[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF AYERST, MCKENNA & HARRISON LTD.]

Sulfonium Analogs of Pharmacologically Active Amines. The Synthesis of ω-(10-Phenothiazinyl)-alkyl-dialkylsulfonium Halides and 2′-(10-Phenothiazinecarboxy)-ethyldialkylsulfonium Halides

BY STANLEY O. WINTHROP AND M. A. DAVIS

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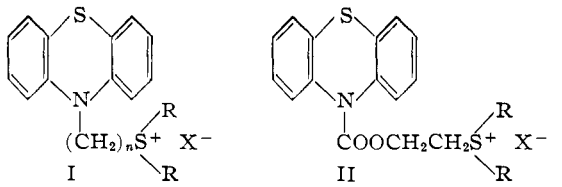
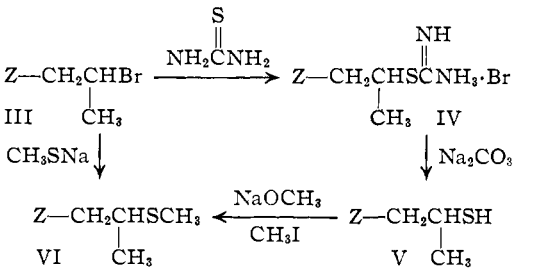
A series of ω-(10-phenothiazinyl)-alkyl alkyl sulfides have been prepared by the interaction of ω-(10-phenothiazinyl)-alkyl halides with alkylmercaptans. Condensation of 10-phenothiazinecarboxy chloride with 2-hydroxyethyl alkyl sulfides gave 2′-(10-phenothiazinecarboxy)-ethyl alkyl sulfides. The sulfides were treated with methyl and ethyl halides to produce the sulfonium salts. The pharmacological activities of these compounds are discussed.

Sulfonium compounds have been considered as analogs of both tertiary and quaternary amines, and a number of sulfonium analogs of pharmacologically active amines have been reported.[1] In some cases this analogy has proved useful in the search for new drugs. In the present investigation, sulfonium analogs of certain phenothiazine derivatives, amines whose pharmacological properties have been extensively studied as they include some important drugs, have been prepared. These compounds may be represented by structures I and II.



I II

A search of the literature did not reveal any ω-(10-phenothiazinyl)-alkyl alkyl sulfides. An attempt to prepare 2′-(10-phenothiazinyl)-ethyl methyl sulfide however has been reported.[2] Phenothiazine and 2-chloroethyl methyl sulfide were condensed together, but only undistillable resins were obtained. It was found that the desired sulfides could be prepared conveniently by the interaction of ω-(10-phenothiazinyl)-alkyl halides and sodium alkyl mercaptides. A second method also was developed which, although longer, circumvented the use of the alkylmercaptan. The preparation of 2′-(10-phenothiazinyl)-1′-methylethyl methyl sulfide illustrates this second route. 10-(2′-Bromopropyl)-phenothiazine (III) was heated under reflux in ethanol with thiourea to give the pseudothiouronium salt IV. Alkaline hydrolysis produced the mercaptan V which, as its sodio derivative, was treated with methyl iodide to give the desired sulfide VI (Z = 10-phenothiazinyl).



III IV V VI

The 2′-(10-phenothiazinecarboxy)-ethyl alkyl sulfides were prepared by the condensation of 10-phenothiazinecarboxy chloride with 2-hydroxyethyl alkyl sulfides in refluxing benzene. Pyridine was used as an acid acceptor and in one case as the reaction solvent.

The sulfonium salts were obtained when the alkyl sulfides were treated with alkyl halides at room temperature. Ether, methanol, nitromethane or an excess of the alkyl halide were used as solvents. Nitromethane was found to give the best yields and pure products. Reaction times ranged from a few hours to a week depending on the reactivity of the alkyl halide. Although heating increased the rate of reaction it also caused decomposition of the sulfonium salt resulting in lower yields. The 2′-(10-phenothiazinecarboxy)-ethyl-dialkylsulfonium halides were particularly heat-sensitive.

Methyl iodide, methyl bromide and ethyl iodide reacted normally to give the desired sulfonium compounds. An abnormal reaction occurred, however, when isopropyl iodide was allowed to react with 3′-(10-phenothiazinyl)-propyl methyl sulfide. The product was 3′-(10-phenothiazinyl)-propyl-dimethylsulfonium iodide and not the expected 3′-(10-phenothiazinyl)-propyl-methylisopropylsulfonium iodide. Similar anomalies have been reported by other workers.[3-5] Recently Weiss and O'Donoghue[1] observed that when 1-cyclohexyl-3-methylmercapto-1-phenylpropan-1-ol was treated with propyl, butyl or amyl iodide, the dimethylsulfonium derivative was obtained in each instance. These investigators propose a mechanism which involves the formation of the normal sulfonium salt to a limited extent. This salt then functions as an alkylating agent, in competition with the alkyl halide, to produce the observed dimethylsulfonium salt. This explanation would serve equally well in the present case.

Pharmacological Activity.—In general the sulfonium compounds exhibited the anticholinergic, antihistaminic and antisecretory activities of the corresponding tertiary and quaternary amines. Table III shows a comparison of these activities for 2′-(10-phenothiazinyl)-1′-methylethyldimethylamine hydrochloride (Promethazine),[6] 2′-(10-phenothiazinyl)-1′-methylethyltrimethylammonium methyl sulfate (Thiazinamon)[6] and 2′-(10-phenothiazinyl)-1′-methylethyldimethylsulfonium iodide.

(1) For a brief review see M. J. Weiss and M. D. O'Donoghue, THIS JOURNAL, **79**, 4771 (1957).

(2) O. Exner, M. Borovicka and M. Protiva, *Coll. Czech. Chem. Comm.*, **18**, 270 (1953).

(3) V. Prelog, *et al.*, *Helv. Chim. Acta*, **27**, 1209 (1944).

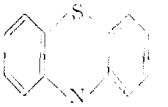
(4) T. R. Lewis and S. Archer, THIS JOURNAL, **73**, 2109 (1951).

(5) F. D. Ray and I. Levine, *J. Org. Chem.*, **2**, 267 (1937).

(6) Therapeutic agents for the treatment of hay fever, asthma and other conditions with an allergic basis.

TABLE I

10-PHENOTHIAZINYL DERIVATIVES

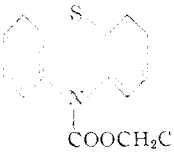


R	Yield, %	M.p.,[a] °C.	Formula	Nitrogen, % Calcd.	Found	Sulfur, % Calcd.	Found	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
$CH_2CH_2SCH_3$[d]	55	52–54	$C_{16}H_{15}NS_2$	5.14	5.34	23.48	23.34	65.84	65.80	5.54	5.35
$CH_2CH_2S^+(CH_3)_2I^-$[e]	42	127–128	$C_{18}H_{18}NS_2I$	3.37	3.28	15.42	15.63	30.54[f]	30.28[f]		
$CH_2CH_2S^+(CH_3)_2Br^-$	50	149–151	$C_{18}H_{18}NS_2Br$	3.80	3.65			21.70[f]	22.68[b,f]		
$CH_2CH_2CH_2SCH_3$	77	174–176[a] (0.15 mm.)	$C_{16}H_{17}NS_2$	4.87	4.92	22.33	22.39	65.84	66.79	5.96	6.00
$CH_2CH_2CH_2S^+(CH_3)_2I^-$[f]	57	139–140	$C_{17}H_{20}NS_2I$	3.26	3.16	14.92	14.95	29.55[f]	29.58[f]		
$CH_2CH(CH_3)SC(NH)NH_2\cdot HBr$[g]	67	187–189	$C_{16}H_{19}N_3S_2Br$	10.60	10.70			48.50	49.05	4.57	4.58
$CH_2CH(CH_3)SH$[h]	83	140–142	$C_{15}H_{15}NS_2$	5.12	5.18			65.81	65.25	5.53	5.42
$CH_2CH(CH_3)SCH_3$[i]	68	75–76	$C_{16}H_{17}NS_2$	4.87	4.76	22.33	21.99	66.84	66.95	5.96	6.23
$CH_2CH(CH_3)S^+(CH_3)_2I^-$[e]	82	125–126	$C_{17}H_{20}NS_2I$	3.26	3.32	14.82	14.82	29.55[f]	29.65[f]		
$CH_2CH(CH_3)SCH_2CH_3$	76	180–182[a] (0.06 mm.)	$C_{17}H_{19}NS_2$	4.65	4.53	21.26	21.11	67.72	67.59	6.35	6.38
$CH_2CH(CH_3)S^+(CH_2CH_3)_2I^-$[c]	23	136–137	$C_{19}H_{24}NS_2I$					27.74[f]	27.69[f]		

[a] Boiling points. [b] Some decomposition was evident during recrystallization. [c] The sulfonium salts invariably melted with decomposition. [d] Recrystallized from ethanol. [e] Recrystallized from an ethanol–ether mixture. [f] Recrystallized from methanol. [g] Recrystallized from a nitromethane–ether mixture. [h] Recrystallized from aqueous ethanol. [i] Recrystallized from hexane. [j] Halide, %.

TABLE II

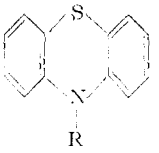
2′-(10-PHENOTHIAZINECARBOXY)-ETHYL ALKYL SULFIDES AND SULFONIUM SALTS



R	Yield, %	M.p.,[a] °C.	Formula	Nitrogen, % Calcd.	Found	Sulfur, % Calcd.	Found	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
SCH_3[b]	51	108–109	$C_{19}H_{19}NS_2O_2$	4.42	4.44	20.22	20.00	60.50	60.60	4.76	4.90
$S^+(CH_3)_2I^-$[c]	75	138–139	$C_{17}H_{18}NS_2O_2I$	3.05	3.26	13.93	13.67	27.62[e]	27.57[e]		
$S^+(CH_3)_2Br^-$[c]	62	146–148	$C_{17}H_{18}NS_2O_2Br$	3.41	3.23	15.55	15.31	19.45[e]	19.75[e]		
SCH_2CH_3[b]	58	82–83	$C_{17}H_{17}NS_2O_2$	4.23	4.31	19.35	19.41	61.65	61.39	5.17	5.15
$S^+(CH_2CH_3)(CH_3)I^-$[c]	11	116–117	$C_{18}N_{20}NS_2O_2I$			13.53	13.80	26.80[e]	26.57[e]		
$S^+(CH_2CH_3)_2I^-$[d]	26	120–121	$C_{19}H_{22}NS_2O_2I$	2.87	2.78	13.15	13.24				

[a] The sulfonium salts invariably melted with decomposition. [b] Recrystallized from hexane. [c] Recrystallized from a methanol–ether mixture. [d] Did not recrystallize since losses due to decomposition were excessive. [e] Halide, %.

TABLE III



R	Relative potencies Vs. acetylcholine[a]	Vs. histamine[a]	Antisecretory[b]
$CH_2CH(CH_3)N(CH_3)_2\cdot HCl$	1	1	1
$CH_2CH(CH_3)N^+(CH_3)_3\cdot CH_3SO_4^-$	2	1	5
$CH_2CH(CH_3)S^+(CH_3)_2I^-$	0.8	0.3	2.5

[a] *In vitro;* inhibition of the contractions induced in isolated strips of guinea pig's ileum by the spasmogenic agent. [b] *In vivo;* using the method of Shay.[7]

Most significantly, the sulfoniums did not show any of the central effects of the tertiary amines. Specifically they had no depressant action on the central nervous system and did not exhibit any anti-Parkinson-like activity. In this respect it appears the sulfoniums resemble more closely the corresponding quaternary amines.

Acknowledgments.—The authors wish to thank Dr. C. I. Chappel of our laboratories for the pharmacological data, Mr. W. J. Turnbull for the analyses and Dr. Gilles Papineau-Couture and Mrs. J. Jachner for numerous infrared spectra.

(7) H. Shay, C. H. Sun and M. Gruinstein, *Gastroenterol.*, **26**, 906 (1954).

Experimental[8]

Starting Materials.—Phenothiazine,[9] 2-chloroethyl *p*-toluenesulfonate,[9] 3-chloropropyl *p*-toluenesulfonate,[9] 2-hydroxyethylmercaptan[9] and 10-phenothiazinecarboxy chloride[10] were available from commercial sources. The following were prepared according to methods described in the literature: 10-(2′-chloroethyl)-phenothiazine,[11] m.p. 97–98° (lit. m.p. 97–98°); 10-(3′-chloropropyl)phenothiazine,[9] m.p. 63–65° (lit. m.p. 60°); 10-(2′-hydroxypropyl)-phenothiazine,[12] b.p. 190–192° at 0.3 mm. (lit. b.p. 192–196° at 0.3 mm.); 10-(2′-bromopropyl)-phenothiazine,[12] m.p. 126–128° (lit. m.p. 125–126°); 2-hydroxyethyl methyl sulfide,[13] b.p. 165–167° (lit. b.p. 157–159°); 2-hydroxyethyl ethyl sulfide,[14] b.p. 180–181° (lit. b.p. 181°).

3′-(10-Phenothiazinyl)-propyl Methyl Sulfide.—10-(3′-Chloropropyl)-phenothiazine (20 g., 0.0725 mole) was dissolved in 400 ml. of absolute ethanol and was added dropwise to a refluxing solution of 9.8 g. (0.18 mole) of sodium methoxide and 10.5 g. (0.22 mole) of methylmercaptan in 100 ml. of absolute ethanol. The addition was complete

(8) All melting points are uncorrected.

(9) Eastman Kodak Co. white label.

(10) Delmar Chemical Co., Montreal, Que.

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

(12) R. Dahlbom, *Acta Chem. Scand.*, **3**, 247 (1949).

(13) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 345.

(14) C. D. Nenitzescu and N. Scarlatescu, *Ber.*, **68B**, 587 (1935).

in 30 minutes and the heating continued for another three hours. The reaction mixture was then added to a large amount of water and the whole extracted with chloroform. The chloroform extracts were dried and evaporated *in vacuo* leaving 16 g. of a heavy oil. The oil residue was purified by distillation at 0.2 mm. and the fraction boiling from 186–190°, 15 g., solidified to yield a white solid, m.p. 46–47°. One recrystallization from ethanol raised the melting point to 52–54° (see Table I).

S-[2'-(10-Phenothiazinyl)-1'-methylethyl]-pseudothiouronium Bromide.—10-(2'-Bromopropyl)-phenothiazine (16.0 g., 0.05 mole) and thiourea (3.8 g., 0.05 mole) were dissolved in 100 ml. of a 1:1 nitromethane–ethanol solution and heated under reflux for eight hours. The solvent was then removed *in vacuo* leaving a viscous oil which crystallized on trituration with nitromethane–ether to give 13.4 g., m.p. 180–184°. Two recrystallizations from nitromethane–ether raised the melting point to 187–189° (see Table I).

2'-(10-Phenothiazinyl)-1'-methylethylmercaptan.—S-[2'-(10-Phenothiazinyl)-1'-methylethyl]-pseudothiouronium bromide (29 g., 0.073 mole) and sodium carbonate (7.8 g., 0.073 mole) were dissolved in 300 ml. of a 1:1 water–ethanol solution and heated under reflux for two hours. The reaction mixture was then diluted with a large volume of water and made just acid with dilute hydrochloric acid causing 16.5 g. of solid to precipitate, m.p. 137–140°. One recrystallization from hexane raised the melting point to 140–142° (see Table I).

2'-(10-Phenothiazinyl)-1'-methylethyl Methyl Sulfide.—2'-(10-Phenothiazinyl)-1'-methylethylmercaptan (8.5 g., 0.0312 mole), sodium methylate (1.77 g., 0.0328 mole) and methyl iodide (4.6 g., 0.0328 mole) were dissolved in 300 ml. of absolute ethanol and the solution heated under reflux for one hour. The ethanol was then removed *in vacuo* and the residue poured into a large quantity of water. The aqueous mixture was extracted with chloroform and the chloroform extracts dried and then evaporated down *in vacuo* leaving 6 g. of solid, m.p. 73–75°. One recrystallization from hexane raised the melting point to 75–76° (see Table I).

2'-(10-Phenothiazinecarboxy)-ethyl Methyl Sulfide.—10-Phenothiazinecarboxy chloride (20.8 g., 0.08 mole), 2-hydroxyethyl methyl sulfide (7.4 g., 0.08 mole) and pyridine (6.4 g., 0.08 mole) were dissolved in 200 ml. of benzene and the solution heated under reflux for six hours. On cooling, the reaction mixture was washed with water and the benzene layer then dried and evaporated down *in vacuo* leaving a viscous oil residue. The residue was taken up in ether and some insoluble material (phenothiazine) was removed. The ether was removed *in vacuo* and the oil remaining solidified on trituration with a little methanol to yield 13 g. of product, m.p. 94–98°. Three recrystallizations from hexane raised the melting point to 108–109° (see Table II).

2'-(10-Phenothiazinyl)-1'-methylethyl-dimethylsulfonium Iodide.—2'-(10-Phenothiazinyl)-1'-methylethyl methyl sulfide (3.5 g.) and methyl iodide (5 g.) were dissolved in 20 ml. of nitromethane and allowed to stand in the dark at room temperature for 18 hours. Upon the addition of ether, 4.3 g. of product precipitated, m.p. 125–126° dec. Recrystallization from an ether–alcohol mixture did not change the melting point (see Table I).

2'-(10-Phenothiazinecarboxy)-ethyl-diethylsulfonium Iodide.—An attempt to prepare this compound using ether as the solvent did not yield any product even after two months. By using nitromethane a 26% yield of the sulfonium salt resulted after one week. 2'-(10-Phenothiazinecarboxy)-ethyl ethyl sulfide (5 g.) and ethyl iodide (10 g.) were dissolved in 25 ml. of nitromethane. After standing for one week a large quantity of ether was added and caused the precipitation of 1.9 g. of product, m.p. 120–121° dec. It was purified by dissolving in methanol and precipitating by the addition of ether without any change in melting point (see Table II).

2'-(10-Phenothiazinecarboxy)-ethyl-dimethylsulfonium Bromide.—2'-(10-Phenothiazinecarboxy)-ethyl methyl sulfide (5 g.) and 20 ml. of a 25% methanolic solution of methyl bromide were dissolved in 50 ml. of nitromethane. After standing for two weeks the reaction mixture was worked up in the usual manner to yield 4.0 g. of product, m.p. 146–147° dec. One recrystallization from a methanol–ether mixture did not raise the melting point (see Table II).

Abnormal Sulfonium Salt from 3'-(10-Phenothiazinyl)-propyl Methyl Sulfide and Isopropyl Iodide.—3'-(10-Phenothiazinyl)-propyl methyl sulfide (9.5 g.) was dissolved in 60 ml. of a 1:1 nitromethane–methanol mixture containing 20 g. of isopropyl iodide and the reaction mixture was heated under reflux for 16 hours. On the addition of ether, 6 g. of product precipitated, m.p. 137–138° dec. One recrystallization from a methanol–ether mixture did not change the melting point. The infrared spectrum was identical with that of 3'-(10-phenothiazinyl)-propyldimethylsulfonium iodide.

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The Reaction of Sodium Nitrite with Ethyl Bromoacetate and with Benzyl Bromide[1,2]

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The reaction of ethyl bromoacetate with sodium nitrite occurs rapidly in dimethylformamide (DMF), but the product is not ethyl nitroacetate; instead, depending on the temperature, oxalic acid or the furoxane II is produced. Treatment of benzyl bromide with sodium nitrite yields benzoic acid as the main product at 25° whereas at −16° phenylnitromethane is obtained in 55% yield; even at −16°, prolonged standing of the reaction mixture gives the diphenylfuroxane I. Evidence is presented for the view that nitrolic acids are intermediates both in the formation of carboxylic acids and furoxanes. The factors controlling the rate at which aliphatic nitro compounds are destroyed by the joint action of a nitrite ester and sodium nitrite are discussed.

The reaction of alkyl halides and α-haloesters with sodium nitrite recently has been shown to provide a very useful synthesis of nitroparaffins[3] and α-nitroesters.[4] However, ethyl bromoacetate was exceptional in that it failed to give any ethyl nitroacetate on treatment with sodium nitrite; while a very rapid reaction occurred no organic product was isolated.[4]

The reaction of sodium nitrite with benzyl bromide is apropos. At 25° only a small amount (*ca.* 7% yield) of phenylnitromethane is obtained, the main products being benzoic acid (37% yield) and nitrous oxide (42% yield). However, the reaction at −16 to −20° gives a 55% yield of phenylnitromethane, provided a reaction time of only three to five hours is employed; longer periods result in diphenylfuroxane (I) formation and a decreased

(1) Paper XVIII in the Series "The Chemistry of Aliphatic and Alicyclic Nitro Compounds."

(2) This research was supported by a grant from the Explosives Department of E. I. du Pont de Nemours and Co.

(3) N. Kornblum, H. O. Larson, D. D. Mooberry, R. K. Blackwood, E. P. Oliveto and G. E. Graham, *Chemistry & Industry*, 443 (1955); THIS JOURNAL, **78**, 1497 (1956); N. Kornblum and J. W. Powers, *J. Org. Chem.*, **22**, 455 (1957).

(4) N. Kornblum, R. K. Blackwood and J. W. Powers, THIS JOURNAL, **79**, 2507 (1957); N. Kornblum and R. K. Blackwood, *Org. Syntheses*, **37**, 44 (1957).