[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE CASE SCHOOL OF APPLIED SCIENCE]

Some Stovaine Analogs[1a]

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As part of a program of research on local anesthetics it was decided to study a series of analogs of stovaine to determine relationships between molecular structure and local anesthetic potency. Systematic studies of structure–potency relationships have been made for two types of compounds closely related to the stovaine analogs, namely, anesthesine analogs[2,3] and novocaine analogs.[4,5,6] In the stovaine series there is a dearth of information comparing isomers and analogs.

The compounds used in the comparative study were the hydrochlorides of β-dimethylamino-α-methyl-α-ethyl-ethyl benzoate (Stovaine), β-diethylamino-α-methyl-α-ethyl-ethyl benzoate, and β-dimethylamino-α,α-dimethyl-ethyl benzoate, previously described in the literature, and β-diethylamino-α,α-dimethyl-ethyl benzoate, β-diethylamino-α-ethyl-ethyl benzoate, and β-diethylamino-β-ethyl-ethyl benzoate, synthesized by the authors.

The aminoesters were prepared from the corresponding dialkylamino-alkanols and benzoyl chloride. The amino alcohols were synthesized from the corresponding chlorohydrins or alkylene oxides with the exception of 2-diethylamino-butanol-1. This was synthesized from 2-amino-butanol-1, a derivative of 1-nitropropane recently made commercially available. The properties of the aminoesters are summarized in Table I.

TABLE I

AMINOESTERS

Compound	Hydrochlorides: M. p., °C. (cor.)	Formula	Chlorine, % Calcd.	Found
β-Dimethylamino-α-methyl-α-ethyl-ethyl benzoate[a]	174 –175	$C_{14}H_{22}O_2NCl$	13.08	13.1
β-Diethylamino-α-methyl-α-ethyl-ethyl benzoate[b]	147.8–148.8	$C_{16}H_{26}O_2NCl$	11.84	11.8
β-Dimethylamino-α,α-dimethyl-ethyl benzoate[c]	199	$C_{13}H_{20}O_2NCl$	13.76	13.65
β-Diethylamino-α,α-dimethyl-ethyl benzoate	149.5–150.0	$C_{15}H_{24}O_2NCl$	12.43	12.1
β-Diethylamino-α-ethyl-ethyl benzoate[d]	.....	$C_{15}H_{24}O_2NCl$	12.43	12.0
β-Diethylamino-β-ethyl-ethyl benzoate[e]	.....	$C_{15}H_{24}O_2NCl$	12.43	12.9

[a] E. Fourneau, *Compt. rend.*, **138**, 766 (1904). [b] E. Fourneau, *J. pharm. chim.*, [7] **2**, 337, 397. [c] Campbell and Campbell, THIS JOURNAL, **60**, 1372 (1938). [d] B. p. (cor.) 120–122° (2 mm.). Picrate, yellow scales from alcohol, m. p. 112°. [e] B. p. (cor.) 124–126° (2 mm.). Picrate, yellow cubes from alcohol and ligroin, m. p. 113–114°.

Table II presents the average induction periods for the aminoesters when tested on the frog's sciatic nerve by the method described by Olson and Whitacre.[7] A more complete discussion concerning the results of the testing appears published elsewhere.

Since the preliminary pharmacological tests indicate β-diethylamino-β-ethyl-ethyl benzoate hydrochloride to be comparable with Novocaine in potency, a new series of local anesthetics, compounds derived in part from the nitroparaffins, is possible.

TABLE II

Compound,[a] benzoate	Average induction time (min.) for stimulus potential of: 27 v.	57 v.	97 v.
β-Dimethylamino-α-methyl-α-ethyl-ethyl	1.23	1.23	1.23
β-Diethylamino-α-methyl-α-ethyl-ethyl	2.44	2.95	3.05
β-Dimethylamino-α,α-dimethyl-ethyl	2.16	2.53	2.60
β-Diethylamino-α.α-dimethyl-ethyl	1.78	2.05	2.29
β-Diethylamino-α-ethyl-ethyl	2.08	2.11	2.13
β-Diethylamino-β-ethyl-ethyl	3.35	3.45	3.53
Novocaine	3.46	3.77	3.82

[a] Dosage, 0.5 ml. of a 5% aqueous solution of the hydrochloride.

Experimental

Butene-1.—One hundred grams of *n*-butyl iodide was added slowly to a solution of 40 g. of potassium hydroxide

(1) (a) Original manuscript received August 5, 1942. (b) From the Doctor's dissertation of Walter T. Olson presented to Case School of Applied Science, May, 1942. Present address: National Advisory Committee for Aeronautics, Cleveland Airport, Cleveland, Ohio.

(2) F. M. Whitacre, *Anesthesia and Analgesia*, **18**, 112 (1939).

(3) Adams, Rideal, Burnett, Jenkins and Dreger, THIS JOURNAL, **48**, 1758 (1926).

(4) Schmitz and Loevenhart, *J. Pharm. Exper. Therap.*, **24**, 159 (1924).

(5) Vliet and Adams, THIS JOURNAL, **48**, 2239 (1926).

(6) Burnett, Jenkins, Peet, Dreger and Adams, *ibid.*, **59**, 2248 (1937).

(7) W. T. Olson and F. M. Whitacre, *Anesthesia and Analgesia*, **21**, 106 (1942).

dissolved in a minimum of alcohol and heated to about 90°. The generated gas was demonstrated to be practically pure butene-1 by preparing the dibromo derivative, b. p. 166°.

1-Chloro-butanol-2.—Butene-1 was conducted through a train of four, individually ice-cooled, 250-ml. gas washing bottles, each of which contained 200 ml. of hypochlorous acid solution. When all of the hypochlorous acid had reacted, the contents of the bottles was salted out and extracted with ether. The product obtained from the dried ether extracts was fractionally distilled. The method of Helferich and Speidel[8] utilizing chloroacetaldehyde and ethylmagnesium bromide was also applied in preparing 1-chlorobutanol-2, b. p. 53–55° (17 mm.); b. p. (literature)[9] 141° (atm.), 52° (15 mm.).

1-Chloro-2-methyl-propanol-2 and isobutylene oxide were obtained from the Eastman Kodak Company.

1-Diethylamino-butanol-2.—Fourteen grams of diethylamine and 11 g. of 1-chloro-butanol-2 in benzene solution were sealed in a thick-walled Carius tube and heated at 120° for twenty-four hours. At the end of this time the tube was cooled and opened. The contents were filtered and the precipitated diethylamine hydrochloride was washed with benzene. The combined filtrate and washings were partially distilled to remove some benzene and excess diethylamine. The benzene solution was then cooled and extracted with about 100 ml. of 15% hydrochloric acid used in portions. The combined hydrochloric acid extracts were boiled down to about 20 ml., cooled and neutralized, and made strongly alkaline with a 10% sodium hydroxide solution. The amino alcohol was extracted from this mixture with several portions of ether. The combined ether extracts were dried with anhydrous sodium sulfate, filtered, and the ether was removed over the water-bath. The oily residue was fractionally distilled under reduced pressure; b. p. 74–75° (22 mm.), 54–55° (7 mm.).[10]

1-Diethylamino-2-methyl-propanol-2.—Fourteen grams of diethylamine and 14 g. of isobutylene oxide and 0.3 ml. of water were heated together in a sealed Carius tube at 105–110° for twenty hours. The cooled tube was opened and the contents rectified by fractional distillation under reduced pressure; b. p. 65–68° (23–25 mm.), 77–78° (36 mm.). Picrate, m. p. 99.2–100.2°, diamond-shaped plates from benzene.[11,12]

2-Diethylamino-butanol-1.—To a solution of 35 g. of sodium carbonate in 150 ml. of water was added 14 g. of 2-amino-butanol-1 (Commercial Solvents Corp., redistilled) and 34 g. of ethyl bromide. The mixture was refluxed until the ethyl bromide disappeared, about two to three hours. After the solution had cooled, it was made strongly alkaline, saturated with salt, and extracted repeatedly with ether. The combined ether extracts were dried with anhydrous magnesium sulfate, filtered, and the ether was removed on the water-bath. The residual yellow oil was fractionated under reduced pressure to give a water-white product, b. p. 86–87° (25 mm.), n_D 1.4310 (25°), slightly soluble in water. The presence of the tertiary amine group in the compound was established. The hydrochloride was prepared as a non-crystallizing oil by conducting dry hydrogen chloride into a benzene solution of the amino alcohol.

Anal. Calcd. for $C_8H_{20}ONCl$: Cl, 19.54. Found: Cl, 19.55.

2-Ethylamino-2-methyl-propanol-1.—An attempt to diethylate 2-amino-2-methyl-propanol-1 (Commercial Solvents) resulted only in 2-ethylamino-2-methyl-propanol-1. The product obtained was recrystallized from ligroin as soft white needles, m. p. 74.5–75.0°. The presence in the compound of both the secondary alcohol and the secondary amine groups was confirmed. The picrate of the amino alcohol was prepared in ether solution and recrystallized from benzene as fine, yellow needles, m. p. 124.7–125.3°. By conducting dry hydrogen chloride into a benzene solution of the 2-ethylamino-2-methyl-propanol-1, the hydrochloride was prepared, m. p. 136.5°.

Anal. Calcd. for $C_6H_{16}ONCl$: Cl, 23.1. Found: Cl, 23.0.

Aminoesters.—The general method of preparation employed was to reflux for about three to six hours equimolecular quantities of benzoyl chloride and the appropriate dialkylaminoalkanol in benzene solution. In cases where the hydrochloride of the resulting aminoester was not obtainable as a crystalline solid, the aminoester was obtained by neutralizing the hydrochloride carefully with sodium bicarbonate and extracting the resulting mixture with ether. The aminoesters were rectified by vacuum distillation. Hydrochlorides were prepared for these latter compounds by conducting dry hydrogen chloride into dry ethereal solutions of the aminoesters.

Summary

The local anesthetic potencies of Stovaine and five analogs are compared, using the frog's sciatic nerve.

The syntheses of 2-diethylamino-butanol-1,2-ethylamino-2-methyl-propanol-1, β-diethylamino-α,α-dimethyl-ethyl benzoate, β-diethylamino-α-ethyl-ethyl benzoate, and β-diethylamino-β-ethyl-ethyl benzoate are described and the essential physical properties recorded.

The first member of a possible series of local anesthetics derived in part from the nitroparaffins is described.

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(8) Helferich and Speidel, *Ber.*, **54**, 2636 (1921).

(9) Montmollin and Matile, *Helv. Chim. Acta*, **7**, 106 (1924).

(10) Houben and Fuhrer, *Ber.*, **47**, 76, 81 (1914).

(11) Krassusky and Stepanoff, *J. prakt. Chem.*, [2] **75**, 241 (1907); **77**, 86, 99 (1908); **115**, 321 (1927).

(12) German Patent 179,627.