[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF SAINT LOUIS UNIVERSITY]

Certain Homologs of Thioprocaine[1]

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Hansen and Fosdick[2] reported the synthesis of several alkyl esters of *p*-aminothiobenzoic acid and of β-diethylamino-ethyl *p*-aminothiobenzoate which they named Thiocaine. Karjala and McElvain[3] reported the synthesis of 2-methylpiperidinopropylthiol- and -thionbenzoates. All these compounds were reported as efficient local anesthetics, so it was thought that further work on thioprocaine homologs would be interesting.

Karjala and McElvain[3] prepared their -thiolbenzoates by coupling mercaptans with acid chlorides. Their yields of substituted mercaptans were quite low in spite of working in an atmosphere of nitrogen. This method was tried as a means of preparing thioprocaine but was discarded when all attempts to prepare β-diethylaminoethyl mercaptan gave the corresponding disulfide.

Six dialkyl aminopropyl *p*-aminobenzoates were prepared essentially according to the method of Hansen and Fosdick

$p\text{-}NO_2C_6H_4COSK \longrightarrow$
$p\text{-}NO_2C_6H_4COSCH_2CH_2CH_2Cl \longrightarrow$
$p\text{-}NH_2C_6H_4COSCH_2CH_2CH_2Cl \longrightarrow$
$p\text{-}NH_2C_6H_4COSCH_2CH_2CH_2NR$

These alkamine esters were isolated as their hydrochlorides and were analyzed for chlorine. The analyses indicate with one exception that the compounds were isolated as their dihydrochlorides; γ-di-*n*-butylaminopropyl *p*-aminothiobenzoate hydrochloride upon analysis gave values for chlorine and sulfur which lie midway between the values calculated for the mono- and dihydrochlorides. Further treatment with dry hydrogen chloride did not alter the analyses, so the compound was believed to be isolated as a mixture of about equal moles of the mono- and the dihydrochlorides.

The alkamine ester hydrochlorides were all somewhat hygroscopic, the γ-di-allylaminopropyl and γ-di-*n*-amylaminopropyl *p*-aminothiobenzoates especially so. Exposure to moist air caused the compounds to become bright yellow in color and partially water insoluble.

Preliminary determinations of their local anesthetic action were made by placing small samples of the hydrochlorides on the tongue and noting the intensity and duration of the anesthetic effect. The diethyl-, di-*n*-propyl- and diisopropylamino derivatives showed mild anesthetic action lasting for ten minutes; the di-*n*-amylamino derivative showed somewhat stronger action lasting twenty-five to thirty minutes, while the diallylamino and the di-*n*-butylamino derivatives showed intense action, lasting for the former ten to twelve minutes and the latter twenty-five to thirty minutes.

It was noted during the preparation of these compounds that exposure of the tender skin between the fingers or on the back of the hand to some intermediate products caused the formation of small water blisters which were very sensitive to heat and water. No attempt was made to study the relative vesicant action of these intermediate thio compounds, or whether they all have that action.

Experimental Part

I. **β,β'-Diethylaminodiethyl Disulfide Hydrobromide.**—In a round-bottomed flask were placed 200 ml. of ethanol and 9.5 g. of sodium. Excess hydrogen sulfide gas was passed into the sodium ethylate to form sodium hydrosulfide. To this was added 50 g. of 1-bromo-2-diethylaminoethane hydrobromide[4] as the dry salt. After the first reaction had subsided the mixture was refluxed for forty-five minutes to complete the reaction. The sodium bromide was filtered from the cooled reaction mixture and the ethanol removed *in vacuo* at 50°. The residue was distilled *in vacuo* giving 13.5 g. (53%) of a light yellow, viscous liquid, boiling at 160° at 16 mm.; 0.6018 g. dissolved in 22.11 g. of benzene caused a 0.543° lowering of the freezing point from which the molecular weight was calculated at 256. The theoretical value is 133 for β-diethylaminoethyl mercaptan and 264 for the disulfide. The compound formed a white crystalline hydrobromide melting at 223° which analyzed for N gave a calculated formula, $C_{12}H_{30}Br_2N_2S_2$.

II. **γ-Chloropropyl *p*-Nitrothiobenzoate.**—In a round-bottomed flask were placed 48 g. of potassium *p*-nitrothiobenzoate and 500 ml. of ethanol. Excess 1-chloro-3-bromopropane was added slowly, the reaction mixture warmed and shaken to start the reaction. The mixture

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(1) This article is condensed from a dissertation submitted by Carl F. Lischer to the faculty of the Graduate School of St. Louis University in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

(2) Hansen and Fosdick, THIS JOURNAL, **55**, 2872 (1933).

(3) Karjala and McElvain, *ibid.*, **55**, 2966 (1933).

(4) Meyer and Hopff, *Ber.*, **54**, 2279 (1921).

TABLE I

	Compound	Yield, %	M. p., °C. corr.	Analytical data Found, %	Calcd., %
I	$[(C_2H_5)_2NCH_2CH_2]_2S_2 \cdot 2HBr$	53	223	N, 6.52	6.57
II	*p*-$NO_2C_6H_4COSCH_2CH_2CH_2Cl$	87	59–60	Cl, 13.57	13.65
III	*p*-$NH_2C_6H_4COSCH_2CH_2CH_2Cl$	90	50–51	Cl, 15.85	15.80
IV	*p*-$NH_2C_6H_4COSCH_2CH_2CH_2N(C_2H_5)_2 \cdot 2HCl$	78	190–191	Cl, 21.21	20.90
V	*p*-$NH_2C_6H_4COSCH_2CH_2CH_2N(C_3H_7)_2 \cdot 2HCl$ (*n*)	60	167	Cl, 19.21	19.31
VI	*p*-$NH_2C_6H_4COSCH_2CH_2CH_2N(C_3H_7)_2 \cdot 2HCl$ (iso)	47	196	Cl, 19.19	19.31
VII	*p*-$NH_2C_6H_4COSCH_2CH_2CH_2N(C_3H_5)_2 \cdot 2HCl$	38	143	Cl, 19.21	19.52
VIII	*p*-$NH_2C_6H_4COSCH_2CH_2CH_2N(C_4H_9)_2 \cdot HCl$ and 2HCl	56	162	Cl[5], 14.75 S[5], 8.61	
IX	*p*-$NH_2C_6H_4COSCH_2CH_2CH_2N(C_5H_{11})_2 \cdot 2HCl$	36	183	Cl, 16.66	16.75

was heated for an hour on the water-bath to complete the reaction. The ethanol was removed by distillation and the product extracted from the residue with ether. After recrystallization from 95% ethanol the γ-chloropropyl *p*-nitrobenzoate formed pale yellow flakes or needles melting at 59° corr. The yield was 52.1 g. or 87% of the theoretical amount.

III. γ-Chloropropyl *p*-Aminothiobenzoate.—Eight and four-tenths grams of finely powdered γ-chloropropyl *p*-nitrothiobenzoate was suspended in a previously cooled mixture of 150 ml. of 95% ethanol and 40 ml. of concentrated hydrochloric acid and stirred for twenty hours at 4° while 10 g. of 100-mesh iron powder was added slowly. The reaction mixture was diluted with four volumes of ice water, neutralized with ammonium hydroxide to a *p*H of around 6 and extracted with ether. The ether extract was dried over calcium chloride and then treated with dry hydrogen chloride gas to precipitate the hydrochloride. This salt when suspended in water hydrolyzed completely and the free base was extracted with ether and recrystallized from 50% aqueous ethanol, giving white needles melting at 50–51°. The yield was 7.8 g. or 90% of the theoretical amount.

IV–IX. γ-Dialkylaminopropyl *p*-Aminothiobenzoates.—One mole of γ-chloropropyl *p*-aminothiobenzoate and 2.4 moles of dialkylamine were heated in a sealed tube for six hours at 100°. The contents of the tube was washed out with ether and the dialkylamine hydrochloride filtered off. The ether and excess amine were removed *in vacuo* at 100°, the residue taken up in dry ether and treated with dry hydrogen chloride. The precipitate formed was treated with water, filtered from insoluble matter, decolorized with charcoal, made basic with ammonium hydroxide and extracted with ether. The ether extract was dried over calcium chloride and treated with dry hydrogen chloride. The hydrochlorides were recrystallized from an ethanol–benzene mixture and gave pale yellow to nearly white crystalline products. These salts were water soluble, although the di-*n*-butylamino and di-*n*-amylamino compounds were only slowly soluble in water, first forming a yellow oil which afterward dissolved. The aqueous solutions were fairly stable to boiling, but became cloudy after standing for several weeks. The salts were hygroscopic and the moist salts turned a brilliant yellow, became partially water insoluble, and had a bitter taste and a garlic-like odor.

Table I gives the yields, melting points, and analytical data obtained for the compounds reported in this paper.

Summary

By the method described β,β'-diethylaminodiethyl disulfide and not β-diethylaminoethyl mercaptan is isolated when 1-bromo-2-diethylaminoethane hydrobromide and sodium hydrosulfide are made to react.

Six γ-dialkylaminopropyl esters of *p*-aminobenzoic acid were prepared and shown to be local anesthetics.

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(5) Theoretical values for the compound are: monohydrochloride 9.88% Cl, 8.98% S; dihydrochloride 18.41% Cl, 8.32% S; average 14.15% Cl, 8.62% S.