4. In the course of the research many new compounds have been synthesized and many old ones prepared by new methods.

5. It was discovered that the benzalamino derivatives of these *p*-aminophenol types offered a very satisfactory form in which to ethylate the phenolic hydroxyl group.

NEW YORK, N. Y.

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

LOCAL ANESTHETICS DERIVED FROM 2-(BETA-HYDROXYETHYL)-PIPERIDINE

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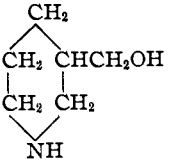
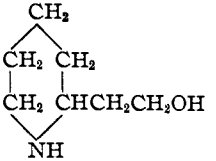
RECEIVED NOVEMBER 5, 1928 PUBLISHED MARCH 6, 1929

Recently Sandborn and Marvel[1] have prepared the *p*-aminobenzoates of certain N-alkyl derivatives of β-piperidylcarbinol and have found that their monohydrochlorides have a strong local anesthetic action combined with a low toxicity. The close structural relation between β-piperidylcarbinol (3-hydroxymethylpiperidine) (I) and 2-(β-hydroxyethyl)-piperidine (II) suggested that similar derivatives of this second amino alcohol might have desirable pharmacological action.



I



II

The starting material for the preparation of these compounds is α-picoline. By the procedure of Ladenburg[2] this with formalin gave 2-(β-hydroxyethyl)-pyridine, which was reduced to the piperidine derivative by means of sodium and alcohol.[3] The nitrogen atom was alkylated by treatment with the corresponding alkyl halide, following the general method used to alkylate β-piperidylcarbinol.[4] These tertiary amino alcohols were treated with *p*-nitrobenzoyl chloride to give the corresponding ester hydrochlorides, which were in turn reduced catalytically by means of hydrogen and the platinum catalyst of Adams and Shriner[5] to the amino ester hydrochlorides. This reduction gave the best product when glacial acetic acid was used as a solvent. When alcohol was used as a solvent a colorless product was obtained at first but on standing it turned red. When

[1] Sandborn and Marvel, THIS JOURNAL, **50**, 563 (1928).

[2] Ladenburg, *Ber.*, **43**, 2378 (1910).

[3] Ladenburg, *Ann.*, **301**, 129 (1898).

[4] Ref. 1, p. 566.

[5] Adams and Shriner, THIS JOURNAL, **45**, 2171 (1923).

the reduction was carried out in glacial acetic acid the product remained colorless.

The pharmacological tests were made by Messrs. H. J. Cannon and H. C. Spruth at the Abbott Laboratories,[6] using a 1% solution of the monohydrochloride of each amino ester on the cornea of a rabbit to determine the onset and duration times. Toxicity was determined by intravenous injection in rabbits.

TABLE I

PHARMACOLOGICAL PROPERTIES

Alkyl group	Ethyl	*n*-Propyl
Average onset, minutes	3	2.25–2.5
Av. duration of anesthesia, min.	15–20	35–40
M.F.D., mg. per kg. of body wt.	Not determined	14–15

It is interesting to note that the difference in structure between these derivatives and those from β-piperidylcarbinol is sufficient to reduce considerably their local anesthetic action. The α-derivatives are slower in their onset time and act for a shorter time than the β-derivatives.

Experimental Part

2-(β-Hydroxyethyl)-piperidine.—From 23 g. of α-picoline and 33 g. of technical formalin heated in sealed tubes at 135° for twelve to fourteen hours, there was obtained 6–7 g. of 2-(β-hydroxyethyl)-pyridine. Reduction of 23 g. of this pyridine derivative with 93 g. of sodium and 1 liter of absolute alcohol gave 13 g. of 2-(β-hydroxyethyl)-piperidine (b. p. 145–146° at 36 mm.). If care was not taken completely to remove the sodium hydroxide solution from the amino alcohol before distillation, there was considerable loss of material due to decomposition.

N-Alkyl 2-(β-Hydroxyethyl)-piperidines.—In a 250-cc. three-necked flask fitted with a condenser, a separatory funnel and a mechanical stirrer, was placed a benzene solution of the amino alcohol, and to it was added from the separatory funnel the alkyl halide. For the methyl derivative methyl iodide was used and the mixture was stirred

TABLE II

PREPARATION AND PROPERTIES OF N-ALKYL 2-(β-HYDROXYETHYL)-PIPERIDINES

Alkyl	Halide, g.	Amino alcohol, g.	N-alkyl yield, g.	B. p., °C.	d_4^{20}	n_D^{20}
Methyl	21	19.5	10	175–178 (35–40 mm.)	0.9840	1.4872
Ethyl	6	12.5	10	136 (27–28 mm.)	.9730	1.4885
n-Propyl	7.5	16	13.5	139–141 (27 mm.)	.9657	1.4905

Since the physical constants were not entirely in agreement with those reported by Ladenburg (ref. 3, pp. 133, 137, 140), the amino alcohols were titrated as a check on their purity.

TITRATIONS

Derivative	Taken, g.	0.1001 *N* HCl, cc.	Formula	Neutral equiv. Calcd.	Found
Methyl	0.1740	19.25	$C_8H_{17}NO$	143	142.2
Ethyl	.1644	17.04	$C_9H_{19}NO$	157	155.6
n-Propyl	.1950	11.46	$C_{10}H_{21}NO$	171	170

[6] The authors desire to express their thanks to Mr. Cannon, Mr. Spruth and the Abbott Laboratories for their assistance in this investigation.

at room temperature for two days. For the ethyl and *n*-propyl derivatives the alkyl bromides were used and the reaction mixtures were heated for eight hours on a steam-bath. A dark gummy material separated from the benzene in each case. The mixture was treated with excess 40% sodium hydroxide solution and the benzene layer was separated. The aqueous layer was extracted once with benzene and the benzene solutions were combined. The benzene was evaporated and the residue was distilled under reduced pressure. The results of the experiments are given in Table II.

N-Alkyl 2-(β-Hydroxyethyl)-piperidine *p*-Nitrobenzoate Hydrochlorides.—These compounds were prepared according to the usual procedure from the amino alcohols and *p*-nitrobenzoyl chloride in benzene solution.[1] The compounds separated from the solution as thick, gummy products. They were obtained crystalline by dissolving in absolute alcohol and precipitating with anhydrous ether. The methyl and *n*-propyl derivatives were especially difficult to obtain in a pure condition and the precipitation had to be repeated several times. The yields were about 55–60%. The results of these experiments are given in Table III.

TABLE III

PROPERTIES AND ANALYSES OF N-ALKYL 2-(β-HYDROXYETHYL)-PIPERIDINE *p*-NITROBENZOATE HYDROCHLORIDES

Alkyl group	M. p., °C.	Subs., g.	0.0549 *N* $AgNO_3$, cc.	Empirical formula	Chlorine, % Calcd.	Found
Methyl	181–182	0.1075	5.88	$C_{15}H_{21}N_2O_4Cl$	10.78	10.66
Ethyl	198–199	.1155	6.13	$C_{16}H_{23}N_2O_4Cl$	10.35	10.34
n-Propyl	124–126	.1020	5.18	$C_{17}H_{25}N_2O_4Cl$	9.94	9.90

N-Alkyl 2-(β-Hydroxyethyl)-piperidine *p*-Aminobenzoate Hydrochlorides.—To a solution of 5 g. of the nitrobenzoyl ester hydrochloride in 200 cc. of solvent was added 0.25 g. of platinum oxide catalyst[5] and the mixture was shaken with hydrogen under about two atmospheres' pressure for about forty-five minutes. The drop in pressure indicated that reduction was complete in about seven minutes. The mixture was filtered to remove the catalyst and the solvent was evaporated. The residue was dissolved in about 75 cc. of absolute alcohol and then about 300 cc. of anhydrous ether was added to precipitate the product. This operation was repeated as often as was necessary to obtain a pure product. When the solvent was absolute alcohol, a nearly colorless product was obtained which turned red on standing. The ethyl derivative was made using this solvent. Glacial acetic acid was used as a solvent for the reduction of the propyl derivative and a better grade of material was obtained, although it was quite difficult to crystallize. The methyl compound has not been obtained in a crystalline form. The properties of the compounds are described in Table IV.

TABLE IV

PROPERTIES AND ANALYSES OF N-ALKYL 2-(β-HYDROXYETHYL)-PIPERIDINE *p*-AMINOBENZOATE HYDROCHLORIDES

Alkyl group	M. p., °C.	Subs., g.	0.1050 *N* $AgNO_3$, cc.	Empirical formula	Chlorine, % Calcd.	Found
Ethyl	238.5–239	0.1034	3.20	$C_{16}H_{25}N_2O_2Cl$	11.33	11.35
n-Propyl	175–176	.1044	3.07	$C_{17}H_{27}N_2O_2Cl$	10.85	10.88

Summary

The monohydrochlorides of the *p*-aminobenzoyl esters of N-ethyl- and N-*n*-propyl-2-(β-hydroxyethyl)-piperidine have been prepared and their local anesthetic values have been determined.

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