1-Phenyl-2-benzenesulfonamido-3-bromopropane (III) from 1-Phenyl-2-amino-3-bromopropane Hydrobromide (I).—To a vigorously stirred solution of 1.5 g. (0.0051 mole) of compound I in 10 ml. of water was added 0.78 ml. (0.0060 mole) of benzenesulfonyl chloride followed immediately by a solution of 0.83 g. (0.010 mole) of sodium carbonate in 10 ml. of water. After the reaction mixture had been stirred for one hour at room temperature, the oily product was extracted with ether. The ether solution was washed thoroughly with water, and dried over magnesium sulfate. Crystallization of the oil obtained on removal of the ether solvent from ethyl alcohol afforded 1.03 g. (57%) of 1-benzene-2-benzenesulfonamido-3-bromopropane, m.p. 22–23°.

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Some Alkyl and Heterocyclic Sulfides and Sulfones

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In connection with some studies on the pharmacological activity of certain sulfur-containing compounds, a series of alkyl and heterocyclic sulfides and sulfones has been prepared. The germicidal properties of some sulfides[1] have been demonstrated. The antistreptococcal activity of 4,4′-diaminodiphenyl sulfone,[2] the antitubercular effect of this and similar compounds,[3–5] and the indicated antimalarial activity[6] of its derivatives suggested the preparation of some quinolyl or other heterocyclic sulfones.

Of interest was the effect of incorporating a fat-soluble group into the molecule with a view toward increased absorption of the drug by the animal body.[7] Also, introduction of the physiologically active dialkylaminoalkyl grouping[8] was considered worthy of investigation.

The unsymmetrical sulfides were prepared by treatment of the sodium mercaptide with the proper organic halide. The sodium mercaptide was best prepared by addition of the mercaptan to a sodium ethoxide–ethanol solution. The sulfones were prepared from the corresponding sulfides by treatment with 30% hydrogen peroxide, with glacial acetic acid as a solvent. Additional derivatives of certain of these compounds have been prepared. Physical constants and analytical data of these sulfides and their derivatives are given in Tables I and II.

Of interest is the observation that quinine is oxidized in animals to 2-hydroxyquinine, thus the 2-substituted quinoline nucleus might be rendered more stable in the animal body.[9]

Results of pharmacological tests of these compounds will be reported elsewhere.

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Experimental

Preparation of the Sulfides.—The sodium mercaptide was prepared by reaction of the theoretical amount of sodium with an excess of absolute ethanol; to the resulting sodium ethoxide solution was added an equivalent amount of mercaptan. Subsequently, the resulting mercaptide was refluxed with an organic halide and the sulfide thus obtained was extracted with ether. Following drying of the ethereal solution over sodium sulfate and removal of the solvent, purification of the sulfide was effected by vacuum distillation, recrystallization from an appropriate solvent, or in some cases both. Recrystallization solvents for the solid sulfides are given in Table I. In the preparation of the heterocyclic alkyl sulfides, the heterocyclic chlorides were employed; and with the dodecyl sulfides, the dodecyl group was introduced *via* the mercaptan. The dialkylaminoalkyl chlorides were prepared in accordance with a previously reported procedure.[10] The preparation of two typical sulfides follows. All melting points in Tables I and II are uncorrected.

2-[*n*-Octadecylmercapto]-quinoline.—To 100 ml. of absolute ethanol was added 0.7 g. (0.03 g. atom) of sodium. After completion of the reaction, 8.6 g. (0.03 mole) of *n*-octadecylmercaptan was added dropwise. After 30 minutes, 5.0 g. (0.03 mole) of 2-chloroquinoline was added dropwise and the resulting solution refluxed for 10 hours. The solvent was then removed by distillation and the residue extracted with an ether–dilute sodium hydroxide mixture. Following separation of the ethereal solution and drying over sodium sulfate, the ether was distilled off. Vacuum distillation of the residue gave a yellow liquid, b.p. 234–240° (0.2 mm.) which solidified on standing. Recrystallization from petroleum ether (b.p. 60–70°) gave 10.7 g. (85%) of white crystals, melting at 53–54°.

Preparation of *n*-Dodecyl γ-Hydroxypropyl Sulfide.—Sodium metal, 34.5 g. (1.5 g. atoms), was cut into small pieces and added slowly to 600 ml. of absolute ethanol until all of the sodium had dissolved (1.5 hours). To this solution was added 303.6 g. (1.5 moles) of *n*-dodecyl mercaptan; then 146 g. (1.54 moles) of trimethylene chlorohydrin was added over a period of one hour to the refluxing sodium mercaptide solution. The reaction mixture was refluxed for 12 hours and then filtered to remove the white precipitate formed. The solvent was distilled from the filtrate to give 413 g. of a solid residue. This solid was then vacuum distilled; there was thus obtained 336.8 g. (86%) of distillate, b.p. 157–159° (0.5 mm.). The product solidified on standing yielding a white solid, m.p. 34–35°.

Preparation of the Sulfones.—The sulfide was dissolved in a minimum amount of glacial acetic acid. An excess of 30% hydrogen peroxide was slowly added and the resulting solution refluxed for 1–4 hours. The sulfone which separated on cooling was filtered and recrystallized from an appropriate solvent (see Table II).

Carbonation of γ-*n*-Dodecylmercaptopropyllithium.—γ-*n*-Dodecylmercaptopropyl chloride (22.4 g., 0.08 mole) was added dropwise, in a dry nitrogen atmosphere, to a vigorously stirred mixture of 1.2 g. (0.17 g. atom) of lithium in 100 ml. of anhydrous ether. This addition required 30 minutes, during which period the ether was gently refluxing. The milky-white mixture was then stirred for 4 hours at room temperature. The mixture was filtered, in a nitrogen atmosphere, through glass wool into a dropping funnel and then added to a Dry Ice–ether slurry,[11] with the tip of the dropping funnel immersed in the slurry. Following return to room temperature, the carbonation mixture was carefully neutralized with dilute hydrochloric acid. The ethereal solution was separated and extracted twice with 5% sodium hydroxide. Removal of the solvent by distillation gave 8.8 g. (43%) of impure di-γ-*n*-dodecylmercaptopropyl ketone, melting at 50–57°. Three recrystallizations from absolute ethanol raised the m.p. to 67–68°. The pure product weighed 6.5 g. (32%). The alkali extract was acidified and shaken with dry ether. From the ethereal solution was obtained 6.2 g. (27%) of γ-*n*-dodecylmercaptobutanoic acid, melting at 51–54°. Two recrystallizations from petroleum ether (b.p. 28–40°) raised the m.p. to 57.5–58.5°. The pure product weighed 4.7 g. (20%).

In another experiment the corresponding Grignard reagent was prepared according to the entrainment method[12]

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TABLE I

PROPERTIES OF SOME ALKYL AND HETEROCYCLIC SULFIDES

No.	Sulfide	Formula	M.p., °C.	B.p., °C.	Yield, %	Sulfur, % Found	Sulfur, % Calcd.	Recrystallization solvent
1	*n*-Dodecyl-*n*-propyl sulfide	*n*-$C_{12}H_{25}SC_3H_7$-*n*	.....	124–125 (0.25 mm.)[a]	62	13.19	13.11	.....
2	*n*-Dodecyl-β-diethylaminoethyl sulfide	*n*-$C_{12}H_{25}SCH_2CH_2N(C_2H_5)_2$	.....	132–133 (0.1 mm.)[b]	69	10.58	10.63	.....
3	*n*-Dodecyl-β-diethylaminoethyl sulfide·HCl	*n*-$C_{12}H_{25}SCH_2CH_2N(C_2H_5)_2$·HCl	101–102	.....	64	9.45	9.48	Diss. in EtOH, pptd. with ether
4	*n*-Dodecyl-γ-diethylaminopropyl sulfide	*n*-$C_{12}H_{25}SCH_2CH_2CH_2N(C_2H_5)_2$	.....	156–157 (0.1 mm.)[c]	80	10.07	10.16	.....
5	*n*-Dodecyl-γ-diethylaminopropyl sulfide·HCl	*n*-$C_{12}H_{25}SCH_2CH_2CH_2N(C_2H_5)_2$·HCl	106–108	.....	73	9.09	9.11	EtOH–ether
6	*n*-Dodecyl-γ-chloropropyl sulfide	*n*-$C_{12}H_{25}SCH_2CH_2CH_2Cl$	.....	153–155 (0.6 mm.)[d]	74	11.21[e]	11.45	.....
7	*n*-Dodecyl-γ-hydroxypropyl sulfide	*n*-$C_{12}H_{25}SCH_2CH_2CH_2OH$	34–35	157–159 (0.5 mm.)	86	12.24	12.30	.....
8	1,6-Di-*n*-dodecylmercaptohexane	(*n*-$C_{12}H_{25}SCH_2CH_2CH_2)_2$	51–53	.....	93	13.03	13.17	Acetone
9	Bis-(γ-*n*-dodecylmercaptopropyl) ketone	(*n*-$C_{12}H_{25}SCH_2CH_2CH_2)_2CO$	67–68	.....	32	12.73	12.46	EtOH
10	γ-*n*-Dodecylmercaptobutanoic acid	*n*-$C_{12}H_{25}SCH_2CH_2CH_2COOH$	57.5–58.5	.....	20	11.04[f]	11.11	Pet. ether, b.p. 28–38°
11	2-γ-*n*-Dodecylmercaptopropylquinoline	$C_9H_6NCH_2CH_2CH_2SC_{12}H_{25}$-*n*	34–36	.....	67	8.76	8.63	EtOH
12	2-γ-*n*-Dodecylmercaptopropylquinoline picrate	$C_9H_6NCH_2CH_2CH_2SC_{12}H_{25}\cdot C_6H_3O_7N_3$	96–98	.....	42	5.61[g]	5.34	EtOH
13	2-[Benzylmercapto]-quinoline[h]	$C_6H_5CH_2SC_9H_6N$	44–44.5	.....	74	12.45	12.76	Pet. ether, b.p. 60–70°
14	2-[Benzylmercapto]-quinoline hydrochloride	$C_6H_5CH_2SC_9H_6N$·HCl	187–190	.....	86	11.34	11.16	EtOH
15	2-[*n*-Dodecylmercapto]-quinoline	*n*-$C_{12}H_{25}SC_9H_6N$	.....	185–188 (2 mm.)[i]	78	9.82	9.73	.....
16	2-[*n*-Hexadecylmercapto]-quinoline[h]	*n*-$C_{16}H_{33}SC_9H_6N$	43–44	.....	62	8.50	8.31	Pet. ether, b.p. 60–70°
17	2-[*n*-Octadecylmercapto]-quinoline[h]	*n*-$C_{18}H_{37}SC_9H_6N$	53–54	.....	85	7.64	7.75	Pet. ether, b.p 60–70°
18	2-Benzothiazolyl-2′-quinolyl sulfide[h]	$C_7H_4SNSC_9H_5N$	0		78	21.69	21.78	Dil. EtOH
19	2-[4-Phenylthiazoyl]-2′-quinolyl sulfide[h]	$C_9H_6SNSC_9H_6N$	80–81	.....	50	19.72	19.95	Pet. ether, b.p. 60–70°
20	2-Benzimidazolyl-2′-quinolyl sulfide[h]	$C_7H_5N_2SC_9H_6N$	32.5–34	.....	60	11.61	11.57	Pet. ether, b.p 77–115°
21	4-[7-Chloroquinolyl]-2′-benzothiazolyl sulfide[j]	$C_7H_4SNSC_9H_5NCl$	138–140[k]	.....	44	19.39	19.49	Pet. ether, b.p. 77–115°

[a] $n^{20}D$ 1.4608. [b] $n^{20}D$ 1.4680. [c] $n^{20}D$ 1.4680. [d] $n^{20}D$ 1.4742. [e] *Anal.* Calcd. for $C_{15}H_{25}SCl$: Cl, 12.67. Found: Cl, 13.02. [f] *Anal.* Calcd. for $C_{16}H_{32}O_2S$: neut. equiv., 289. Found: neut. equiv., 292. [g] *Anal.* Calcd. for $C_{30}H_{40}O_7N_4S$: N, 9.33. Found: N, 9.59. [h] Prepared from 2-chloroquinoline and the appropriate mercaptans. [i] $n^{20}D$ 1.5508. [j] Prepared from 2-mercaptobenzothiazole and the appropriate halide. [k] With decomposition.

TABLE II

PROPERTIES OF SOME ALKYL AND HETEROCYCLIC SULFONES

No.	Sulfone	Formula	M.p., °C.	Yield, %	Sulfur, % Found	Sulfur, % Calcd.	Recryst. solvent
1	*n*-Dodecylmethyl sulfone	*n*-$C_{12}H_{25}SO_2CH_3$	83–84	59	12.76	12.90	EtOH
2	*n*-Dodecyl-*n*-propyl sulfone	*n*-$C_{12}H_{25}SO_2C_3H_7$-*n*	66.5–67	48	11.79	11.60	EtOH
3	*n*-Dodecyl-*n*-butyl sulfone	*n*-$C_{12}H_{25}SO_2C_4H_9$-*n*	63–64	53	10.90	11.04	EtOH
4	*n*-Dodecyl-γ-chloropropyl sulfone	*n*-$C_{12}H_{25}SO_2CH_2CH_2CH_2Cl$	78–79	59	10.22[a]	10.31	Et_2O
5	*n*-Dodecyl-γ-hydroxypropyl sulfone	*n*-$C_{12}H_{25}SO_2CH_2CH_2CH_2OH$	87–88	36	10.84	10.96	Et_2O
6	1,6-Di-*n*-dodecylsulfonylhexane	(*n*-$C_{12}H_{25}SO_2CH_2CH_2CH_2)_2$	140–141	75	11.58	11.63	$CHCl_3$
7	Bis-(γ-*n*-dodecylsulfonylpropyl) ketone	(*n*-$C_{12}H_{25}SO_2CH_2CH_2CH_2)_2CO$	153–154	66	11.30	11.08	Pyridine
8	γ-*n*-Dodecylsulfonylbutanoic acid	*n*-$C_{12}H_{25}SO_2CH_2CH_2CH_2COOH$	130–130.5	80	10.04[b]	10.00	Acetone
9	2-Quinolyl benzyl sulfone	$C_6H_5CH_2SO_2C_9H_6N$	187–190	54	11.42	11.33	MeOH

[a] *Anal.* Calcd. for $C_{15}H_{31}O_2SCl$: Cl, 11.40. Found: Cl, 11.39. [b] *Anal.* Calcd. for $C_{16}H_{32}O_4S$: neut. equiv., 321. Found: neut. equiv., 320.

and then carbonated to give a 72% yield of γ-*n*-dodecylmercaptobutanoic acid. The above yields are based on the amount of γ-*n*-dodecylmercaptopropyl chloride employed.

Preparation of 2-γ-*n*-Dodecylmercaptopropylquinoline.—An ethereal solution of γ-*n*-dodecylmercaptopropyllithium was prepared from 28 g. (0.10 mole) of γ-*n*-dodecylmercaptopropyl chloride and 1.5 g. of lithium in a manner similar to that described above. To this organolithium compound in ether was added over a period of 3 minutes, 6.5 g. (0.05 mole) of redistilled quinoline. The reaction mixture turned yellow, later red and heat was evolved. Thirty minutes later the reaction was hydrolyzed with ice-water. Following drying of the light yellow ethereal solution over sodium sulfate and distillation of the solvent, 26.6 g. of yellow oil was obtained. This was heated with 6 ml. of nitrobenzene for 20 minutes at 180°. The resulting deep red oil was vacuum distilled. The brown oily residue (16.6 g.) was dissolved in 50 ml. of hot absolute ethanol and was boiled with a solution containing 20 g. of picric acid and 50 ml. of 95% ethanol for 15 minutes. Thus, 18.6 g. of yellow crystals was obtained. Three crystallizations from absolute ethanol gave 12.6 g. (42%) of crystals melting at 96–98°.

A mixture of 15 g. of the picrate and 100 ml. of 5% sodium hydroxide was refluxed for 5 hours. The mixture was cooled and extracted with ether. A brown oil (7.8 g., 84% based on the amount of picrate used) was obtained, which solidified on standing (m.p. 32–38°). One recrystallization from absolute ethanol gave 6.2 g. (67%) of product, m.p. 34–36°. Further recrystallization did not improve the melting point.

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The Solubility and Transition Point of Lithium Chromate

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Data reported by earlier workers for the solubility of lithium chromate at 18,[1] 20[2] and 30°[3] are not consistent. Further, while the usual composition of the salt is the dihydrate, our observations confirm the findings of Retgers[4] that an anhydrous salt separates from the aqueous solution on boiling. It therefore seemed desirable to determine the solubility over the range 0 to 100°, and the temperature of transition between the dihydrate and the anhydrous salt.

Experimental

The material used for the solubility experiments was recrystallized $Li_2CrO_4 \cdot 2H_2O$, prepared from lithium hydroxide monohydrate and chromic anhydride. It was found to contain 99.85% $Li_2CrO_4 \cdot 2H_2O$ based on its hexavalent chromium content, 0.006% Cl and 0.021% SO_4. It was necessary to remove traces of trivalent chromium and insoluble matter from the solutions before the final crystallization; this was done by oxidation with a small amount of sodium hypochlorite and filtrations. The final product consisted of bright yellow crystals. Solubility[5] and transition point[6] were determined by previously described methods. The following results were obtained:

Temp., °C.	Solubility, wt. % Li_2CrO_4	Solid phase
0.7	47.27	$Li_2CrO_4 \cdot 2H_2O$
7.2	47.74	$Li_2CrO_4 \cdot 2H_2O$
10.4	47.89	$Li_2CrO_4 \cdot 2H_2O$
20.0	48.60	$Li_2CrO_4 \cdot 2H_2O$
29.8	49.62	$Li_2CrO_4 \cdot 2H_2O$
40.2	50.66	$Li_2CrO_4 \cdot 2H_2O$
50.1	52.10	$Li_2CrO_4 \cdot 2H_2O$
60.0	53.52	$Li_2CrO_4 \cdot 2H_2O$
70.0	55.27	$Li_2CrO_4 \cdot 2H_2O$
74.6		$Li_2CrO_4 \cdot 2H_2O + Li_2CrO_4$
75.1	56.17	Li_2CrO_4
80.0	56.34	Li_2CrO_4
90.0	56.57	Li_2CrO_4
100.0	56.82	Li_2CrO_4

The values when plotted yield smooth curves. For the dihydrate, the equation

$$S = 47.25 + 0.05037T + 0.0009143T^2$$

fits the observed data with an average deviation of 0.05% and a maximum deviation of 0.09%. For the anhydrous salt, the equation

$$S = 52.646 + 0.06265T - 0.0002096T^2$$

fits the data with an average deviation of 0.01% and a maximum deviation of 0.02%. Calculation of the concentration at the transition temperature gives: from the dihydrate equation, 56.10% Li_2CrO_4; from the anhydrous salt equation, 56.15% Li_2CrO_4.

A value of 56.12% Li_2CrO_4 is therefore reported for the solution concentration in equilibrium with the two solid phases at the transition temperature of 74.6°.

As might be expected from the relatively slight change of solubility of both phases with temperature and the oblique angle of intersection of the two solubility curves, the heat effect on transition is very small, and is estimated to be of the order of 1–2 kcal./mole, as contrasted with 15 kcal./mole reported[7] for the $Na_2CrO_4 \cdot 10H_2O$–$Na_2CrO_4 \cdot 6H_2O$ transition. It was necessary to heat and cool at rates in the order of 0.01°/minute to detect the thermal breaks, which were obtained at 74.6° on both heating and cooling.

Of the previous solubility determinations, only that of Schreinemakers,[3] who reported 49.94% Li_2CrO_4 at 30°, is in agreement with the present work.

An attempt was made to determine the temperature of the ice–dihydrate eutectic. This proved to be below −60°; equipment and measuring facilities were not available to investigate lower temperatures.

An unusual characteristic of the anhydrous salt is its ready solubility in the lower alcohols. Sodium chromate is soluble to the extent of only 0.35%[8] in methanol and even less in ethanol at room temperature. Other anhydrous chromates are virtually insoluble in alcohols. Anhydrous lithium chromate was prepared for study by slowly boiling a saturated solution of the dihydrate. The yellow crystals were 99.83% Li_2CrO_4. An approximate determination of the solubility of the salt in commercial absolute methanol and ethanol was made by rotating sealed containers containing these compounds with an excess of lithium chromate in a constant temperature bath for eight hours. The bottles were protected from light by a covering of black tape, since alcoholic solutions of lithium chromate, although stable for more than two months in the dark, were found to undergo decomposition fairly rapidly, with deposition of hydrous chromic chromate, when exposed to light. The following results were obtained:

Temp., °C.	Solubility, wt. % Li_2CrO_4 Methanol	Ethanol
0.5	13.4	1.6
24.4	15.7	1.8

The dihydrate is somewhat more soluble than the anhydrous salt, but its true solubility in alcohols cannot be determined, since the salt is dehydrated by these solvents.

Anhydrous lithium chromate was found to be insoluble in ether, and soluble only to the extent of about 25 p.p.m., as judged by color, in acetone. The low solubility in acetone explains the previously reported[5] decomposition of lithium dichromate to lithium chromate in acetone solution.

Density of the dihydrate and the anhydrous salt was determined by immersion in toluene in a pycnometer: Li_2CrO_4, d^{25}_4 2.426; $Li_2CrO_4 \cdot 2H_2O$, d^{25}_4 2.149.

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The Reaction of Silver *n*-Perfluorobutyrate with *n*-Perfluoropropyl Iodide and with 1,2-Dibromo-1-chlorotrifluoroethane

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Several attempts were made to synthesize perfluorinated esters by the reaction of silver salts of