot 10H_2O$ as stable phase in the ternary system;

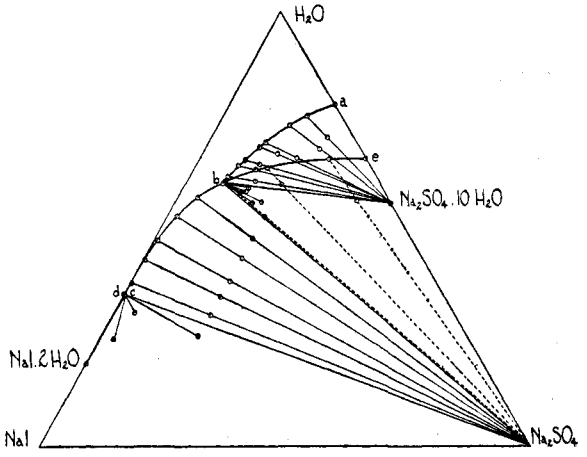


Fig. 3.—25° Isotherm: NaI–Na_2SO_4–H_2O.

point b, an isothermally invariant solution in equilibrium with both hydrated and anhydrous Na_2SO_4; the curve b-c, solutions in equilibrium with anhydrous Na_2SO_4 as solid phase; point c, the isothermally invariant solution for the two solid phases Na_2SO_4 and $NaI \cdot 2H_2O$; and the very short curve c-d, the solubility curve of $NaI \cdot 2H_2O$. The curve b-e is the metastable extension of the solubility curve b-c, of Na_2SO_4, point e being the metastable solubility of anhydrous Na_2SO_4 in water at 25°.

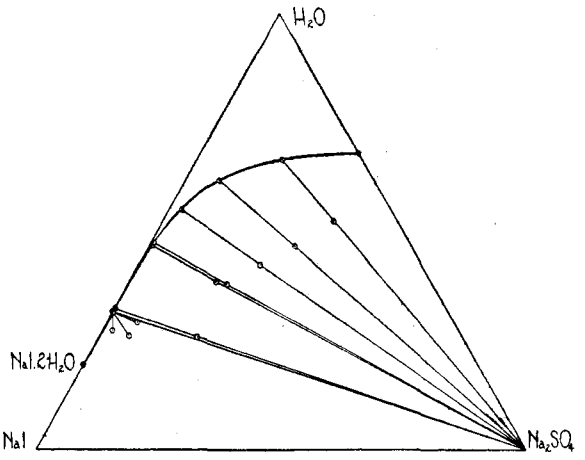


Fig. 4.—45° Isotherm: NaI–Na_2SO_4–H_2O.

Acknowledgment.—The author wishes to express his thanks to Dr. Nicholas S. Yanick, formerly of this Department, for his help in some of the experimental work of this paper.

Summary

Solubility measurements are given for the systems KI–K_2SO_4–H_2O (at 25°) and NaI–Na_2SO_4–H_2O (at 15, 25 and 45°); these salt pairs form neither double salts nor solid solutions at the temperatures reported.

NEW YORK, N. Y. RECEIVED APRIL 21, 1936

[CONTRIBUTION FROM THE LABORATORIES OF THE WM. S. MERRELL COMPANY]

Phenyl Urethan Anesthetics. II

BY E. S. COOK AND T. H. RIDER

The value of phenyl urethans as local anesthetics has been pointed out by Rider.[1] The present paper continues work in this field and deals largely with phenyl urethans of γ-dialkylaminopropanols ($R_2NCH_2CH_2CH_2OH$). Two esters of dialkylaminoisopropyl alcohols ($R_2NCH_2CHOHCH_3$) and the phenyl urethan of β-diethylaminoethanol are included.

These compounds are of particular interest because they are isomeric with the *p*-aminobenzoates, several of which have found considerable use as local anesthetics. The *p*-aminobenzoate homologs of compounds 4 and 9 (see Table I) are marketed as butyn and procaine, respectively, and the *p*-aminobenzoate homologs of compounds 2, 3,[2] and 6[3] have been prepared and found to possess local anesthetic activity.

(1) T. H. Rider, (a) THIS JOURNAL, **52**, 2115 (1930); (b) *ibid.*, **52**, 2583 (1930); (c) *J. Pharmacol.*, **39**, 457 (1930); (d) *ibid.*, **47**, 255 (1933).

Experimental Part

Amino Alcohols.—Beta-diethylaminoethanol, γ-diethylaminopropanol, and γ-di-*n*-butylaminopropanol were obtained from the Eastman Kodak Company and redistilled. The other γ-dialkylaminopropanols (dimethylamino-, di-*n*-propylamino-, piperidino- and methylphenethylamino-) were prepared by condensing the proper secondary amine with trimethylene bromohydrin in the absence of a solvent.

(2) O. Kamm, R. Adams and E. H. Volwiler, U. S. Patents 1,358,750 and 1,358,751; E. H. Volwiler, *Science*, **53**, 145 (1921); H. L. Schmitz and A. S. Loevenhart, *J. Pharmacol.*, **24**, 159 (1924).

(3) A. C. Cope and S. M. McElvain, THIS JOURNAL, **53**, 1587 (1931).

TABLE I

PHENYL URETHAN HYDROCHLORIDES OF AMINO ALCOHOLS

	Compound, urethan hydrochloride	Formula	Chlorine, % Calcd.	Found		M. p., °C. (corr.)
1	γ-Dimethylaminopropylphenyl	$C_{12}H_{19}O_2N_2Cl$	13.71	13.89	13.80	131–132.5
2	γ-Diethylaminopropylphenyl	$C_{14}H_{23}O_2N_2Cl$	12.37	12.57	12.55	140.5–142.5
3	γ-Di-*n*-propylaminopropylphenyl	$C_{16}H_{27}O_2N_2Cl$	11.27	11.33	11.31	159.5–160.5
4	γ-Di-*n*-butylaminopropylphenyl[a]	$C_{18}H_{31}O_2N_2Cl$	10.35	10.48	10.43	123–124
5	γ-Piperidinopropylphenyl	$C_{15}H_{23}O_2N_2Cl$	11.87	11.81		169–169.5
6	γ-(Methylphenethyl)-aminopropylphenyl	$C_{19}H_{25}O_2N_2Cl$	10.17	10.23	10.20	192.5–193.5
7	1-Diethylaminopropanol-2-phenyl	$C_{14}H_{23}O_2N_2Cl$	12.37	12.52	12.55	137.5–138.5
8	1-Piperidinopropanol-2-phenyl	$C_{15}H_{23}O_2N_2Cl$	11.87	11.23	11.17[b]	88–89.5
9	β-Diethylaminoethylphenyl[c]	$C_{13}H_{21}O_2N_2Cl$	13.00	13.04	13.05	142.5–143.5

[a] Previously prepared by Rider, ref. 1b. [b] Difficult completely to free from solvent. [c] Previously prepared by Rider[a] and reported by Fromherz [*Arch. Exptl. Path. Pharmakol.*, **76**, 257 (1914)]; m. p. given as 138–139°.

All were heated under reflux except dimethylamine (used as the 33% aqueous solution) which required a sealed tube. Usually no condensing agent was employed, but potassium carbonate was used successfully in several cases. The reaction mixtures were treated with potassium hydroxide solution, extracted repeatedly with ether, dried over potassium hydroxide, and the ether was removed. The alcohols were distilled either *in vacuo* or at atmospheric pressure. All of these alcohols are recorded in the literature with the exception of γ-(methylphenethyl)-aminopropanol. For this alcohol the methylphenethylamine was prepared from β-phenylethylamine, benzaldehyde, and methyl iodide by the method of Decker and Becker[4] with modifications suggested by Buck.[5] The amine was condensed with trimethylene bromohydrin as above. γ-(Methylphenethyl)-aminopropanol is a rather viscous, water-white liquid with a very slight violet fluorescence. It distils at 155–157° at 12 mm.

Anal. Calcd. for $C_{12}H_{19}ON$: N, 7.25. Found: N, 7.01.

1-Diethylamino- and 1-piperidinopropanol-2 were prepared by condensing the amines with propylene oxide. A sealed tube was necessary for the diethylamine but not for the piperidine. This method, which apparently has not been applied before to the preparation of these two compounds, gave 80% yields of amino alcohols, identical in all properties with those obtained from the corresponding chloro- or bromohydrin.

Phenyl Urethan Hydrochlorides.—Equimolar quantities of the amino alcohol and phenyl isocyanate were refluxed in absolute ether until disappearance of the odor of phenyl isocyanate. After cooling the reaction mixture, the hydrochloride was precipitated by adding a solution of hydrogen chloride in dry ether. The hydrochloride usually precipitated as a solid but 1-piperidinopropanol-2-phenyl urethan hydrochloride came down as an oil and considerable difficulty was encountered in crystallizing it. All the hydrochlorides were crystallized from a mixture of ethyl acetate and acetone except the γ-(methylphenethyl)-amino compound which was purified from absolute alcohol. The melting points and analyses of the compounds are given in Table I.

Pharmacological Properties.—In Table II data relative to the local anesthetic activity and toxicity of these compounds are given. All tests were made with 1% solutions of the hydrochlorides in distilled water. The third and fourth columns give the time in minutes required for the production of sensory and motor anesthesia in the exposed sciatic nerve of the frog.[6] The fifth column gives the duration of anesthesia after a one-minute application of the solution to the cornea of the rabbit.[6] Column six gives the approximate minimum lethal dose in milligrams per kilo by subcutaneous injection into guinea pigs.

TABLE II

PHARMACOLOGICAL PROPERTIES

Compound	*p*H, 1% Solution (quinhydrone electrode)	Time of onset of anesthesia, min. Sensory	Motor	Duration of anesthesia, min. Cornea	Toxicity mg./kg.
Cocaine	5.10	4	14	30	60
Procaine	5.50	6	18.5	Incomplete	400
1	5.82	6	36.5	Incomplete	..
2	5.98	3.5	27	14	150
3	6.46	2.75	21.75	24.5	150
4	5.93	2	10.5	65.5	150
5	5.88	3	16.5	17	150
6	5.40	3	28.75	91.5	75
7	6.48	3.25	16.5	16	150
8	5.47	3	25.5	35	200
9	6.25	3.75	14	11	150

It will be observed that the two derivatives of isopropyl alcohol (7 and 8) show some superiority over their primary alcohol isomers (2 and 5) in anesthetic activity and are less toxic as well. The one compound here reported with two dissimilar alkyl groups on nitrogen (6) has the highest anesthetic activity of the compounds tested but is extremely toxic. An increase in anesthetic power is found as the size of the nitrogen alkyls increases behavior which is duplicated in other series of anesthetics, but no progressive increase in toxicity is observed. The surprising similarity in toxici-

(4) H. Decker and P. Becker, *Ann.*, **395**, 362 (1913).

(5) J. S. Buck, THIS JOURNAL, **52**, 4119 (1930); **54**, 3661 (1932).

(6) T. H. Rider, *J. Pharmacol.*, **39**, 329 (1930).

ties of these compounds is worthy of comment. The results were checked several times and are believed to be accurate within 30%. The diethylaminoethylphenyl urethan is less active than either of the propanol homologs, which, again, is in accord with previous observations on the influence of the length of the alcohol chain, but it is no less toxic. The propanol compounds are more effective on the exposed nerve, by the test which measures onset time rather than duration, than the corresponding mono- and diphenyl urethans of dialkylamino propanediols[1a] but the reverse is usually true with respect to corneal anesthesia. Other comparative tests indicate that the diphenyl urethans of propanediols (such as diothane) are more effective as topical anesthetics, and while giving a slower onset time likewise give considerably more prolonged duration of anesthesia following intradermal injection.

The phenyl urethans here reported are more active on the rabbit's cornea than such of the isomeric *p*-aminobenzoates as have been prepared and tested.[2,3] This same behavior has been observed for the corresponding esters of piperidinopropanediol[7] as well as for the phenyl urethan and *p*-aminobenzoate of 2-diethylamino-3-hydroxy-1,2,3,4-tetrahydronaphthalene.[8] These facts prompt the suggestion that the phenyl urethan configuration confers more topical anesthetic activity upon a molecule than does the isomeric *p*-aminobenzoate group.

Acknowledgment.—We wish to thank Dr. R. S. Shelton for assisting in the pharmacological work and Mr. Karl Bambach for the analyses.

Summary

The phenyl urethans of a number of dialkylaminopropanols have been prepared and shown to have local anesthetic properties. It is suggested that the phenyl urethan group is more active in causing anesthesia of the mucous surfaces than the isomeric *p*-aminobenzoate group.

(7) E. W. Scott and T. H. Rider, THIS JOURNAL, **55**, 804 (1933).
(8) E. S. Cook and A. J. Hill, to be published.

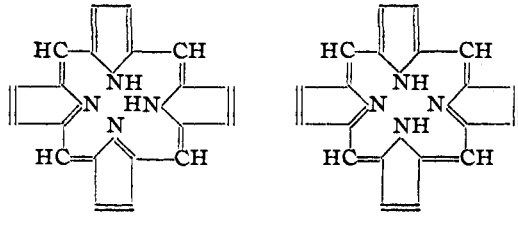
CINCINNATI, OHIO RECEIVED APRIL 6, 1936

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Studies in the Pyrrole Series. I. The Preparation of Certain N-Methyl Pyrroles[1]

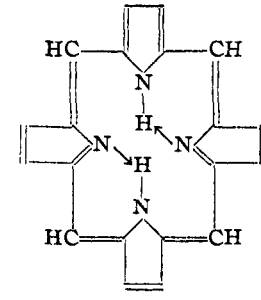
BY ALSOPH H. CORWIN[2] AND WM. M. QUATTLEBAUM, JR.[3]

If we accept Küster's formulation of the porphyrin nucleus as proved and exclude "resonance isomers," the following isomeric forms should be possible



These will be referred to as N-isomers.

Fischer[4] has suggested the simpler possibility of N-isomerism in di-pyrryl methenes but has not demonstrated its existence. Since N-isomers of the salts of methenes with mineral acids would be "resonance isomers," a separation should be achieved only by fractionation of the free bases. Likewise with the porphyrins, the salts with acids would be "resonance isomers." As a result we should not expect to find examples of N-isomerism among the synthetic porphyrins made by acid melts unless the free bases had been fractionated subsequently by a procedure not involving the use of acid. Conant and Bailey[5] have pointed out that differences between N-isomers should be destroyed by conversion into metallic complexes but found no porphyrins which exhibited this phenomenon.



(1) From the doctoral dissertations of Alsoph H. Corwin, Harvard University, 1932, and Wm. M. Quattlebaum, Jr., Harvard University, 1934. The authors wish to acknowledge their indebtedness to Dr. James B. Conant for suggesting this field of research and their appreciation of his advice and guidance in the direction of the work.
(2) Present address, Department of Chemistry, The Johns Hopkins University, Baltimore, Md.
(3) Present address, Carbide and Carbon Chemicals Corp., South Charleston, W. Va.
(4) Fischer, *Z. physiol. Chem.*, **128**, 63 (1923).
(5) Conant and Bailey, THIS JOURNAL, **55**, 796 (1933).