3.8 Å. region. For a given glyceride the beta-b long spacing exceeds that of beta-a by about 2 Å.

Beta-a is invariably obtained from the melt and may sometimes be obtained by solvent crystallization. Highly stable at room temperature, it transforms to beta-b near the m. p. Beta-b, apparently the only thermodynamically stable form, is obtained by transformation of beta-a and commonly by solvent crystallization.

It is notable that no alpha-like patterns were observed, although they are readily obtained with 1-mono- and triglycerides.

Purely on the basis of similarity in X-ray diffraction patterns, it is suggested that a structural similarity may exist between beta-a diglyceride forms and beta-2 triglyceride forms and between beta-b (diglyceride) and beta-3 (triglyceride).

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[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Sulfur-Containing Amines. VIII.[1] Local Anesthetics. III

BY R. O. CLINTON, U. J. SALVADOR AND S. C. LASKOWSKI

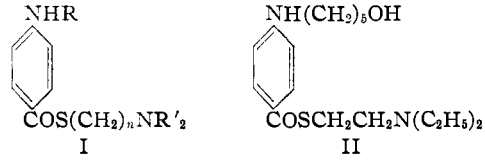
In extending previous investigations[2,3] there have been prepared a number of dialkylaminoalkyl thiol esters derived from various nuclei, for testing as local anesthetics.

In comparison to the oxygen analogs, very few local anesthetics of the dialkylaminoalkyl thiol ester type have appeared in the literature. Karjala and McElvain[4] have recorded the preparation of 3-(2-methylpiperidyl-1)-propyl thiolbenzoate hydrochloride, the thiol analog of Metycaine, by a four step synthesis *via* 3-bromopropyl thiolbenzoate. Lischer and Jordan[5] prepared a short series of 3-dialkylaminopropyl 4-aminothiolbenzoate hydrochlorides *via* 3-chloropropyl 4-nitrothiolbenzoate, in which the terminal tertiary amino group varied from diethylamino to diamylamino. Sergievskaya and Kropacheva[6] investigated a series of diethylamino-ethyl, -propyl and -butyl naphthalene-1-thiolcarboxylates and 4-aminonaphthalene-1-thiolcarboxylates. These compounds were reported by the authors to possess high anesthetic potency without irritation or other untoward effects. Further, a patent[7] reported the properties of three diethylaminoethyl 4-alkoxythiolbenzoate hydrochlorides, prepared by the action of a 4-alkoxybenzoyl chloride on 2-bromoethanethiol and subsequent reaction with a secondary amine.

An important advantage of simple local anesthetics of the types of Apothesine and Metycaine is the lack of PABA interference in clinical usage. It was felt in the present work that simple thiolbenzoates and thiolcinnamates might, while satisfying this condition, in addition possess lowered toxicity while retaining activity. Certain examples of these types have been prepared.

A few additional examples of diphenylthiolacetates[3,8] were prepared, since pharmacological screening has indicated that these compounds are strong local anesthetics, in analogy with other antispasmodics of related type.

A further interesting type of thiol ester is that related to Thiocaine.[2,9] This ester possesses a high therapeutic index in relation to Procaine[9]; similar high activity in analogous types is reported by Lischer and Jordan.[5] This series has therefore been widely extended, through variation of the dialkylaminoalkyl grouping. Of greater interest, insofar as activity is concerned, are the dialkylaminoalkyl thiol esters, (I), related to Tetracaine. A series of these compounds was prepared,



I II

either by reductive alkylation of the parent 4-aminothiolbenzoate, or by the reaction between a dialkylaminoalkanethiol and a 4-alkylaminobenzoyl chloride hydrochloride. A new example of this type was prepared by using 5-hydroxypentanal as the alkylating agent, to yield the compound II. The effect on activity of the inclusion of a hydroxyl group in this position of the nucleus has not been previously determined.

Several thiol esters derived from 2-butyloxyquinoline-4-carboxylic acid were also prepared, to determine whether the high toxicity and irritation associated with the Nupercaine series could be decreased through inclusion of a sulfur linkage in the ester group. Further, two examples of the 4-alkoxythiolbenzoate type[7] were prepared from the acid chloride and a thiol, to enable evaluation in comparison with the 4-aminothiolbenzoate analogs.

(1) Paper VII, Clinton, Salvador and Laskowski, THIS JOURNAL, **71**, 1300 (1949).

(2) Albertson and Clinton, *ibid.*, **67**, 1222 (1945).

(3) Clinton and Salvador, *ibid.*, **68**, 2076 (1946).

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

(5) Lischer and Jordan, *ibid.*, **59**, 1623 (1937).

(6) Sergievskaya and Kropacheva, *J. Gen. Chem.* (*U. S. S. R.*), **10**, 1737 (1940) (*C. A.*, **35**, 4003 (1941)).

(7) Harris and Braker, U. S. Patent 2,342,142.

(8) Richardson, U. S. Patent 2,390,555 (1945); Dupré, Lévy and Tchoubar, *Compt. rend. soc. biol.*, **140**, 477 (1946); Tchoubar and Letellier-Dupré, *Bull. soc. chim.*, 792 (1947).

(9) Hansen and Fosdick, THIS JOURNAL, **55**, 2872 (1933); *J. Pharmacol.*, **50**, 323 (1934); Nolle, *Farm. i. Farmacol.* (*U. S. S. R.*), (1937) No. 2, 1 [*C. A.*, **34**, 3820 (1940)].

TABLE I

DIALKYLAMINOALKYL INTERMEDIATES $R_2N(CH_2)_nX$

			Compound					Analyses, %		Picrate	Analyses, % Nitrogen[a]	
R_2	n	X	M. p. or b. p., °C.	Mm.	$n^{25}D$	Yield, %	Formula	Calcd.	Found	M. p., °C.	Calcd.	Found
C_6H_{12}[b]	2	OH	87.0	8	1.4788	86	$C_8H_{17}NO$[c]	N, 9.85	9.80	109–111[d]	3.76	3.75
C_6H_{12}[b]	2	Cl.HCl	184–185		....	98	$C_8H_{17}Cl_2N$[e]	N, 7.07	7.00	.....	...	...
C_6H_{12}[b]	2	Cl	88.0	16	1.4721	65	$C_8H_{16}ClN$[f]	N, 8.66	8.62	136.1–136.7	3.58	3.62
C_6H_{12}[b]	2	SCH_4ClN_2[g]	226–227		....	94	$C_9H_{21}Cl_2N_3S$	S, 11.69	11.84	.....	...	...
C_6H_{12}[b]	2	SH	96.5–97	14	1.4974	57	$C_8H_{17}NS$	N, 8.79	8.87	117–118	3.61	3.62
C_5H_{10}[h]	2	OH	72	8	1.4683	56	$C_7H_{15}NO$[i]	N, 10.84	10.67	103–104[j]	11.72	11.79
C_5H_{10}[h]	2	SCH_4ClN_2[g,l]	205–208		....	96	$C_8H_{19}Cl_2N_3S$	S, 12.32	12.52	.....	...	...
C_5H_{10}[h]	2	SH	74.0–74.5	11	1.4898	44	$C_7H_{15}NS$	N, 9.64	9.63	.....	...	...
C_4H_8O[m]	3	SCH_4ClN_2[g,n]	218–220		....	95	$C_8H_{19}Cl_2N_3S$	S, 11.61	11.70	.....	...	...
C_4H_8O[m]	3	SH	110–112	11–12	1.4962	42	$C_7H_{15}NOS$	N, 8.69	8.72	129–130	3.59	3.59
C_6H_{12}[b]	3	Cl.HCl[o]	177.2–178.2		....	97	$C_8H_{19}Cl_2N$[p]	N, 6.60	6.85	.....	...	...
C_6H_{12}[b]	3	SCH_4ClN_2[g]	186–188		....	97	$C_{10}H_{23}Cl_2N_3S$	S, 11.12	11.16	.....	...	...
C_6H_{12}[b]	3	SH	95.5	6	1.4950	53	$C_9H_{19}NS$	N, 8.08	8.13	116–118	3.48	3.48

[a] See ref. 22. [b] 2-Methylpiperidyl-1. [c] Calcd.: OH, 11.96. Found: OH, 12.18. [d] The picrolonate, yellow plates from absolute alcohol, melted at 185–186°. *Anal.* Calcd. for $C_{18}H_{25}N_5O_6$: N,[a] 3.44. Found: N,[a] 3.46. [e] Calcd.: Cl, 35.79. Found: Cl, 35.86. [f] Calcd.: Cl, 21.93. Found: Cl, 21.60. [g] Isothiouronium chloride hydrochloride. [h] 2-Methylpyrrolidyl-1. [i] Calcd.: OH, 13.16. Found: OH, 13.37. [j] The picrolonate, canary yellow needles from absolute alcohol, melted at 168–169°. *Anal.* Calcd. for $C_{17}H_{23}N_5O_6$: N,[k] 7.12. Found: N,[k] 6.93. [k] Nitro nitrogen, determined by titration with titanous chloride in glacial acetic acid solution. [l] From the chloride hydrochloride, m. p. 187–188°; unpublished work by Dr. A. W. Ruddy of these Laboratories. [m] 4-Morpholinyl. [n] From the chloride hydrochloride, described by Adams and Whitmore, THIS JOURNAL, **67**, 735 (1945). [o] The free base has been described by McElvain, ref. 14. [p] Calcd.: Cl, 33.42. Found: Cl, 33.20.

In most of the above series an attempt has been made to vary the basic ester portion of the molecule sufficiently to ascertain variations of toxicity and activity accompanying such changes.

Complete pharmacological data will be published at a later date by Dr. F. P. Luduena and Dr. T. J. Becker of these laboratories.

Experimental[10]

3-Dialkylaminopropanols.—Substantial improvements in yield were made in the synthesis of certain 3-dialkylaminopropanols, through modification of the conventional secondary amine-trimethylene chlorohydrin procedure of Adams, *et al.*[11,12] This synthesis is illustrated by the description in detail of the preparation of **3-(2-methylpiperidyl-1)-propanol**. A mixture of 770 g. (7.78 moles) of 2-methylpiperidine,[13] 368 g. (3.89 moles) of trimethylene chlorohydrin, 800 ml. of absolute alcohol and 30 g. of sodium iodide or potassium iodide, was refluxed with stirring for twenty-four hours. The stirred reaction mixture, after cooling, was treated with a solution of 90 g. (3.9 moles) of sodium in 1500 ml. of absolute alcohol, filtered, and the filtercake was washed well with ether. The filtrate was distilled at atmospheric pressure, with mechanical stirring, through a twelve-inch Vigreux column to a head temperature of 122°, reserving the fraction of b. p. 105–122° for recovery of 2-methylpiperidine. The still residue was diluted with three volumes of ether, filtered, and distilled, first at atmospheric pressure and then *in vacuo*. Redistillation gave 582 g. (95% yield based on trimethylene chlorohydrin or 92% yield based on recovered 2-methylpiperidine) of colorless product, b. p. 105–108° at 10–11 mm., $n^{25}D$ 1.4769 (lit.,[14] 60% yield, b. p. 112° at 15 mm., $n^{20}D$ 1.4780).

In a similar manner **3-(4-morpholinyl)-propanol** was prepared in 92% yield (twice distilled), b. p. 109–111° at 7–8 mm., $n^{25}D$ 1.4745 (lit.[15] 75% yield, b. p. 147–149° at 21 mm., $n^{25}D$ 1.4743), and **3-(1-piperidyl)-propanol** was prepared in 93% yield (twice distilled), b. p. 93.5–95° at 9 mm., $n^{25}D$ 1.4755 (lit.[12], 82% yield, b. p. 149° at 68 mm.; see also Brill[16]).

Dialkylaminoalkanethiols.—The two new dialkylaminoethanols used in the present work were prepared by the reaction between a secondary amine and ethylene oxide in boiling methanol, by a method similar to that of Pollard.[17] The alcohols were converted to the chloride hydrochlorides by treatment with thionyl chloride in chloroform solution. The thiols were then prepared by methods previously outlined.[18] The new compounds are listed in Table I.

Dialkylaminoalkyl Thiolbenzoates, Thiolcinnamates and Diphenylthiolacetates.—These compounds were prepared with little difficulty by the usual method. The thiol ester hydrochlorides were usually obtained crystalline directly from the reaction; however, in certain cases (*e. g.*, 2-(2-methylpiperidyl-1)-ethyl diphenylthiolactate) it was necessary to purify the isolated base by transference from acid to base twice, with appropriate washings. The hydrochlorides were crystallized from absolute alcohol–ethyl acetate or acetone–ethyl acetate. These compounds are listed in Table II.

2-(2-Methylpiperidyl-1)-ethyl 4-butyloxythiolbenzoate hydrochloride was prepared in quantitative yield by the reaction between 2-(2-methylpiperidyl-1)-ethanethiol and 4-butyloxybenzoyl chloride[19] in dry benzene. The compound crystallized from absolute alcohol in rosets of white needles, m. p. 171.4–173.0°.

Anal. Calcd. for $C_{19}H_{30}ClNO_2S$: Cl, 9.53; S, 8.61. Found: Cl, 9.32; S, 8.74.

In a similar manner there was obtained **2-diethylaminoethyl 4-hexyloxythiolbenzoate hydrochloride**, as white needles from ethyl acetate, m. p. 125.0–126.3°.

Anal. Calcd. for $C_{19}H_{32}ClNO_2S$: C, 61.02; H, 8.62; S, 8.57. Found: C, 61.13; H, 8.58; S, 8.65.

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

(11) Adams, *et al.*, THIS JOURNAL, **59**, 2249 (1937).

(12) *Cf.* also the novel synthesis of these compounds by Hromatka, *Ber.*, **75**, 131 (1942).

(13) Prepared in 90% yield by the reduction of 2-methylpyridine (4 moles) with Raney nickel (40 g.) at 1000 lb. and 190°. The reduction required three hours. *Cf.* Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison, Wisconsin, 1937, pp. 64–67.

(14) McElvain and Carney, THIS JOURNAL, **68**, 2592 (1946).

(15) Cheney and Bywater, *ibid.*, **64**, 970 (1942); *cf.* Gardner and Haenni, *ibid.*, **53**, 2763 (1931), and ref. 12.

(16) Brill, *ibid.*, **47**, 1134 (1925).

(17) Pollard, *ibid.*, **57**, 1988 (1935).

(18) Clinton, Salvador, Laskowski and Suter, *ibid.*, **70**, 950 (1948).

(19) Rohmann, U. S. Patent 2,081,712 (1937).

TABLE II

THIOL ESTERS

R_2	n	Derivative	M. p., °C.	Formula	Analyses, % Calcd.	Found	Calcd.	Found
			Thiolbenzoates, $C_6H_5COS(CH_2)_nNR_2$					
$(C_2H_5)_2$	2	Hydrochloride	137–138.5	$C_{13}H_{20}ClNOS$	N, 5.12	5.41	S, 11.72	11.97
$(C_2H_5)_2$	3	Hydrochloride	93.6–96.2	$C_{14}H_{22}ClNOS$	Cl, 12.32	12.32	S, 11.14	11.32
$(C_2H_5)_2$	4	Hydrochloride	115.5–116.5	$C_{15}H_{24}ClNOS$	Cl, 11.76	11.98	N, 4.64	4.50
C_5H_{10}[a]	3	Hydrochloride	171–172.5	$C_{15}H_{22}ClNOS$	Cl, 11.82	11.90	N, 4.67	4.64
C_6H_{12}[b]	2	Hydrochloride	200.5–201.5	$C_{15}H_{22}ClNOS$	Cl, 11.82	11.72	S, 10.69	10.68
C_6H_{12}[b,c]	3	Hydrochloride	138.2–139.4	$C_{16}H_{24}ClNOS$	Cl, 11.30	11.10	S, 10.22	10.12
			Diphenylthiolacetates, $(C_6H_5)_2CHCOS(CH_2)_nNR_2$					
C_4H_8O[d]	2	Hydrochloride	205.4–206.5	$C_{20}H_{24}ClNO_2S$	Cl, 9.38	9.19	S, 8.48	8.38
C_6H_{12}[b]	2	Phosphate	170.5–171.0	$C_{22}H_{30}NO_5PS$	N, 3.10	2.96	S, 7.10	7.12
C_6H_{12}[b]	3	Hydrochloride	162–163.5	$C_{23}H_{30}ClNOS$	Cl, 8.77	8.55	S, 7.93	7.98
			Thiolcinnamates, $C_6H_5CH{=}CHCOS(CH_2)_nNR_2$					
$(CH_3)_2$	2	Hydrochloride	178.5–179.4	$C_{13}H_{18}ClNOS$	N, 5.15	5.15	S, 11.79	11.97
$(C_2H_5)_2$	2	Hydrochloride	156.5–158	$C_{15}H_{22}ClNOS$	Cl, 11.82	11.91	N, 4.67	4.65
$(C_2H_5)_2$	3	Hydrochloride	110–113.8	$C_{16}H_{24}ClNOS$	Cl, 11.30	11.41	S, 10.22	10.45
$(C_2H_5)_2$	4	Hydrochloride	131.8–133	$C_{17}H_{26}ClNOS$	Cl, 10.82	10.85	N, 4.27	4.21
C_5H_{10}[a]	3	Hydrochloride	177–179.5	$C_{17}H_{24}ClNOS$	N, 4.29	4.35	S, 9.83	9.98
C_6H_{12}[b]	2	Hydrochloride	193.3–194.6	$C_{17}H_{24}ClNOS$	Cl, 10.88	10.63	S, 9.83	9.82
C_6H_{12}[b]	3	Hydrochloride	163–165	$C_{18}H_{26}ClNOS$	Cl, 10.43	10.18	S, 9.43	9.54
			p-Nitrothiolbenzoates, $NO_2C_6H_4COS(CH_2)_nNR_2$					
$(CH_3)_2$	2	Hydrochloride[e]	191.6–194.2	$C_{11}H_{15}ClN_2O_3S$	Cl, 12.19	11.99	S, 11.03	10.99
$(C_2H_5)_2$	3	Hydrochloride	125–127	$C_{14}H_{21}ClN_2O_3S$	Cl, 10.65	10.35	S, 9.63	9.68
$(C_2H_5)_2$	4	Hydrochloride	160.5–162	$C_{15}H_{23}ClN_2O_3S$	Cl, 10.22	10.10	S, 9.24	9.32
C_4H_8O[d]	2	Hydrochloride	209.6–211	$C_{13}H_{17}ClN_2O_4S$	Cl, 10.65	10.62	S, 9.63	9.83
C_4H_8O[d]	3	Hydrochloride[f]	201–202	$C_{14}H_{19}ClN_2O_4S$	Cl, 10.23	10.08	S, 9.24	8.99
C_5H_{10}[a]	2	Hydrochloride	175–176.6	$C_{14}H_{19}ClN_2O_3S$	Cl, 10.72	10.73	S, 9.69	9.94
C_5H_{10}[a]	3	Hydrochloride	206–207.5	$C_{15}H_{21}ClN_2O_3S$	Cl, 10.28	10.07	S, 9.30	9.30
C_6H_{12}[b]	2	Hydrochloride	163.5–165.9	$C_{15}H_{21}ClN_2O_3S$	Cl, 10.28	10.00	S, 9.30	9.29
C_6H_{12}[b]	3	Hydrochloride	184–186	$C_{16}H_{23}ClN_2O_3S$	S, 8.93	8.72	...	...
C_5H_{10}[g]	2	Hydrochloride[h]	171.4–172	$C_{14}H_{19}ClN_2O_3S$	Cl, 10.72	10.45	S, 9.69	9.92
C_6H_{10}[g]	2	Picrate	194.5–196.0	$C_{20}H_{21}N_5O_{10}S$	N,[i] 2.67	2.67	...	...
			p-Aminothiolbenzoates, $NH_2C_6H_4COS(CH_2)_nNR_2$					
$(CH_3)_2$	2	Phosphate	187–189.2	$C_{11}H_{19}N_2O_5PS$	N, 8.64	8.41	S, 9.94	9.98
$(C_2H_5)_2$	3	Phosphate[j]	209.8–210.6	$C_{14}H_{25}N_2O_5PS$	N, 7.68	7.38	S, 8.79	8.82
$(C_2H_5)_2$	4	Phosphate	199.2–200.8	$C_{15}H_{27}N_2O_5PS$	N, 7.40	7.22	S, 8.47	8.32
C_4H_8O[d]	2	Phosphate	207–208	$C_{13}H_{21}N_2O_6PS$	S, 8.80	8.84	[k]	[k]
C_4H_8O[d]	2	Base	161–162	$C_{13}H_{18}N_2O_2S$	N, 10.52	10.30	...	...
C_4H_8O[a]	3	Phosphate	129–135.6	$C_{14}H_{23}N_2O_6PS$	N, 7.40	7.21	S, 8.47	8.50
C_5H_{10}[a]	2	Phosphate	204–206	$C_{14}H_{23}N_2O_5PS$	S, 8.85	8.79	[l]	[l]
C_5H_{10}[a]	2	Base	122.5–123.5	$C_{14}H_{20}N_2OS$	N, 10.60	10.32	S, 12.13	12.04
C_5H_{10}[a]	3	Phosphate[m]	210–211.2	$C_{15}H_{25}N_2O_5PS$	N, 7.44	7.22	S, 8.52	8.62
C_6H_{12}[b]	2	Phosphate	196.7–197.8	$C_{15}H_{25}N_2O_5PS$	S, 8.52	8.64	[n]	[n]
C_6H_{12}[b]	2	Base	98.5–99.5	$C_{15}H_{22}N_2OS$	S, 11.52	11.81	...	...
C_6H_{12}[b]	3	Flavianate[o]	223.4–224.0	$C_{68}H_{84}N_{10}O_{19}S_5$	S, 10.65	10.79	N, 3.72[p]	3.89
$(C_2H_5)_2$[q]	[r]	Phosphate	147–151	$C_{16}H_{29}N_2O_5PS$	N, 7.14	7.03	[s]	[s]
			p-Butylaminothiolbenzoates, $C_4H_9NHC_6H_4COS(CH_2)_nNR_2$					
$(CH_3)_2$	2	Dihydrochloride	157–161.5	$C_{15}H_{26}Cl_2N_2OS$	Cl, 20.07	20.07	S, 9.07	8.96
$(C_2H_5)_2$	2	Dihydrochloride	142.6–145.6	$C_{17}H_{30}Cl_2N_2OS$	Cl, 18.59	18.65	S, 8.40	8.52
$(C_2H_5)_2$	2	Citrate	154.6–156	$C_{23}H_{36}N_2O_8S$	N, 5.60	5.42	S, 6.40	6.22
$(C_2H_5)_2$	3	Dihydrochloride	138–139.8	$C_{18}H_{32}Cl_2N_2OS$	N, 7.08	7.34	S, 8.10	7.95
$(C_2H_5)_2$	4	Dihydrochloride	103.2–107	$C_{19}H_{34}Cl_2N_2OS$	Cl, 17.32	17.03	S, 7.83	7.72
C_4H_8O[d]	2	Dihydrochloride	196.4–199.2	$C_{17}H_{28}C_2N_2O_2S$	Cl, 17.93	17.65	S, 8.11	8.08
C_4H_8O[d]	2	Base	67–68	$C_{17}H_{26}N_2O_2S$	N, 8.68	8.40	....	...

TABLE II (*Continued*)

R₂	n	Derivative	M. p., °C.	Formula	Analyses, % Calcd.	Found	Calcd.	Found
C_4H_8O[d]	3	Dihydrochloride[f]	192.6–197.2	$C_{17}H_{30}Cl_2N_2O_2S$	Cl, 17.32	17.36	S, 7.83	7.66
C_5H_{10}[a]	2	Dihydrochloride	200.4–203.4	$C_{18}H_{30}Cl_2N_2OS$	Cl, 18.02	17.75	S, 8.15	7.92
C_6H_{10}[a]	2	Base	65.5–67.0	$C_{18}H_{28}N_2OS$	N, 8.74	8.64	....	...
C_6H_{10}[a]	3	Dihydrochloride	186–188.4	$C_{19}H_{32}Cl_2N_2OS$	Cl, 17.40	17.35	S, 7.87	7.68
C_6H_{12}[b]	2	Sesquiphosphate[u]	112.5–124.5	$C_{38}H_{69}N_4O_{14}P_3S_2$	S, 6.66	6.79	N, 5.82	5.78
C_6H_{12}[b]	3	Dihydrochloride	170.8–173.4	$C_{20}H_{34}Cl_2N_2OS$	Cl, 16.82	16.51	S, 7.60	7.69
C_5H_{12}[b]	3	Picrolonate	134–137	$C_{30}H_{40}N_6O_6S$	N,[i] 4.57	4.32	...	...

[a] 1-Piperidyl. [b] 2-Methylpiperidyl-1. [c] Reported (ref. 4) m. p. 137–138°. [d] 4-Morpholinyl. [e] Reported m. p. 187° (dec.) [Renshaw, Dreisbach, Ziff and Green, THIS JOURNAL, **60**, 1765 (1938)]. [f] The crude base crystallized in pale yellow plates from dilute alcohol, m. p. 62.5–64.0°. [g] 2-Methylpyrrolidyl-1. [h] The crude base had m. p. 53–55° (from Skellysolve B). [i] Ref. 22. [j] *Cf.* ref. 5. [k] Calcd.: H_3PO_4, 26.90. Found: H_3PO_4, 26.70. [l] Calcd.: H_3PO_4, 27.05. Found: H_3PO_4, 26.80. [m] The base crystallized from dilute alcohol as an unstable hydrate, m. p. 78–80°, and from benzene–Skellysolve B in the anhydrous form, m. p. 60–61°. [n] Calcd.: H_3PO_4, 26.05. Found: H_3PO_4, 25.96. [o] The compound formed a flavianate with a base to flavianic acid ratio of 3:2. [p] Nitro nitrogen, by titration with titanous chloride in glacial acetic acid solution. [q] For the 4-nitrothiolbenzoate see ref. 3. [r] 4-Diethylamino-1-methylbutyl-. [s] Calcd.: C, 48.96; H, 7.44. Found: C, 49.01; H, 7.22. [t] The crude base had m. p. 50–52° (from benzene–Skellysolve B). [u] Calcd.: H_3PO_4, 30.54. Found: H_3PO_4, 31.00.

2-Diethylaminoethyl 2-butyloxyquinoline-4-thiolcarboxylate hydrochloride, from the cinchonyl chloride[20] and the thiol, formed pale yellow cottony needles from absolute alcohol–ethyl acetate–ether, m. p. 161–162°. The compound was difficultly soluble in water.

Anal. Calcd. for $C_{20}H_{29}ClN_2O_2S$: S, 8.08; Cl, 8.93. Found: S, 8.00; Cl, 8.70.

3-(Piperidyl-1)-propyl 2-butyloxyquinoline-4-thiolcarboxylate hydrochloride crystallized from absolute alcohol–ethyl acetate in slender white needles, m. p. 149–150°.

Anal. Calcd. for $C_{22}H_{31}ClN_2O_2S$: S, 7.58; Cl, 8.38. Found: S, 7.47; Cl, 8.36.

Dialkylaminoalkyl 4-Alkylaminothiolbenzoates.—The preparation of the intermediate dialkylaminoalkyl 4-nitrothiolbenzoates was effected by the reaction between 4-nitrobenzoyl chloride and the thiol in cold benzene, or in a chloroform–water–sodium bicarbonate admixture.[18] These compounds are listed in Table II. Reduction to the 4-aminothiolbenzoates was preferably carried out by a method similar to that of West,[21] since the ferrous sulfate–ammonia method used with similar types[18] offered no evident advantages in this case. Certain of the resulting dialkylaminoalkyl 4-aminothiolbenzoates (see Table II) were obtained crystalline. In the case of 2-(2-methylpyrrolidyl-1)-ethyl 4-nitrothiolbenzoate, a pure 4-amino base could not be isolated, nor were pure salts obtained from this compound.

The dialkylaminoalkyl 4-alkylaminothiolbenzoates were prepared either by reductive alkylation of the 4-amino compounds with an aldehyde in the presence of zinc dust and acetic acid, or directly from a 4-alkylaminobenzoyl chloride hydrochloride and a dialkylaminoalkanethiol. The former method was found preferable, since purification was more easily effected. The bases thus obtained were in most cases mobile, pale yellow oils, which readily yielded crystalline salts. The dialkylaminoalkyl 4-butylaminothiolbenzoates are listed in Table II; other homologs and a representative example of the reductive alkylation procedure appear below.

2-Diethylaminoethyl 4-Butylaminothiolbenzoate.—A stirred mixture of 20.0 g. (0.079 mole) of 2-diethylaminoethyl 4-aminothiolbenzoate,[2] 20.6 g. (0.32 mole) of zinc dust, 19.5 g. (0.33 mole) of glacial acetic acid and 100 ml. of benzene was brought to reflux on the steam-bath. During the course of twenty minutes there was added dropwise a solution of 6.9 g. (0.096 mole) of *n*-butyraldehyde in 20 ml. of benzene. After the addition was complete, refluxing and stirring were continued for an additional hour. The resulting mixture was filtered and the zinc–zinc acetate precipitate was washed thoroughly with warm dilute acetic acid and with benzene. The cooled filtrate, after being made basic to litmus with 35% sodium hydroxide solution, was filtered if necessary and the benzene layer separated. A further extraction of the aqueous layer with benzene, followed by concentration of the dried benzene extract *in vacuo*, gave 23.0 g. of residual mobile, pale yellow oil.

2-Diethylaminoethyl 4-propylaminothiolbenzoate, from the 4-amino compound[2] and propionaldehyde; the **picrate** crystallized from alcohol in canary-yellow needles, m. p. 129.5–131.3°.

Anal. Calcd. for $C_{22}H_{29}N_5O_8S$: N,[22] 5.35. Found: N,[22] 5.22.

The **dihydrochloride** crystallized from absolute alcohol–acetone–ethyl acetate in massive, pale yellow prisms, m. p. 152.4–153.5°.

Anal. Calcd. for $C_{16}H_{28}Cl_2N_2OS$: Cl, 19.30; S, 8.73. Found: Cl, 19.30; S, 8.77.

2-Diethylaminoethyl 4-Amylaminothiolbenzoate, Method A.—Reductive alkylation of ethyl 4-aminobenzoate with *n*-valeraldehyde gave a 95% yield of **ethyl 4-amylaminobenzoate**, white prisms from Skellysolve B, m. p. 54.0–55.0°.

Anal. Calcd. for $C_{14}H_{21}NO_2$: N, 5.95. Found: N, 6.05.

Saponification of the ester with aqueous-alcoholic sodium hydroxide solution gave a 99% yield of **4-amylaminobenzoic acid**, white needles from dilute alcohol, m. p. 135.5–136.5°.

Anal. Calcd. for $C_{12}H_{17}NO_2$: N, 6.76. Found: N, 6.65.

The acid was converted to the chloride hydrochloride either by the phosphorus pentachloride procedure of Graf and Langer[23] or the thionyl chloride procedure of Mndzhoyan[24]; the resulting 4-amylaminobenzoyl chloride hydrochloride was used without purification because of instability. Condensation with 2-diethylaminoethanethiol in benzene gave, after several purifications by crystallization and conversion to the base, a 45% yield of 2-diethylaminoethyl 4-amylaminothiolbenzoate as a pale yellow oil.

Method B.—The reductive alkylation of 2-diethylaminoethyl 4-aminothiolbenzoate[2] with *n*-valeraldehyde gave a 90% yield of an easily purified base.

The **picrate** formed pale orange needles from alcohol, m. p. 120.2–121.2°.

Anal. Calcd. for $C_{24}H_{33}N_5O_8S$: N,[22] 5.08. Found: N,[22] 4.83.

(20) Gardner and Hammel, THIS JOURNAL, **58**, 1360 (1936); see also ref. 1.

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

(22) Basic amino nitrogen, by titration with perchloric acid in acetic acid solution.

(23) Graf and Langer, *J. prakt. Chem.*, **148**, 161 (1937).

(24) Mndzhoyan, *J. Gen. Chem. (U. S. S. R.)*, **16**, 1033 (1946); [*C. A.*, **41**, 2737 (1947)].

A crystalline dihydrochloride was also isolated, but its extreme hygroscopicity prevented purification for analysis.

2-Diethylaminoethyl 4-heptylaminothiolbenzoate citrate, prepared from the base (reductive alkylation with *n*-heptaldehyde) and citric acid monohydrate in acetone, crystallized in rosets of tiny white needles from absolute alcohol-ethyl acetate, m. p. 123–124° (dec.).

Anal. Calcd. for $C_{26}H_{42}N_2O_8S$: N, 5.16; S, 5.91. Found: N, 4.70; S, 6.04.

2-Diethylaminoethyl 4-(5-hydroxyamylamino)-thiolbenzoate, from the 4-amino base[2] and 5-hydroxypentanal,[25,26] crystallized from benzene–Skellysolve B in large white prisms, m. p. 72.3–73.6°.

Anal. Calcd. for $C_{18}H_{30}N_2O_2S$: N, 8.28; S, 9.47. Found: N, 8.15; S, 9.53.

(25) Woods and Sanders, THIS JOURNAL, **68**, 2111 (1946); *Org. Syn.*, **27**, 43 (1947). Comparable yields were obtained when the preparation was modified by saturation of the neutralized hydrolysis mixture with ammonium sulfate, followed by a single ether extraction. This obviates the continuous ether extraction.

(26) The final reflux period, after the addition of the hydroxyaldehyde, was extended to two hours.

The **picrate** formed tiny orange-yellow needles from alcohol, m. p. 96.6–98.2°.

Anal. Calcd. for $C_{24}H_{33}N_5O_9S$: N,[22] 4.94. Found: N,[22] 4.79.

The **phosphate** crystallized from alcohol-acetone in rosets of white cottony needles, m. p. 163.6–164.4°.

Anal. Calcd. for $C_{18}H_{33}N_2O_6PS$: S, 7.35; H_3PO_4, 22.46. Found: S, 7.34; H_3PO_4, 22.51.

Summary

There has been described the preparation of a series of dialkylaminoalkyl thiol esters derived from the benzoyl, cinnamoyl, 4-aminobenzoyl, 4-alkylaminobenzoyl, 4-alkoxybenzoyl and 2-butyloxyquinoline-4-carbonyl nuclei. Modifications in the preparation of certain intermediates, leading to increased yields, have also been described.

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On an Alkaloid of *Kopsia Fruticosa*. I

BY A. BHATTACHARYA, A. CHATTERJEE[1] AND P. K. BOSE

Kopsia fruticosa, A.D. (*Apocynaceae*) is a large, evergreen shrub of the East Indies, which has been now naturalized in India. It was used as an arrow poison. All *Kopsia* species so far investigated have been found to contain alkaloids. Thus, a crystalline alkaloid has been isolated from the seeds of *K. flavida* Bl.[2]; the presence of three other alkaloids has been reported in *K. arborea* Bl., *K. albiflorum*, Bl., and *K. Roxburghii*[2] Bl. From *K. fruticosa* we have obtained a new alkaloid, kopsine, $C_{22}H_{26}N_2O_4$, m. p. 217–218° (dec.), $[\alpha]^{20}D$ +16.4° (in ethyl alcohol), and we wish to report its isolation and properties. Our mature leaves contained 0.12% kopsine and in the bark 0.06% was found (on the basis of dry weight). Thus, for large scale extraction, the leaves were preferred. Kopsine (in alcohol) is neutral to litmus. The solution shows green fluorescence. Its molecular extinction curve is represented in Fig. 1. The curve shows the maxima at 240 and 283 mμ and minima at 264, 279 and 286 mμ. The absorption spectra of kopsine are similar to those of indole alkaloids.[3,4] Kopsine does not show a coloration with ferric chloride but it gives the following reactions: concentrated sulfuric acid, colorless in the cold, pinkish upon heating; Erdmann reagent, gradual appearance of apple-green color; Fröhde reagent, solution slowly turns pink; Mandelin reagent, dissolves the alkaloid with permanganate-like color which gradually turns olive-green.

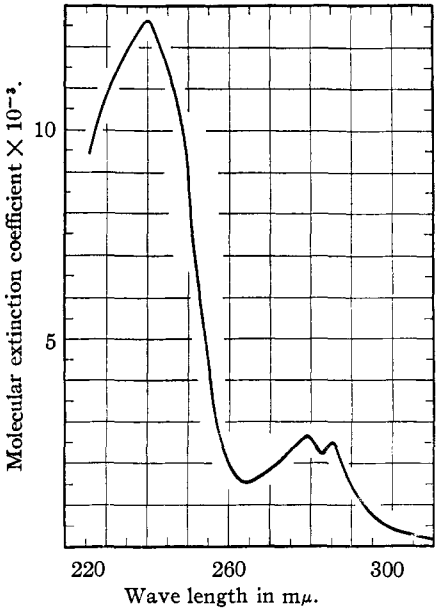

Fig. 1.—Molecular extinction curve of kopsine in alcohol.

A solution of kopsine in hydrochloric or sulfuric acid produces an orange precipitate with potassium bismuth iodide, a yellow precipitate with picric acid and a white precipitate with potassium mercuric iodide. (So far it has not been possible to prepare kopsine salts with some common mineral acids (HCl, HNO_3 and H_2SO_4, etc.) because of resinification). It forms, however, well defined

(1) Née Mookerjee.

(2) M. Greshoff, *Ber.*, **23**, 3537 (1890).

(3) M. S. Kharasch, D. W. Stanger, M. A. Bloodgood and R. R. Legault, *Science*, **83**, 36 (1936).

(4) W. A. Jacobs, L. C. Craig and A. Rothen, *ibid.*, **83**, 166 (1937).