

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°.

CHEMISTRY DEPARTMENT
BOSTON UNIVERSITY
BOSTON, MASSACHUSETTS

Some Alkyl and Heterocyclic Sulfides and Sulfones

BY HENRY GILMAN, ROBERT K. INGHAM AND T. C. WU

RECEIVED APRIL 19, 1952

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 sulfides¹ 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 activity⁶ 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 grouping⁸ 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.

(1) N. E. Foss, F. Dunning and G. L. Jenkins, *THIS JOURNAL*, **56**, 1978 (1934).

(2) G. A. H. Buttle, D. Stephenson, S. Smith, T. Dewing and G. E. Foster, *Lancet*, **1**, 1331 (1937).

(3) N. Rist, F. Block and V. Hamon, *Ann. Inst. Pasteur*, **64**, 203 (1940).

(4) G. W. Raiziss, *Science*, **98**, 350 (1943).

(5) L. L. Bambas, *THIS JOURNAL*, **67**, 671 (1945).

(6) H. Heymann and L. F. Fieser, *ibid.*, **67**, 1979 (1945).

(7) H. Gilman and S. P. Massie, *ibid.*, **71**, 744 (1949).

(8) (a) H. Gilman and R. M. Pickens, *ibid.*, **47**, 245 (1925); (b) H. Gilman, L. C. Heckert and R. McCracken, *ibid.*, **50**, 437 (1928); (c) H. Gilman and M. A. Plunkett, *ibid.*, **71**, 3667 (1949).

(9) (a) F. E. Kelsey, E. M. K. Geiling, F. K. Oldham and E. H. Dearborn, *J. Pharmacol.*, **80**, 391 (1944); (b) J. F. Mead and J. B. Koepfli, *J. Biol. Chem.*, **154**, 507 (1944).

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*-Dodecylmercaptopropyl lithium.— 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 method¹²

(10) H. Gilman and D. A. Shirley, *THIS JOURNAL*, **66**, 888 (1944).

(11) H. Gilman and J. A. Beel, *ibid.*, **71**, 2328 (1949).

(12) M. V. Grignard, *Compt. rend.*, **198**, 625 (1934).