[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Sulfur-containing Amines. V. Local Anesthetics. I

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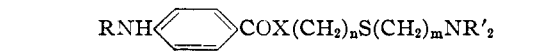
In continuation of the investigation proceeding in these laboratories on the effect of sulfur-interrupted basic side chains on pharmacological activity[1] there have been prepared a number of local anesthetic type compounds derived from sulfur-containing amines. The majority of these compounds contain the *p*-aminobenzoyl nucleus, as in (I) or (II). As variants of this type, the *p*-amino group has been altered to a *p*-*n*-butylamino group (III), and the amide linkage has been changed from secondary to tertiary (IV). No



I, X = O, R = H III, X = NH, R = n-C_4H_9
II, X = NH, R = H IV, X = NC_2H_5, R = H

compounds of these types have previously been described in the literature.

Although considerable work has been carried out on investigations of *p*-aminobenzoates, very few *p*-aminobenzamides are described in the literature. Wenker[2] described a short series of N-alkyl and N,N-dialkyl *p*-aminobenzamides, the higher homologs of which were strong surface anesthetics. Einhorn[3] has patented a series of N-(2-dialkylaminoethyl)-*p*-alkylaminobenzamides and ascribes to this series a high local anesthetic activity. Blicke, Parke and Jenner[4] prepared a number of N-(2-dialkylaminoethyl)- and N-(3-dialkylaminopropyl)-4-amino-1-naphthoamides, whose activity was less than that of the corresponding esters. The well known compound 2-butoxy-N-(2-diethylaminoethyl)-cinchoninamide hydrochloride (nupercaine) possesses a very high activity, but also a high toxicity. In general, it appears from statements in the literature that conversion of the ester linkage to the amide linkage in these local anesthetic types produces a moderate to large increase in activity, but the therapeutic index is not affected advantageously.

The favorable toxicity ratios obtained with therapeutically active compounds by inclusion of the thio linkage[5] in the basic side chain indicated that this desirable property might also be obtained in other series. In order to determine both the effect of sulfur on toxicity and the effect as a "weighting" atom in the basic side chain (*i. e.*, considered as equivalent to two methylene groups), the series was extended to include *p*-aminobenzamides containing basic side chains interrupted by oxygen, and in both types the number of methylene groups in the side chain was widely varied.

The basic side chains used in the present work were mostly prepared by methods previously reported.[1,6] However, the sulfur-interrupted basic side chains containing the —$SCH_2CH_2NH_2$ termination were most conveniently prepared by a modification of the method of Brighton and Reid,[7] involving reaction between a thiol and 2-bromoethylamine in the presence of a base. When solutions of equimolecular amounts of thiol and 2-bromoethylamine hydrobromide in methanol were treated with two equivalents of sodium methoxide at −10° to 0° there were obtained 70–90% yields of the desired amines.

Attempts to prepare the 2-(dialkylaminoalkylmercapto)-ethylamines through reaction of a dialkylaminoalkyl halide with 2-aminoethylisothiouronium bromide hydrobromide and a base, or through reaction of a dialkylaminoalkylisothiouronium chloride hydrochloride with 2-bromoethylamine hydrobromide and a base, resulted in considerably lower yields than were obtainable by the above described procedure.

This series of compounds has been tested for local anesthetic activity following subcutaneous administration around the external canthus of rabbits' eyes. The compounds showed varying degrees of activity; at present, however, the data are insufficient to classify them according to activity. A complete report will be published by Dr. T. J. Becker and Dr. F. P. Luduena of these Laboratories at a later date.

Experimental[8]

Isothiouronium Salts.—All of the isothiouronium salts used in the present work were prepared by refluxing equimolecular amounts of a dialkylaminoalkyl chloride

TABLE I

ISOTHIOURONIUM SALTS $R_2N(CH_2)_nSC(NH)NH_2 \cdot 2HX$

R_2	n	Yield, %	M. p., °C.	Formula	Nitrogen analyses, % Calcd.	Found
H_2[a]	2	87	194–195	$C_4H_9N_3S \cdot 2HBr$	14.95	14.89
$(n\text{-}C_4H_9)_2$	2	78	131.5–133	$C_{11}H_{25}N_3S \cdot 2HCl$	13.81	13.66
$(n\text{-}C_4H_9)_2$[b]	3	80	142–144	$C_{12}H_{27}N_3S \cdot 2HCl$	13.20	12.92
C_5H_{10}[c,d]	2	96	225–225.5	$C_8H_{17}N_3S \cdot 2HCl$	16.16	16.02
C_4H_8O[e]	2	80	233–235	$C_7H_{15}N_3OS \cdot 2HCl$	15.98	15.70

[a] Calcd.: S, 11.41. Found: S, 11.58. [b] Calcd.: S, 10.07. Found: S, 10.20. [c] N-Piperidyl. [d] Calcd.: Cl, 27.25. Found: Cl, 27.14. [e] N-Morpholinyl.

(1) For the preceding paper in this series see Laskowski and Clinton, THIS JOURNAL, **69**, 519 (1947).

(2) Wenker, *ibid.*, **60**, 1081 (1938).

(3) Einhorn, U. S. Patent 2,073,100 (1937).

(4) Blicke, Parke and Jenner, THIS JOURNAL, **62**, 3316 (1940).

(5) Huber, Bair, Boehme, Laskowski, Jackman and Clinton, *ibid.*, **67**, 1849 (1945); Huber, Bair, Laskowski, Jackman and Clinton, *ibid.*, **68**, 322 (1946).

(6) Clinton, Suter, Laskowski, Jackman and Huber, *ibid.*, **67**, 594 (1945).

(7) Brighton and Reid, *ibid.*, **65**, 458 (1943).

(8) All melting points and boiling points are corrected. The authors are indebted to Mr. Morris E. Auerbach and staff for the analyses.

hydrochloride (or bromide hydrobromide) and thiourea in three to four volumes of ethanol for six to twenty-four hours.[9] The shorter time could be used with ethyl chlorides or bromides; the longer period is preferable with propyl chlorides and with higher dialkylaminoethyl chlorides. Usually the isothouronium salt partially crystallized during the reflux period. The reaction mixture was cooled, filtered and the filtrate concentrated to a small volume. The combined crops of crystalline material were then recrystallized to a constant melting point, usually from absolute ethanol–ethyl acetate. New isothiouronium salts are listed in Table I.

Thiols.—Two modifications were used in the preparation of the thiols. Examples of each method follow:

2-Dimethylaminoethanethiol.[10] **Method A.**—One mole of 2-dimethylaminoethylisothiouronium chloride hydrochloride (m. p. 182–183°; ref. 10 gives m. p. 181–182°) was dissolved in 350 ml. of warm water and treated with an aqueous solution of two moles of sodium hydroxide in 100 ml. of water. Upon working up by a method analogous to that previously described[9] there was obtained a 22% yield of colorless product, b. p. 142–146° at 750 mm. In this and similar cases of low molecular weight thiols the loss of product by ether co-distillation is very high.

Method B.—For the preparation of large amounts of 2-diethylaminoethanethiol[9] it was found more convenient to proceed as follows:

A mixture of 855 g. (5.00 moles) of 2-chlorotriethylamine hydrochloride, 380 g. (5.00 moles) of thiourea and 3000 ml. of water was refluxed for five hours. The cooled solution was treated with a solution of 408 g. (10.00 moles) of 97% sodium hydroxide in 1000 ml. of water, the mixture saturated with salt, and extracted with ether. The ethereal solution was dried over anhydrous potassium carbonate, filtered, and the ether distilled through an efficient column at atmospheric pressure. The residue was distilled *in vacuo*. There were thus obtained yields of 45–60% of theory of colorless product, b. p. 46–48° at 4 mm.

An additional method, namely, the conversion of the isothiouronium salts to thiols by means of alkoxides in alcohols, is at present being investigated. Preliminary results indicate that this reaction is complicated by the formation of by-products other than the desired thiols (*e. g.*, the corresponding dialkylaminoalkylmercaptoalkanes). These results will be made the subject of a later communication.

The new thiols prepared in the present work are listed and characterized in Table II.

2-(Dialkylaminoalkylmercapto)-ethylamines

2-(2-Diethylaminoethylmercapto)-ethylamine.—Method A.—In a one-liter three-neck flask, equipped with a mechanical Hershberg-type stirrer, internal thermometer and dropping funnel, was placed 102.5 g. of 2-bromoethylamine hydrobromide,[11] 66.5 g. of 2-diethylaminoethanethiol and 400 ml. of methanol. The mixture was cooled to −10° by means of an external ice–salt–Dry Ice bath and there was added during forty-five minutes, with stirring, a solution of 23.0 g. of sodium in 400 ml. of methanol. During the addition of the first half of the sodium methylate solution, no exothermic effect was noted; addition of the second half produced an exothermic reaction. The internal temperature was maintained at −10° throughout this addition. The cold bath was removed and stirring was continued for an additional two hours. The flask was equipped with a 24″ Claisen–Vigreux column and the methanol was distilled with stirring at atmospheric pressure. The semi-solid residue was triturated with several portions of ether, the combined ether triturates were concentrated by distillation, and the residual oil fractionated *in vacuo*. There was obtained 81 g. (92% yield) of colorless product, b. p. 92–94° at 1.1 mm., $n^{20}D$ 1.4912. The dithiocarbamate-alcoholate had m. p. 142–143° (d.).[6]

Method B.—Treatment of a mixture of 124 g. of 2-diethylaminoethylisothiouronium chloride hydrochloride[9] and 102.5 g. of 2-bromoethylamine hydrobromide in 400 ml. of absolute ethanol with a solution of 46.0 g. of sodium in 1000 ml. of absolute ethanol at −10°, under the general conditions outlined in Method A above, gave 47.0 g. (53%) of 2-(2-diethylaminoethylmercapto)-ethylamine. Variation of the temperature during the reaction (*e. g.*, between −15° and 5°) did not improve the yield; however, preparation of the thiol *in situ* by the addition of the equivalent amount of sodium ethylate to the isothiouronium salt at 25°, followed by the addition of 2-bromoethylamine hydrobromide and sodium ethylate at −10°, increased the yield to 84%.

Method C.—Treatment of an equimolecular mixture of 2-aminoethylisothiouronium bromide hydrobromide and 2-chlorotriethylamine hydrochloride in absolute ethanol with four equivalents of sodium ethylate at −10° gave an 18% yield of 2-(2-diethylaminoethylmercapto)-ethylamine. Temperature variation (*e. g.*, between −15° and 10°), or difference in mode of addition of the reaction components did not markedly improve the yield. In all cases substantial amounts of N^1,N^4-diethylpiperazinium diethochloride[12] were formed.

The new 2-(dialkylaminoalkylmercapto)-ethylamines prepared in the present work are given in Table II. All of these compounds were prepared by Method A at −10° in methanol. The yields given represent material boiling within a two degree range; the boiling points reported are those of the analytically pure samples. The thiols used in the preparation of these amines are described in References 1 and 6, in the text above, and in Table II. Characterizing derivatives are listed in Table II.

2-(2-Diethylaminoethylmercapto)-diethylamine.—2-Hydroxydiethylamine[13] was converted by 48% hydrobromic acid to **2-bromodiethylamine hydrobromide**, essentially by the general procedure of Cortese.[11] The compound was obtained in 79% yield, white prisms from absolute ethanol–ether, m. p. 200–203°.

Anal. Calcd. for $C_4H_{10}BrN\cdot HBr$: N, 6.01. Found: N, 5.87.

The bromoamine was condensed with 2-diethylaminoethanethiol in methanol at −10° as described in Method A above, to yield 83% of the desired product, b. p. 88.5° at 0.20 mm., $n^{25}D$ 1.4765.

Anal. Calcd. for $C_{10}H_{24}N_2S$: N, 13.58; S, 15.53. Found: N, 13.50; S, 15.80.

The **dipicrate** formed canary-yellow prisms from dilute ethanol, m. p. 127.0–128.5°.

Anal. Calcd. for $C_{22}H_{30}N_8O_{14}S$: S, 4.82. Found: S, 4.80.

2-(2-Diethylaminoethoxy)-ethylamine.—A mixture of 253.5 g. of 2-chloro-2′-phthalimidoethyl ether,[14] 219 g. of diethylamine and 1500 ml. of ethanol was refluxed for thirty hours, and then concentrated to dryness *in vacuo*. The residual paste was taken up in water and extracted with three 200 ml. portions of ether. Washing and evaporation of the ether gave 218 g. of crude **2-(2-phthalimidoethoxy)-triethylamine** as a mobile light brown oil. The **hydrochloride** formed white prisms from absolute ethanol–ethyl acetate, m. p. 141–142°.

Anal. Calcd. for $C_{14}H_{23}ClN_2O_3$: N, 8.57; Cl, 10.85. Found: N, 8.57; Cl, 10.93.

Cleavage of the phthalimido base with hydrazine hydrate in the usual manner[15] gave a 61% yield (based on 2-phthalimido-2′-chloroethyl ether) of colorless product, b. p. 78.0° at 4.00 mm., $n^{25}D$ 1.4430.

(9) *Cf.* Albertson and Clinton, THIS JOURNAL, **67**, 1222 (1945).

(10) J. H. Williams, Doctoral Dissertation, New York University, 1933; Renshaw, Dreisbach, Ziff and Green, THIS JOURNAL, **60**, 1765 (1938).

(11) Cortese, *ibid.*, **58**, 191 (1936).

(12) Gough and King, *J. Chem. Soc.*, 2437 (1928); Eisleb, *Ber.*, **74**, 1433 (1941).

(13) Obtained through the courtesy of Sharples Chemicals, Inc.

(14) Cretcher, Koch and Pittenger, THIS JOURNAL, **47**, 1173 (1925).

(15) Ing and Manske, *J. Chem. Soc.*, 2348 (1926).

TABLE II

R_2	X	n	m	Yield,[a] %	Bases M. p. or B. p., °C./mm.	$n^{25}D$	Formula	Analyses, % Calcd.	Found
Thiols, $R_2N(CH_2)_nSH$									
$(n\text{-}C_4H_9)_2$	..	2	..	83[b]	138/26[c]	....	$C_{10}H_{23}NS$	N, 7.39	7.51
$(n\text{-}C_4H_9)_2$	..	3	..	65[d,e]	112/2	1.4994	$C_{11}H_{25}NS$	N, 6.88	6.23
C_5H_{10}[f]	..	2	..	72[d]	85/11	1.4995	$C_7H_{15}NS$	S, 22.07[g]	21.90
C_4H_8O[h]	..	2	..	54[d]	101/15	1.5030	$C_6H_{13}NOS$	S, 21.77	21.62
2-(Dialkylaminoalkylmercapto)-ethylamines, $R_2N(CH_2)_nSCH_2CH_2NH_2$									
$(CH_3)_2$	..	2	..	72	53/0.04	1.4660	$C_6H_{16}N_2S$	N, 18.90	18.80
$(C_2H_5)_2$	..	3	..	78	64/ .04	1.4882	$C_9H_{22}N_2S$	N, 14.72	14.92
$(n\text{-}C_4H_9)_2$	..	2	..	61	90/ .01	1.4813	$C_{12}H_{28}N_2S$	S, 13.79	13.79
$(n\text{-}C_4H_9)_2$	..	3	..	44	115/ .01	1.4800	$C_{13}H_{30}N_2S$	N, 11.37	11.18
C_5H_{10}[f]	..	2	..	81	81/ .15	1.5145	$C_9H_{20}N_2S$	[k]	[k]
C_5H_{10}[f]	..	3	..	74	101/ .10	1.5118	$C_{10}H_{22}N_2S$	N, 13.85	13.56
C_4H_8O[h]	..	2	..	75	109/ .25	1.5198	$C_8H_{18}N_2OS$	S, 16.85	16.96
p-Nitrobenzamides, $NO_2C_6H_4CONH(CH_2)_nX(CH_2)_mNR_2$									
$(CH_3)_2$	S	2	2	73	64.5[n]	....	$C_{13}H_{19}N_3O_3S$	N, 14.15	14.35
$(C_2H_5)_2$	S	2	2	92	oil	....	.....	.....	...
$(C_2H_5)_2$	S	3	2	96	oil	....	.....	.....	...
$(C_2H_5)_2$	S	2	3	96	oil	....	.....	.....	...
$(C_2H_5)_2$	S	3	3	99	oil	....	.....	.....	...
$(C_2H_5)_2$	S[p]	2	2	98	oil	....	.....	.....	...
$(n\text{-}C_4H_9)_2$	S	2	2	95	oil	....	.....	.....	...
C_6H_{10}[f]	S	2	2	92	69.5–70.5[n]	....	$C_{16}H_{23}N_3O_3S$	N, 12.45[q]	12.29
C_5H_{10}[f]	S	2	3	93	61.5–62.5[n]	....	$C_{17}H_{25}N_3O_3S$	N, 11.96[s]	11.82
C_4H_8O[h]	S	2	2	95	101.5–102.0[n]	....	$C_{15}H_{21}N_3O_4S$	N, 4.13[t,u]	4.14
$(C_2H_5)_2$	O	2	2	99	51.5–52.0[n]	....	$C_{15}H_{23}N_3O_4$	N, 13.59	13.50
$(C_2H_5)_2$	O	3	2	99	oil	....	.....	.....	...
$(C_2H_5)_2$	O	3	3	99	oil	....	.....	.....	...
p-Aminobenzamides, $H_2NC_6H_4CONH(CH_2)_nX(CH_2)_mNR_2$									
$(CH_3)_2$	S	2	2	58	oil	....	.....	.....	...
$(C_2H_5)_2$	S	2	2	75	70–71[n]	....	$C_{15}H_{25}N_3OS$	N[v], 14.22	14.04
$(C_2H_5)_2$	S	3	2	92	oil	....	.....	.....	...
$(C_2H_5)_2$	S	2	3	93	104–105.5[n]	....	$C_{16}H_{27}N_3OS$	N[w], 13.58	13.56
$(C_2H_5)_2$	S	3	3	86	oil	....	$C_{17}H_{29}N_3OS$	N[x], 4.33	[aa], 4.17
$(C_2H_5)_2$	S[bb]	2	2	90	oil	....	$C_{17}H_{29}N_3OS$	N[x], 4.33	[cc], 4.08
$(n\text{-}C_4H_9)_2$	S	2	2	99	oil	....	.....	.....	...
C_6H_{10}[f]	S	2	2	98	oil	....	.....	.....	...
C_5H_{10}[f]	S	2	3	98	92.8–94.8[n]	....	$C_{17}H_{27}N_3OS$	N[z], 4.36	[ee], 4.28
C_4H_8O[h]	S	2	2	90	oil	....	.....	.....	...
$(C_2H_5)_2$	O	2	2	98	67.5–68.5[n]	....	$C_{15}H_{25}N_3O_2$	N, 15.04	14.98
$(C_2H_5)_2$	O	3	2	79	oil	....	.....	.....	...
$(C_2H_5)_2$	O	3	3	96	oil	....	$C_{17}H_{29}N_3O_2$	N[t], 4.56	[kk], 4.21

Anal. Calcd. for $C_8H_{20}N_2O$: N, 17.48. Found: N, 17.16.

The **dipicrate** formed small, canary-yellow prisms from ethanol, m. p. 130.5–131.5°.

Anal. Calcd. for $C_{20}H_{26}N_8O_{15}$: N, 18.12. Found: N, 18.21.

3-(2-Diethylaminoethoxy)-propylamine and 3-(3-diethylaminopropoxy)-propylamine were prepared by the method of Whitmore, *et al.*,[16] in comparable yields. The amines were characterized through the **dithiocarbamates**, m. p. 134.5–136.0° and 119–121.5°, respectively.

Anal. Calcd. for $C_{10}H_{22}N_2OS_2$: S, 25.55. Found: S, 25.74. Calcd. for $C_{11}H_{24}N_2OS_2$: S, 24.25. Found: S, 23.74

(16) Whitmore, *et al.*, THIS JOURNAL, **66**, 725 (1944).

2-(2-Diethylaminoethylmercapto)-ethyl *p*-Nitrobenzoate.—To a cooled solution of 79.5 g. of *p*-nitrobenzoyl chloride in 300 ml. of dry benzene was added a cold solution of 75 g. of 2-(2-diethylaminoethylmercapto)-ethanol[6] in 200 ml. of dry benzene over a period of fifteen minutes with vigorous stirring and maintenance of the internal temperature below 5°. The mixture was then allowed to warm to room temperature, and treated with a slight excess of 35% sodium hydroxide solution with cooling. The benzene layer was separated and concentrated *in vacuo*, yielding 91.6 g. (66%) of crude product as a yellow mobile oil. The *picrate* crystallized in yellow needles from a large volume of ethanol, m.p. 154–155°.

Anal. Calcd. for $C_{21}H_{25}N_5O_{11}S$: S, 5.77. Found: S, 5.77.

3-(2-Diethylaminoethylmercapto)-propyl *p*-Nitrobenzoate.—The condensation of 3-(2-diethylaminoethyl-

TABLE II (*Continued*)

Characterizing derivatives

Derivative	M. p., °C.	Formula	Analyses, % Calcd.	Found
Picrate	147.5–148.5	$C_{16}H_{26}N_4O_7S$	S, 7.66	7.56
Picrate	90–92	$C_{17}H_{28}N_4O_7S$	S, 7.41	7.14
Hydrochloride	204–205	$C_7H_{16}ClNS$	N, 7.71	7.68
Picrate	113–115	$C_{12}H_{16}N_4O_8S$	S, 8.51	8.28
Dithiocarbamate	143–144[i]	$C_7H_{16}N_2S_3$	N, 12.49	12.44
Dithiocarbamate	123.5–124.5[i]	$C_{10}H_{22}N_2S_3$	N, 10.51	10.51
Dithiocarbamate[j]	94.5–96.5[i]	$C_{13}H_{30}N_2OS_3$	N, 8.58	8.39
Dithiocarbamate[j]	120–122[i]	$C_{14}H_{32}N_2OS_3$	N, 8.23	8.10
Dithiocarbamate[l]	143.5–144.5[i]	$C_{12}H_{25}N_2OS_3$	[m]	[m]
Dithiocarbamate	155–156[i]	$C_{11}H_{22}N_2S_3$	N, 10.06	9.91
Dipicrate	99–101	$C_{20}H_{24}N_8O_{15}S$	S, 4.94	4.95
Picrate	156–157	$C_{19}H_{22}N_6O_{10}S$	S, 6.09	6.46
Picrate[o]	120–122	$C_{21}H_{26}N_6O_{10}S$	S, 5.78	5.77
Picrate	120.5–123.5	$C_{22}H_{28}N_6O_{10}S$	S, 5.63	5.60
Picrate	111.5–112.5	$C_{22}H_{28}N_6O_{10}S$	S, 5.63	5.67
Picrate	102.5–105.0	$C_{23}H_{30}N_6O_{10}S$	S, 5.50	5.49
Chloroplatinate	154–155[i]	$C_{17}H_{29}Cl_6N_3O_3PtS$	Pt, 25.57	25.80
Picrate	79.5–80.5	$C_{25}H_{34}N_6O_{10}S$	S, 5.25	5.12
Picrate[r]	142–143	$C_{22}H_{26}N_6O_{10}S$	S, 5.66	5.71
Picrate	115.0–115.5	$C_{23}H_{28}N_6O_{10}S$	S, 5.53	5.45
Picrate	145.5–146.5	$C_{21}H_{24}N_6O_{10}S$	S, 5.63	5.59
Flavianate	190.5–192.0	$C_{25}H_{29}N_5O_{12}S$	S, 5.14	5.16
Picrate	113.5–114.8	$C_{22}H_{28}N_6O_{11}$	N, 15.21	15.00
Picrate	94.5–95.5	$C_{23}H_{30}N_6O_{11}$	N, 14.84	14.73
Diphosphate	133–135	$C_{13}H_{27}N_3O_9P_2S$	N, 9.07	8.84
Dipicrate[w]	132.5–135	$C_{27}H_{31}N_9O_{15}S$	S, 4.25	4.36
Citrate	108–117[i]	$C_{22}H_{35}N_3O_8S$	N[x], 8.37	8.21
Dipicrolonate	117–118	$C_{36}H_{35}N_7O_6S$	S, 3.82	3.82
.....	.....	.....	.....	...
Dipicrate	133–133.5	$C_{29}H_{35}N_9O_{15}S$	S, 4.07	4.16
Dipicrate	94.5–95.5	$C_{31}H_{39}N_9O_{15}S$	S, 3.95	4.03
Dihydriodide	210–212[i]	$C_{16}H_{27}I_2N_3OS$	N[dd], 7.46	7.17
Diflavianate[ff,gg]	245–247[i]	$C_{37}H_{39}N_7O_{17}S_3$	S, 10.10	10.11
Dihydrochloride	236–238.5	$C_{15}H_{25}Cl_2N_3O_2S$	S[hh], 8.38	8.27
Dihydrochloride	177–179	$C_{15}H_{27}Cl_2N_3O_2$	N[ii], 11.93	11.87
Citrate	111–113.5	$C_{22}H_{35}N_3O_9$	N[jj], 8.65	8.45
.....	.....	.....	.....	...

[a] Yields are based on the pure product except in the case of the *p*-nitrobenzamides. [b] Preparation method A in text. [c] German Patent 631,016, *via Chem. Abs.*, **30**, 6008 (1936), reported b. p. 73–74° at 2 mm. [d] Preparation method B in text. [e] Yield 79% by preparation method A. [f] 1-Piperidyl. [g] Calcd.: C, 57.88; H, 10.41. Found: C, 57.63; H, 10.30. [h] 4-Morpholinyl. [i] With decomposition. [j] Hydrate. [k] Calcd.: C, 57.39; H, 10.70. Found: C, 57.75; H, 10.69. [l] Alcoholate. [m] Calcd.: C. 46.41; H, 8.44. Found: C, 46.66; H, 8.26. [n] M. p., °C. [o] Citrate, m. p. 103–105°. *Anal.* Calcd. for $C_{21}H_{31}N_3O_{10}S$: C, 48.73; H, 6.04. Found: C, 48.91; H, 6.05. [p] N-ethyl-N-(2-(2-diethylaminoethylmercapto)-ethyl)-*p*-nitrobenzamide. [q] Calcd.: S, 9.50. Found: S, 9.63. [r] Phosphate, m. p. 177.5–178.5°. *Anal.* Calcd. for $C_{16}H_{26}N_3O_7PS$: N, 9.66. Found: N, 9.82. [s] Calcd.: S, 9.12. Found: S, 8.99. [t] Tertiary amino nitrogen by titration with perchloric acid in glacial acetic acid solution. [u] Calcd.: S, 9.44. Found: S, 9.31. [v] Calcd.: S, 10.85. Found: S, 10.85. [w] Dihydrochloride; m. p. 172.5–174. Calcd. for $C_{15}H_{25}N_3OS\cdot 2HCl$: N, 11.41; Cl, 19.25. Found: N, 11.26; Cl, 19.18. [x] Calcd.: S, 6.39; Found: S, 6.46. [y] Calcd.: S, 10.36. Found: S, 10.36. [z] Aromatic amino nitrogen by diazotization. [aa] Calcd.: S, 9.89. Found: S, 9.51. [bb] N-Ethyl-N-(2-(2-diethylaminoethylmercapto)-ethyl)-*p*-aminobenzamide. [cc] Calcd.: S, 9.89. Found: S, 9.25. [dd] Calcd.: S, 5.69. Found: S, 5.88. [ee] Calcd.: S, 9.97. Found: S, 10.11. [ff] Shown to be a diflavianate rather than a monoflavianate by determination of aromatic nitrogen. Calcd.: N, 1.47. Found: N, 1.47. [gg] Dihydriodide, m. p. 200° (d.). Calcd. for $C_{17}H_{29}I_2N_3OS$: N, 7.27; S, 5.55. Found: N, 7.12; S, 5.72. [hh] Calcd.: Cl, 18.55. Found: Cl, 18.55. [ii] Calcd.: Cl, 20.13. Found: Cl, 20.11. [jj] Calcd.: C, 54.42; H, 7.26. Found: C, 54.20; H, 7.33. [kk] Tertiary aliphatic nitrogen by titration. Calcd.: N, 4.56. Found: N, 4.56.

mercapto)-propanol[6] with *p*-nitrobenzoyl chloride by the above method gave a 70% yield of the base; pale yellow mobile oil, b. p. 178–180° at 0.1 mm.

Anal. Calcd. for $C_{16}H_{24}N_2O_4S$: N, 8.23. Found: N, 8.16.

The **picrate** formed tiny, canary-yellow needles from ethanol, m.p. 91.5–92.5°.

Anal. Calcd. for $C_{22}H_{27}N_5O_{11}S$: S, 5.63. Found: S, 5.66.

1-(2-**Dimethylaminoethylmercapto**)-isopropyl *p*-**Nitrobenzoate Hydrochloride.**—This compound was obtained directly from the alcohol[1] and *p*-nitrobenzoyl chloride by the above method, small white prisms from absolute ethanol–ether, m. p. 133.7–135°.

Anal. Calcd. for $C_{14}H_{21}ClN_2O_4S$: S, 9.19. Found: S, 9.40.

p-**Nitrobenzamides.**—The condensation of *p*-nitrobenzoyl chloride with the dialkylaminoalkylmercaptoalkylamines could be carried out in cold, dry benzene, as outlined above for the alcohols. The crude yields averaged 70–80%, but under these conditions decomposition and side-reactions were extensive, and the products were very difficult to purify. The following general method was found preferable:

To a solution of 37.8 g. of sodium bicarbonate in 240 ml. of water was added 52.8 g. of 2-(2-diethylaminoethylmercapto)-ethylamine. To the resulting mechanically stirred mixture was added dropwise during one hour a solution of 66.9 g. of *p*-nitrobenzoyl chloride in 600 ml. of dry chloroform at room temperature. The addition proceeded smoothly, without large exothermic effects or vigorous carbon dioxide evolution. After stirring for an additional hour the chloroform layer was separated and the water layer extracted with an additional 50 ml. of chloroform. After washing the combined chloroform layers successively with dilute sodium bicarbonate solution and with water, they were dried over Drierite and concentrated *in vacuo*. The pale yellow, mobile residue of **N-(2-(2-diethylaminoethylmercapto)-ethyl)-*p*-nitrobenzamide** weighed 91.2 g. (92% crude yield). The compound could not be obtained in crystalline form.

Attempts to distil the *p*-nitrobenzamide bases at pressures as low as 10^{-5} mm. failed, due to extensive decomposition at the boiling point. However, in certain cases the bases could be obtained crystalline after purification through a suitable derivative.

The *p*-nitrobenzamide bases prepared in the present work are described and characterized by derivatives in Table II.

2-(2-**Diethylaminoethylmercapto**)-ethyl *p*-**Aminobenzoate.**—The reduction of the nitro compound was carried out with reduced iron powder and hydrochloric acid in aqueous alcoholic solution, by a method analogous to that of West.[17] There was obtained a 92% yield of crude product as a pale yellow, mobile oil. The **phosphate hydrate** crystallized from ethanol in tiny white needles, m. p. 141–145°.

Anal. Calcd. for $C_{15}H_{27}N_2O_6PS\cdot H_2O$: N, 6.79. Found: 6.63.

By a similar reduction there was prepared **3-(2-diethylaminoethylmercapto)-propyl *p*-aminobenzoate** in 95% yield. The pale yellow mobile oil could not be induced to crystallize. The **picrate** formed golden yellow needles from ethanol, m. p. 125–126°.

Anal. Calcd. for $C_{22}H_{29}N_5O_9S$: S, 5.94. Found: S, 5.90.

The **citrate** crystallized in rosets of small white needles from absolute ethanol–ethyl acetate, m. p. 103–104.5°.

Anal. Calcd. for $C_{28}H_{34}N_2O_9S$: N, 5.57; S, 6.37. Found: N, 5.35; S, 6.44.

1-(2-**Dimethylaminoethylmercapto**)-**isopropyl *p*-aminobenzoate diphosphate** formed white prisms from ethanol–ether, m. p. 128–130°.

Anal. Calcd. for $C_{14}H_{28}N_2O_{10}P_2S$: N, 5.86; S, 6.70. Found: N, 5.88; S, 6.75.

p-**Aminobenzamides.**—Reduction of the *p*-nitrobenzamide bases by means of reduced iron–hydrochloric acid gave crude yields of 40–50% of impure *p*-aminobenzamides. The yields and purity were substantially improved through the use of ferrous sulfate and ammonia for the reduction:

A three-liter beaker was mounted on a small electric hotplate and equipped with a Hershberg-type mechanical stirrer, an internal thermometer, and two 250-ml. dropping funnels. In one funnel was placed a solution of 42.5 g. of N-(2-(2-diethylaminoethylmercapto)-ethyl)-*p*-nitrobenzamide in 320 ml. of ethanol and in the second was placed a mixture of 135 ml. of concentrated ammonium hydroxide (28%) and 150 ml. of water. A solution of 255 g. of pure ferrous sulfate heptahydrate in 900 ml. of water was prepared in the beaker and heated to 80–85°. While the ferrous sulfate solution was stirred vigorously the contents of the dropping funnels were added dropwise during forty-five minutes, maintaining the ratio so that the mixture in the beaker always remained alkaline. The internal temperature was maintained at 80–85° during this addition, and for an additional one hour of stirring. The volume was maintained nearly constant by the occasional addition of alcohol. Filter-cel was then added to the hot mixture and the slurry was filtered, the filterpad being washed thoroughly with warm ethanol. The ethanol was distilled from the filtrate *in vacuo*, the aqueous residue was made strongly alkaline with concentrated aqueous ammonia, and extracted with ethyl acetate. After drying the combined extracts over Drierite the ethyl acetate was removed *in vacuo*, finally at 60° and 0.05 mm. There was thus obtained 29.5 g. (76%) of **N-(2-(2-diethylaminoethylmercapto)-ethyl)-*p*-aminobenzamide.** Crystallization from ethyl acetate–Skellysolve B gave pure material with but little loss.

The *p*-aminobenzamide bases could not be distilled without decomposition at pressures as low as 10^{-5} mm. The above procedure gave analytically pure material in most cases, however. A number of attempts were made to catalytically reduce the sulfur-containing nitro-bases, using a variety of catalysts and conditions. In all cases catalyst poisoning was rapid and reduction failed. Catalytic reduction of the non-sulfur-containing nitro-bases proceeded readily with Raney nickel or platinum.

The *p*-aminobenzamides prepared in the present work are described, and characterized by derivatives, in Table II.

N-(2-(2-Diethylaminoethylmercapto)-ethyl) *p*-*n*-Butylaminobenzamide.[18]—A mixture of 59.0 g. of N-(2-(2-diethylaminoethylmercapto)-ethyl)-*p*-aminobenzamide, 52.2 g. of pure zinc dust (4 mole proportion), 49.2 ml. of glacial acetic acid (4.10 mole proportion) and 200 ml. of dry benzene was stirred and heated under reflux. To this mixture was added dropwise during thirty minutes a solution of 17.4 g. (1.21 mole proportion) of *n*-butyraldehyde in 20 ml. of dry benzene. After stirring under reflux for an additional one hour the mixture was filtered hot and the filter cake was washed thoroughly with hot benzene. The filtrate (two layers) was made strongly basic to litmus with 35% sodium hydroxide solution, the benzene layer was separated, and the aqueous layer was extracted with two further portions of benzene. The combined benzene extracts were dried over Drierite, decolorized with Darco G-60, and concentrated *in vacuo*, finally at 60° and 0.05 mm. for three hours. The product was a viscous, pale yellow oil.

Anal. Calcd. for $C_{19}H_{33}N_3OS$: S, 9.13; N, 11.98. Found, S, 9.16; N, 11.70.

The **dipicrate** crystallized from glacial acetic acid in small, yellow-orange prisms, m. p. 148–149°.

Anal. Calcd. for $C_{31}H_{39}N_9O_{15}S$: S, 3.96. Found: S, 3.99.

(17) West, *J. Chem., Soc.*, **127**, 494 (1925).

(18) This procedure is an adaptation of the general method of German Patent 491,856 (*Frdl.*, **16**, 356 (1927)).

Summary

There has been described the preparation of a series of dialkylaminoalkylmercaptoalkyl *p*-aminobenzoates and N-(dialkylaminoalkylmercaptoalkyl)-*p*-aminobenzamides, and several of their oxygen analogs. Preliminary pharmacological data indicate a high local anesthetic activity coupled with low toxicity for certain of these compounds.

RENSSELAER, NEW YORK RECEIVED JULY 29, 1947

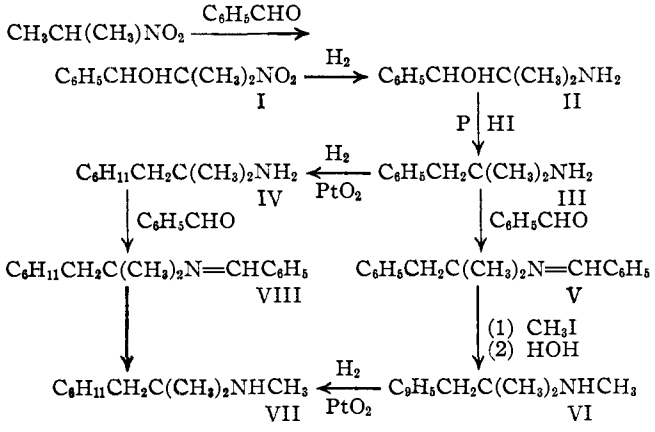
[CONTRIBUTION FROM THE SCIENTIFIC LABORATORIES, FREDERICK STEARNS & COMPANY, DIVISION OF STERLING DRUG, INC.]

Preparation of α,α-Dimethyl- and N,α,α-Trimethyl-β-cyclohexylethylamine

BY BERNARD L. ZENITZ,[1a] ELIZABETH B. MACKS[1b] AND MAURICE L. MOORE[1c]

Since it was found that the series of β-cyclohexylalkylamines previously reported[2a] possesses pressor activity and produces little nervous stimulation, two additional members of this series, α,α-dimethyl-β-cyclohexylethylamine (IV) and its N-methyl derivative (VII), were prepared and their pharmacological activity was investigated.

The following synthetic scheme was employed[2b].



The condensation of benzaldehyde with 2-nitropropane, using an adaptation of Kamlet's procedure,[3] gave only poor yields (8–12%) of the nitro alcohol (I) whereas substantially higher yields were obtained when the condensation was carried out with sodium ethoxide in alcohol.

Gakenheimer and Hartung[4] observed that the catalytic hydrogenation of certain aliphatic nitro alcohols in neutral medium resulted in a fission of the nitro alkanol chain, but that the reduction proceeded satisfactorily in an acid medium. Similar results were experienced in this investigation. Catalytic hydrogenation of the nitro alcohol (I) in neutral alcoholic solution with a palladium-charcoal catalyst at 80° and sixty pounds pressure appeared to produce a fission of the molecule since a strong amine odor was detectable in the reaction mixture and none of the desired amino alcohol could be isolated. However, in the presence of acetic acid, hydrogenation produced a satisfactory yield of the amino alcohol (II).

In addition, the reduction was also accomplished with sodium amalgam and with zinc and acetic acid, the best yield being obtained by this last method.

α,α-Dimethyl-β-phenylethylamine (III) has been obtained by Shelton and Van Campen, Jr.,[5] by the catalytic hydrogenation of α,α-dimethyl-β-chloro-β-phenylethylamine. Mentzer and co-workers[6] have also reported its preparation by the action of slaked lime on *sym*-bis-(α,α-dimethyl-β-phenylethyl)-urea at 230° and by the hydrolysis of α,α-dimethyl-β-phenylethylisocyanate with concentrated hydrochloric acid, but their melting point of 147–148° for the hydrochloride is not in agreement with the 199–200° obtained by us or with the 195–196° reported by Shelton and Van Campen, Jr.

In the present investigation, an attempt to dehydroxylate the amino alcohol (II) by the catalytic reduction method of Rosenmund and Karg[7] was unsuccessful but the dehydroxylation was accomplished with red phosphorus and hydriodic acid, the method previously employed by Suter and Docken.[2b] The phenylalkylamine (III) obtained was N-methylated by the Becker and Decker method, and these two amines were then converted to their corresponding cyclohexyl analogs (IV and VII) by the general catalytic hydrogenation procedure previously described.[2a]

In order to obtain the secondary amine (VII)

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(2a) Zenitz, Macks and Moore, THIS JOURNAL, 69, 1117 (1947).

(2b) Although only compound III has been described in the literature (refs. 5 and 6), C. M. Suter in a personal communication indicated that compounds I, III, and VI were previously prepared at Northwestern University by Suter and Docken and that II has been obtained in the laboratories of Commercial Solvents Corp. Compound IV has been mentioned in a patent (ref. 5), but no physical constants were given.

(3) Kamlet, U. S. Patent 2,151,517, March, 1939.

(4) Gakenheimer and Hartung, *J. Org. Chem.*, 9, 85 (1944).

(5) Shelton and Van Campen, Jr., U. S. Patent 2,408,345, Sept., 1946.

(6) (a) Mentzer, *Compt. rend.*, 213, 581 (1941); (b) Mentzer, Buu-Hoi and Cagniant, *Bull. soc. chim.*, 9, 813 (1942).

(7) Rosenmund and Karg, *Ber.*, 75, 1854 (1942).