[CONTRIBUTION FROM MELLON INSTITUTE OF INDUSTRIAL RESEARCH, AND E. R. SQUIBB AND SONS]

Local Anesthetics Containing the *ac*-Tetrahydro-beta-naphthylamine Pressor Group[1]

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Attempts are being made continually to prepare local anesthetics with vasoconstricting properties in order to eliminate the use of pressor drugs (usually epinephrin) to localize and synergize the local anesthetic action.[4] Until recently,[5] however, the compounds synthesized to this end have shown little or no pressor action on pharmacological assay.

Although the powerful pressor activity of *ac*-tetrahydro-β-naphthylamine is well known,[6] no attempt has been made previously to employ this amine as the nitrogen-containing portion of a local anesthetic molecule. It is known[7] that the introduction of an acid group, such as the acetyl or formyl, on the nitrogen atom, completely reverses the vasoconstricting and pyretic properties of *ac*-tetrahydro-β-naphthylamine, whereas the replacement of a hydrogen atom by an alkyl group changes them only in degree. There is a double action if an acid and alkyl group are both introduced. However, it was believed possible that the reversal effect of the acyl groups might not take place if the acyl groups were separated from the pressor amine portion by means of an alkylene group. As shown later, this hope was not realized in the large number of local anesthetics prepared.

Experimental Part

The *ac*-tetrahydro-β-naphthylamine was prepared according to the directions given in "Organic Syntheses."[8]

Preparation of the (*ac*-Tetrahydro-β-naphthylamino)-alkanol Hydrochlorides.—The general literature methods were changed in some respects. Two molecular equivalents of freshly distilled *ac*-tetrahydro-β-naphthylamine, one molecular equivalent of ethylene chlorohydrin (or trimethylene chlorohydrin) and some xylene (as diluent) were placed in a round-bottomed 3-necked flask equipped with a thermometer, reflux condenser and glass tubing reaching to the bottom of the flask through which a steady stream of dry nitrogen was passed during the entire reaction. The nitrogen prevents almost completely the formation of the usual red color. The flask and contents were immersed in an oil-bath, the temperature of the flask contents was raised to 110° and the reaction was allowed to continue for three hours at a temperature of 110–115°. The mixture was cooled, a large excess of ether added and the precipitated *ac*-tetrahydro-β-naphthylamine hydrochloride was filtered off and washed repeatedly with ether.

The ether-xylene filtrate was chilled, and both nitrogen and dry hydrogen chloride were passed slowly through the solution, until precipitation of the amino alcohol hydrochloride was complete. The precipitate was filtered off and washed well with ether, then recrystallized from isopropyl alcohol to a constant melting point with a yield of 80–85%. The compounds are white crystalline solids, soluble in water, acetone and the different alcohols, but insoluble in ether and benzene.

Beta-(*ac*-tetrahydro-β-naphthylamino)-ethanol Hydrochloride (m. p. 183.8–184.8°).[9]—*Anal.* (Volhard). Calcd. for $C_{12}H_{18}NOCl$: Cl, 15.58. Found: Cl, 15.59, 15.64.[10]

Gamma-(*ac*-tetrahydro-β-naphthylamino)-propanol Hydrochloride (m. p. 161°).—*Anal.* Calcd. for $C_{13}H_{20}NOCl$: Cl, 14.67. Found: Cl, 14.75, 14.89.

Preparation of the Esters.—These were prepared essentially by general methods reported in the literature[11] in which one molecular equivalent of the (*ac*-tetrahydro-β-naphthylamino)-alkanol hydrochloride was allowed to react with 1.5 molecular equivalents of the acyl chloride until no further hydrogen chloride was evolved. No attempt was made to work out the conditions for optimum yields, but these were satisfactory in most cases. The reaction product was washed repeatedly with ether to remove the excess acid chloride, and was then recrystallized from mixtures of methyl and isopropyl alcohols.

In most cases, little trouble was experienced in securing nicely crystalline hydrochlorides. Certain aliphatic derivatives, however, as the caproyl, propionyl and furylacryloyl, produced gums and were not secured in pure form. The *p*-toluene sulfonyl chloride seemed to react normally[12] with formation of a compound containing chlorine but the halogen was not precipitated by silver nitrate in nitric acid solution. The compound produced appreciable anesthesia when applied to the tongue, but it has not yet been separated completely from about 25% of inert material.

The nitro esters were reduced with iron and hydrochloric acid.[13] The aminobenzoates were isolated and tested as

(1) Presented before the Division of Medicinal Chemistry at the Pittsburgh Meeting of the American Chemical Society, September 7–11, 1936.

(2) Industrial Fellow, E. R. Squibb and Sons Industrial Fellowship, Mellon Institute.

(3) E. R. Squibb and Sons, Brooklyn, N. Y.

(4) Hartung, Munch and Kester, THIS JOURNAL, **54**, 1526 (1932), for literature references.

(5) Alles and Knoefel, *J. Pharmacol.*, **48**, 268 (1933); *Arch. intern. pharmacodynamie*, **47**, 96 (1934).

(6) Fränkel, "Die Arzneimittel-Synthese," 6th Edition, Verlag Julius Springer, Berlin, 1927.

(7) Cloetta and Waser, *Arch. exptl. Path. Pharmakol.*, **73**, 398 (1913).

(8) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, 1932, p. 486.

(9) All melting points recorded in this paper are U. S. P., corrected.

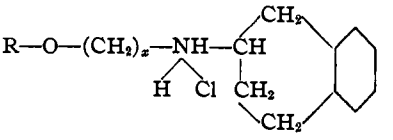
(10) The authors are indebted to Dr. W. W. Mills and Miss Elinor Sackter of the Mellon Institute analytical department for many of the assays.

(11) McElvain, THIS JOURNAL, **48**, 2240 (1926); Thayer and McElvain, *ibid.*, **50**, 3351 (1928).

(12) Compare Gilman and Pickens, *ibid.*, **47**, 245 (1925).

(13) Cope and McElvain, *ibid.*, **53**, 1591 (1931).

the dihydrochlorides. The compounds have the general formula



where R represents an aliphatic or aromatic group, and x is 2 or 3. All of the compounds are white, crystalline solids of limited solubility in water which, in some cases, did not permit of pharmacologic testing. A table of the chlorine (Parr bomb method) assays with melting points is given.

TABLE I

PHYSICAL CONSTANTS OF THE HYDROCHLORIDES

R	x	M. p., °C.	Chlorine, % Calcd.	Found (av.)
p-Nitrobenzoyl	3	228–229	9.07	8.96
m-Nitrobenzoyl	3	173.4–177.4	9.07	9.00
Benzoyl[a]	2	214.9	10.69	10.65
Benzoyl[b]	3	195.6	10.25	10.02
m-Aminobenzoyl	2	205–206	18.51	18.20
m-Nitrobenzoyl	2	216–217	9.41	9.59
Cinnamoyl	2	194–195.8	9.91	9.77
Cinnamoyl	3	204.8–206.8 (dec.)	9.54	9.43
p-Chlorobenzoyl	2	219–220	19.37	19.15
p-Chlorobenzoyl	3	188.8–189.8	18.65	18.51
p-Nitrobenzoyl	2	236.2	9.40	9.25
p-Aminobenzoyl	2	223.3	18.51	18.31
β-Phenylpropionyl	3	95.0 (indef.)	9.48	9.80
o-Nitrobenzoyl	2	232–233	9.41	9.33
o-Aminobenzoyl	2	150	18.51	18.20
p-Iodobenzoyl	2	232	...	...[c]
Phthaloyl	2	185–186	12.11	12.33

[a] Sulfate (m. p. 216–218°). Calcd. for $C_{28}H_{44}N_2O_8S$: S (Parr bomb), 4.65. Found: S, 4.70. [b] Picrate (m. p. 83.86°). Calcd. for $C_{28}H_{23}NO_2 \cdot HOC_6H_2(NO_2)_3$: N, 10.40. Found: N, 10.02. [c] Calcd.: I, 27.74. Found: I, 27.58.

Pharmacologically,[14] the compounds showed no mydriatic action on the rabbit's cornea, and produced no blanching of tissues when injected intradermally or subcutaneously in guinea pigs. The onset of anesthesia was usually delayed, although the duration and depth of anesthesia was satisfactory in most cases. However, the steep slope of the dose-effect curves and the marked difference between the duration of anesthesia following endermic and subcutaneous injections of the same concentration in the guinea pig were undesirable characteristics. The compounds were not irritating. Kymograph tracings of their action on the blood pressure of the rabbit revealed a sudden drop in the pressure, with considerable disturbance of the rhythm as the blood pressure rose gradually again to normal.

It should be recorded, too, that *ac*-tetrahydro-β-naphthylamine hydrochloride, in practical concentrations (up to 1%), does not exhibit sufficient peripheral vasoconstriction to synergize or localize the effect of a local anesthetic such as procaine (up to 2%). Injections were made subcutaneously in guinea pigs. These results are similar to those obtained with ephedrine.[15]

The authors wish to record their appreciation of the helpful advice of Dr. George D. Beal, Assistant Director of Mellon Institute.

Summary

Two new alkanol derivatives of *ac*-tetrahydro-β-naphthylamine have been prepared and described.

From these two derivatives, a series of seventeen new local anesthetics has been prepared. Although possessing, in most cases, satisfactory local anesthetic properties, they lack vasopressor characteristics.

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(14) The authors are grateful to Mr. H. A. Holaday and associates of the E. R. Squibb and Sons Biological Laboratories, New Brunswick, N. J., for these assays.

(15) Meeker, *J. Lab. Clin. Med.*, **17**, 773 (1932).