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HYDRAZINE DERIVATIVES. I. BENZALTHIO- AND BISBENZALDITHIO-SALICYLHYDRAZIDES

LEON KATZ, LAWRENCE S. KARGER, WILLIAM SCHROEDER, AND
MURRAY S. COHEN

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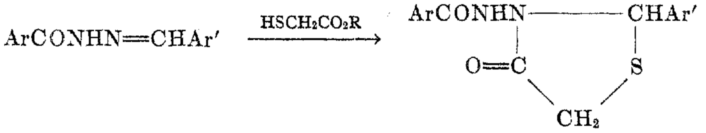
In a previous investigation[1] a series of benzalbenzhydrazides was synthesized which possessed significant antifungal activity. It was our original intention to incorporate the sulfur atom into the molecule by preparing thiazolidones using the reaction elaborated by Surrey (1a) and Long and Troutman (1b) for the synthesis of related compounds.



Although the addition of either thioglycolic acid or the corresponding ethyl ester to several model compounds was unsuccessful, the widespread usage of sulfur-containing fungicides (2) caused us to continue our efforts to introduce sulfur into the benzalbenzhydrazide molecule. One of the most obvious and facile routes involved the introduction of the thiol group in the benzhydrazide moiety, *e.g.*, the preparation of thiosalicylhydrazide. For reasons which will become apparent later in the text the decision to synthesize thiosalicylhydrazide as the initial member of this new series was a fortunate one. The synthesis of thiosalicylhydrazide and derivatives thereof is outlined in Flow Sheet I.

Dithiosalicylic acid (6) was reduced by alkaline sodium hydrosulfite to thiosalicylic acid. The acid was esterified in methanolic hydrochloric acid and the resultant ester was caused to react with hydrazine hydrate to produce the thiosalicylhydrazide hereafter designated as TSH.

An alternative route to TSH and one which proved to be more expedient in laboratory practice depended on the preparation of dimethyl dithiosalicylate (19) from the requisite diacid chloride (19).

Thionyl chloride and dithiosalicylic acid were refluxed together to form the diacid chloride which was not isolated but was freed of excess thionyl chloride and, in turn, was caused to react with methanol to produce the diester in 71% over-all yield. Reaction of the diester with four to six equivalents of hydrazine hydrate afforded TSH in 90% yield.

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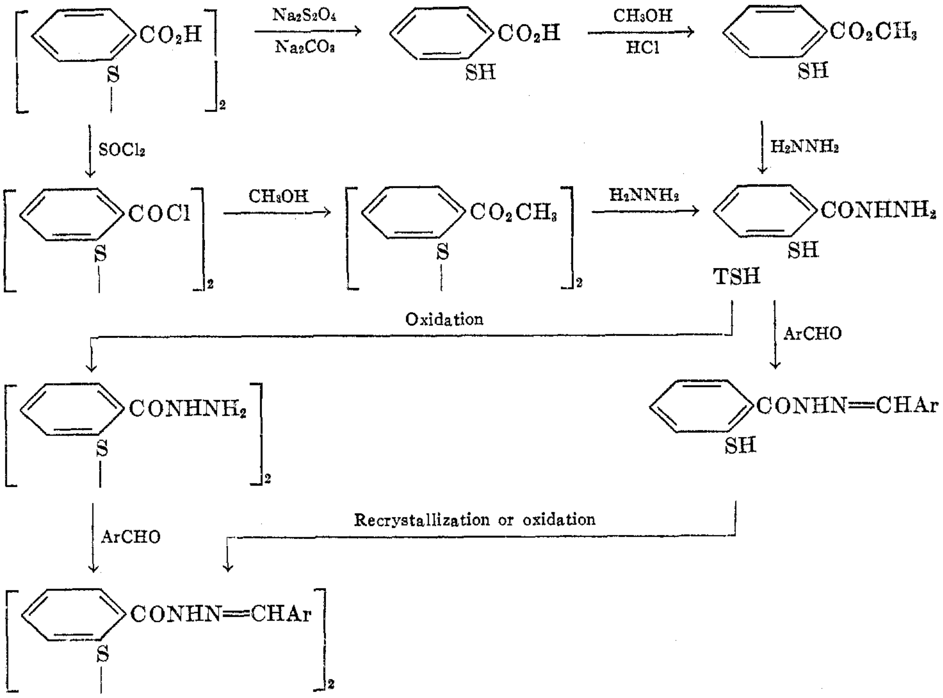
[1] The preparation and microbiological testing of simple derivatives of hydrazine was prompted by the following observations: (a) the reported stimulatory effect of benzal derivatives of pyrazinoic acid hydrazide (3) and (b) the demonstration of the efficacy of thiosemicarbazones in human tuberculosis (4). The investigation gained added impetus with the dramatic announcement of the effect of isonicotinic acid hydrazide against tuberculosis (5). The results of this preliminary screening have not been published.

FLOW SHEET I



TSH was condensed with carbonyl compounds and crystalline derivatives separated from the reaction mixture. When these derivatives were recrystallized the melting point rose as much as 30–70° in almost all cases. This was especially true when recrystallization was effected from high-boiling solvents and it was soon recognized that disulfides were being produced. This was confirmed by treating the unpurified reaction products in pyridine with an equivalent amount of a 2% solution of iodine in pyridine and comparing this disulfide with that formed by recrystallization. Additional confirmation was gained by preparing dithiosalicylhydrazide, DTSH, from TSH by oxidation with pyridine and iodine or by oxidation with air, causing it to react with the respective benzaldehyde, and comparing the derivative with the originally formed disulfide. When it was possible to recrystallize the thiol derivative either quickly or from a low-boiling solvent mixture such as aqueous methanol, disulfide formation was averted or minimized.

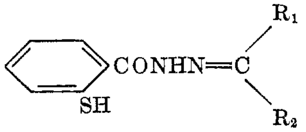
In several instances in which the melting point did not rise sharply it was demonstrated that disulfides had been formed directly during the condensation reaction. An example of this was the reaction of TSH with anisaldehyde. The condensation product was soluble in the original reaction medium and continued boiling converted the thiol to the disulfide. It was possible in this and similar cases to run the reaction in aqueous methanol so that the initially formed benzalthiosalicylhydrazide precipitated from solution directly as it formed.

Specific examples were encountered which did not show the characteristic oxidation behavior during recrystallization regardless of the conditions used. The products prepared from TSH and salicylaldehyde or 2-hydroxyacetophenone, respectively, did not oxidize during purification as evidenced by argentometric titration and consumption of iodine.

Condensation of TSH with monosaccharides resulted likewise in thiol derivatives which could not be oxidized to disulfides by recrystallization or by pyridine and iodine.

TABLE I

DERIVATIVES OF THIOSALICYLHYDRAZIDE



R1	R2	YIELD, %	M.P., °C.[a]	EMPIRICAL FORMULA	ANALYSES			
					Calc'd		Found	
					C	H	C	H
H	2-Hydroxyphenyl	90	176–177.5[b]	$C_{14}H_{12}N_2O_2S$	61.76	4.41	61.53	4.35
H	3-Hydroxyphenyl	90	165–168[c]	$C_{14}H_{12}N_2O_2S$	61.76	4.41	61.54	4.67
CH_3	2-Hydroxyphenyl	97	172–175[d]	$C_{15}H_{14}N_2O_2S$	62.94	4.89	63.01	4.68
H	2-Ethoxyphenyl	85	160–161[d]	$C_{16}H_{16}N_2O_2S$	64.21	5.02	64.46	5.12
H	2-*n*-Butoxyphenyl	85	138–141[e]	$C_{18}H_{20}N_2O_2S$	65.85	6.09	65.80	5.87
H	2,4-Dichlorophenyl	94	214–216[f]	$C_{14}H_{10}Cl_2N_2O_2S$[i]				
CH_3	4-Methoxystyryl	97	172–177[g]	$C_{18}H_{18}N_2O_2S$	66.26	5.52	66.25	5.25
H	D-Glucosyl	70	178–179[h]	$C_{13}H_{18}N_2O_6S$	47.26	5.49	47.39	5.34
H	L-(+)Arobinosyl	98	175–176[h]	$C_{12}H_{16}N_2O_5S$	47.99	5.37	47.96	5.40
H	D-(+)-Xylosyl	78	159–160[h]	$C_{12}H_{16}N_2O_5S$	47.99	5.37	48.14	5.19

[a] The melting points in some instances are given as a range due to instability of these compounds at the melting point. Recrystallized from: [b] ethanol; [c] *n*-butanol; [d] aqueous Methyl Cellosolve (2-methoxyethanol); [e] aqueous methanol; [f] aqueous methanol by dissolving in methanol with potassium hydroxide and adding glacial acetic acid to neutralize. The solid crystallized in shining platelets; [g] from aqueous acetic acid; [h] from water. [i] This material was analyzed for N: Calc'd, 8.61; Found, 8.28.

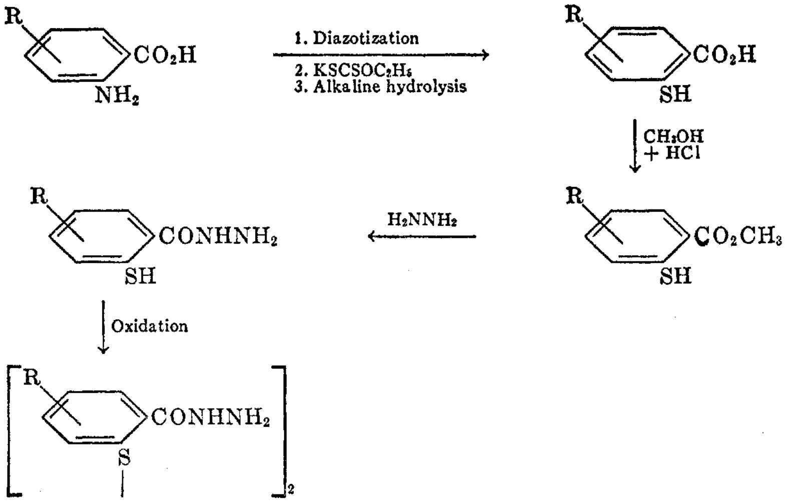
Data are tabulated in Table I for those derivatives of TSH for which analytical results are available.

In the reaction of thiosalicylhydrazide with an aldehyde the formation of both *syn* and *anti* forms are possible. Likewise in the reaction of dithiosalicylhydrazide one would *a priori* predict the occurrence of the three geometric isomers, *syn-syn*, *syn-anti*, and *anti-anti*. The facile conversion of most benzalthiosalicylhydrazides to the disulfides precluded the isolation of the *syn* and *anti* isomers of this series and it is noteworthy to point out that the disulfide obtained by recrystallization of the thiol was identical with that formed by oxidation of the thiol with pyridine-iodine or that formed from DTSH and the respective carbonyl component. Although only one entity has ever been isolated in the disulfide series, it is impossible to assign it an absolute geometric configuration.

In order to correlate microbiological activity with chemical structure an extensive investigation of related compounds was undertaken, which included placing the thiol group in the 3 and 4 position with respect to the carbohydrazido moiety, preparing S-methyl TSH, benz-substituted derivatives of TSH and DTSH, 2-methylsulfonylbenzhydrazide, and reducing the >C=N— grouping of a hydrazone derivative.

The preferred method of synthesis for the substituted thiolbenzhydrazides and the corresponding disulfides is diagrammed in Flow Sheet II.

FLOW SHEET II

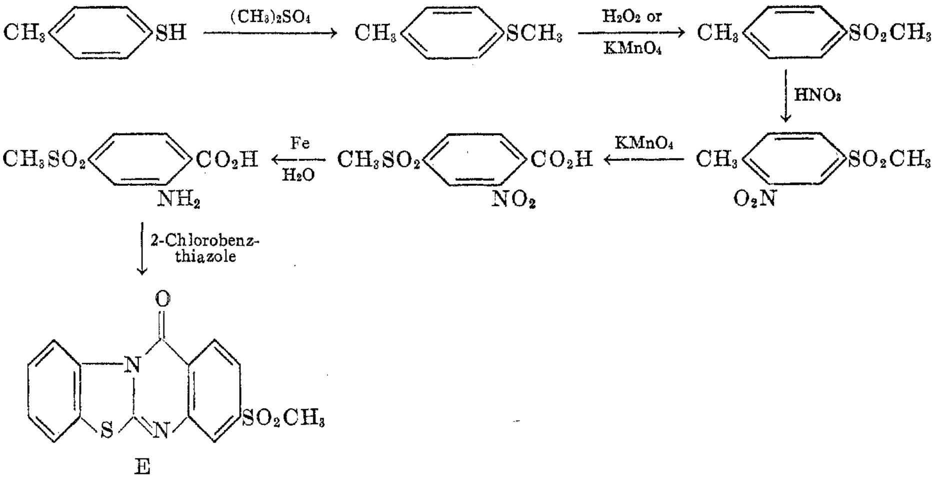


Although most of the requisite anthranilic acids have been described, the syntheses of 4-methylsulfonyl- and 4-methoxy-anthranilic acids are worthy of mention.

The schematic outline for the preparation of the former acid and a cyclized derivative is contained in Flow Sheet III.

4-Thiocresol was methylated with dimethylsulfate (11) and the resultant sulfide was oxidized to the methyl tolyl sulfone (12) with hydrogen peroxide or potassium permanganate. The latter reagent gave a cleaner product in better yield but the procedure suffered from the use of large volumes of solvents. Nitration of the sulfone with nitric acid afforded a 93% yield of the nitro derivative, m.p. 118–119°, presumably the 2-nitrotolyl methyl sulfone. We deemed it desirable to differentiate this nitro compound from the isomeric 3-nitrotolyl methyl sulfone prepared by Schimmelschmidt and Thomae (13), m.p. 122–124°. This was accomplished by continuing the reaction sequence to the anthranilic acid. The oxidation of the nitrotolyl methyl sulfone with potassium permanganate in aqueous pyridine according to the procedure of Leonard and Boyd (14) yielded the substituted benzoic acid which was reduced smoothly with iron and water to the amino acid. This acid exhibited a deep blue fluorescence, a property common to many anthranilic acid derivatives, and condensed easily with 2-chlorobenzothiazole to yield E. The cyclization reaction is characteristic of anthranilic acids (15) and confirms the position of the original nitro group as shown in Flow Sheet III.

FLOW SHEET III



The preparation of 4-methoxyanthranilic acid by oxidation of the corresponding 4-methoxy-2-nitrotoluene and subsequent reduction has been described by Ullman and Dootson (16). An alternative synthesis starting from the requisite 2-acetamino-4-methoxytoluene was carried out by Lesser (17). A third method of preparing this acid was accomplished by the present authors using the readily available 4-methoxy-2-nitroaniline.[2] By diazotization and replacement the amino group was exchanged for the cyano group in 98 % yield. Hydrolysis of the cyano derivative afforded an 80 % yield of the known nitro acid (16). Considerable difficulty was encountered initially in the hydrolysis since alkaline conditions caused degradation. When 60–80 % sulfuric acid was used it was necessary to heat the reaction mixture at 100° for 72 hours to obtain good yields; a proportional loss in yield occurring if the reaction time was shortened. Reduction of the nitro acid with iron and dilute hydrochloric acid proceeded smoothly to give the desired 4-methoxyanthranilic acid in 94 % yield. This synthesis has the advantage of avoiding the poor and costly oxidation of the respective toluene derivatives.

The use of potassium ethyl xanthate on the diazotized anthranilic acids and subsequent alkaline hydrolysis gave uniformly good yields of the required thiolbenzoic acids (75–90 %) and by decomposing the diazonium salt at 70–80°

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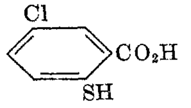
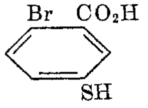
[2] Obtained from Antara Chemicals, Division of General Dyestuff Corp.

no untoward reaction was experienced. Methanolic hydrochloric acid gave excellent yields of the corresponding methyl esters which were converted to the hydrazides by treatment with hydrazine hydrate.

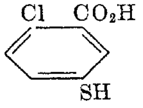
There exists in the literature a certain degree of uncertainty regarding the 5-chloro and 5-bromothiosalicylic acids. Krishna and Singh (7) in examining the course of the modified Reimer-Tiemann reaction with thiophenols included *p*-chloro- and *p*-bromo-thiophenols in their investigation. For some inexplicable reason they assigned the following different structures A and B to the acid derivatives obtained from the corresponding thiophenols:



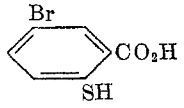
A



B



C



D

The uncertainty surrounding the identity of the former acid was resolved by Hart, McCelland, and Fowkes (9) who chlorinated dithiosalicylic acid and reduced the dichloro derivative, m.p. 316–320°, to 5-chlorothiosalicylic acid, m.p. 193°. In the present investigation 5-chlorothiosalicylic acid synthesized from 5-chloroanthranilic acid (8) agreed in properties with the compound prepared by Hart, *et al.* and the disulfide obtained by oxidation melted at 330°. The compound described by Krishna and Singh, m.p. 110°, can only be 2-chloro-5-thiolbenzoic acid (C).

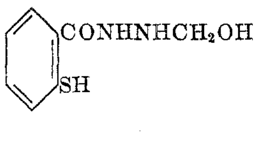
In the preparation of 5-bromothiosalicylic acid from the corresponding anthranilic acid (10) a compound of melting point 210–211° was obtained. This agrees with the melting point of 210° for the compound prepared by Krishna and Singh from 4-bromothiophenol. It would appear that the postulated structure for the Reimer-Tiemann product is in error and that this derivative is actually the substituted thiosalicylic acid (D).

In a like manner *m*- and *p*-thiolbenzhydrazide and their corresponding disulfides were prepared from the readily available amino acids.

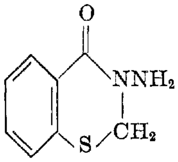
S-Methylthiosalicylhydrazide and 2-methylsulfonylbenzhydrazide resulted from treatment of the prerequisite methyl esters with hydrazine hydrate.

Reduction of benzalthiosemicarbazones to benzylthiosemicarbazides with sodium amalgam (18) has been reported. In extending this method to 2,4-dichlorobenzalthiosalicylhydrazide the reaction did not proceed smoothly and it was necessary to resort to the more elegant electrolytic process. In this manner the 2,4-dichlorobenzalthiosalicylhydrazide was reduced at a mercury cathode in 50% aqueous piperidine. During the concentration of the electrolyzed solution and subsequent purification the disulfide of N-(2,4-dichlorobenzyl)thiosalicylhydrazide was isolated.

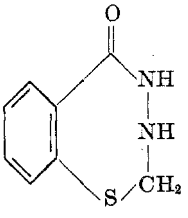
In order to create a more water-soluble derivative of TSH which of itself possessed definite antifungal activity, an attempt was made to prepare the N-methylol compound (F) using conditions described for the successful methylolation of nicotinamide (20). From the reaction mixture a compound with an empirical formula of $C_8H_8N_2OS$ (M.W. 180) was isolated. An ebullioscopic molecular weight determination in glacial acetic acid resulted in a value of 183 comparing favorably with that calculated. This material was insoluble in aqueous hydrochloric acid or sodium hydroxide but dissolved readily in methanolic potassium hydroxide or hydrochloric acid. No reaction could be effected between the unknown and *p*-chlorobenzaldehyde ruling out all compounds with an unsubstituted amino group such as G. The presence of a free thiol group or a disulfide linkage was contraindicated by the solubility and molecular weight data respectively. The only logical alternative structure appeared to be H.



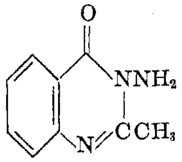
F



G



H



J

Zerewitinoff active hydrogen determinations with either J (28) or 3-aminoquinazolone-2 (29), which were chosen as model compounds, gave one active hydrogen at room temperature and a second active hydrogen at 100°. The unknown yielded two active hydrogens at room temperature suggesting that the active hydrogens were on different atoms, a suggestion which is compatible with the postulated structure, H.

BIOLOGICAL RESULTS

From the work carried out to date it is apparent that the thiol or disulfide group must be contiguous to the carbohydrazido group for maximum effectiveness; derivatives of 3- or 4-mercaptobenzhydrazide or the corresponding disulfides were devoid of antifungal or antibacterial activity. In general the disulfides are more effective *in vitro* than the free thiol compounds; alkylation of the thiol group, however, destroys all activity. The most effective carbonyl compounds were either quinoline 2- or 4-aldehydes or benzaldehydes containing chlorine atoms in the 2,4 or 3,4 positions or alkoxy substituents in the 2 position. Derivatives of sugars, benzalacetones, or heterocyclic aldehydes other than quinoline were not as effective. Reduction of the double bond —C=N— did not affect the degree of activity.

In determining the effect of nuclear substitution in the thiosalicylhydrazide moiety it was evident that halogen in either the 3,4, or 5 position enhanced the activity.

Table III contains the activity of the dithiosalicylhydrazone of quinoline-4-aldehyde (I), of *bis*-(2,4-dichlorobenzal)dithiosalicylhydrazide (II), of *bis*-(2,4-dichlorobenzal)-5,5′-dichlorodithiosalicylhydrazide (III), and of *bis*-(2-methoxybenzal)-5,5′-dichlorodithiosalicylhydrazide (IV) against some representative bacteria and fungi.

EXPERIMENTAL[3, 4]

Preparation of alkoxybenzaldehydes. A modification of the method of Buu-Hoï (See Table IIIA for reference) was used. In a three-necked 500-ml. flask, equipped with a stirrer and reflux condenser, were placed 0.275 mole of potassium hydroxide, 0.25 mole of hydroxybenzaldehyde, and 150 ml. of water. This mixture was stirred until solution was complete, whereupon 0.5 mole of alkyl iodide was added. The mixture was heated to reflux and stirred for 20–24 hours. At the end of this period, the reaction mixture was cooled and the layers were separated. The aqueous layer was extracted with three 100-ml. portions of ether, and the ether extracts were combined with the organic layer. This solution was extracted with three 100-ml. portions of 5% sodium hydroxide to remove any unreacted aldehyde, and then extracted with water until the water wash was neutral. The organic extract was dried over sodium sulfate. The solvent was removed on a steam-bath, and the unreacted alkyl iodide and corresponding alcohol were distilled under a moderate vacuum. The final product was obtained by vacuum-distillation.

In the preparation of 2-(2-chloroethoxy)benzaldehyde 0.25 mole of 1-chloro-2-bromoethane was used and 100 ml. of xylene was added to the reaction mixture at the start of the reaction. For the basic ethers 0.275 mole of diethylaminoethyl chloride hydrochloride was employed and the potassium hydroxide usage was raised to 0.55 mole to compensate for the additional hydrochloric acid.

For the preparation of 2-formylphenoxyacetic acid a mixture of 0.275 mole of chloroacetic acid, 0.75 mole of sodium hydroxide, 0.25 mole of salicylaldehyde, and 250 ml. of water was heated to reflux for 20 hours. After cooling and acidification with 6 *N* sulfuric acid an oil was obtained which crystallized quickly. This material was recrystallized from hot water.

Thiosalicylic acid. Into a 1-l. three-necked flask equipped for heating and stirring were placed 40 g. (0.13 mole) of dithiosalicylic acid, 350 ml. of water, and 38.2 g. (0.36 mole) of sodium carbonate. To the resulting solution was added 31.4 g. (0.18 mole) of sodium hydrosulfite and the reaction mixture was heated to refluxing in the course of 25–30 minutes. The original dark brown solution lightened in color to amber and carbon dioxide was evolved. The hot solution was poured into a 2-l. beaker, chilled to room temperature, and acidified with 100 ml. of 12 *N* hydrochloric acid. Because of the copious evolution of sulfur dioxide it is advisable to use good ventilation. The cream-colored solid was collected by filtration quickly and washed with 250–350 ml. of water to remove traces of sulfur dioxide. The precipitate which formed in the filtrate was primarily elemental sulfur. After drying at 55–60° *in vacuo* for 10–15 hours 36 g. (90%) of thiosalicylic acid, m.p. 165–168°, was obtained. Thiosalicylic acid of this grade reverted to the disulfide very easily and it was essential to keep the solid in a well sealed container.

Methyl thiosalicylate. This material was prepared according to the directions of Friedlander (21). Dry hydrogen chloride was passed through a refluxing solution of thiosalicylic acid in ten volumes of methanol for 8–10 hours. Distillation of the reaction mixture afforded 80–85% yields of methyl thiosalicylate, boiling at 115–119° at 1–2 mm., plus small amounts of methyl dithiosalicylate; m.p. 130–132°.

Thiosalicylhydrazide. Into a 300-ml. round-bottom flask equipped with Glas-Col heater and reflux condenser were placed 30 g. (0.177 mole) of methyl thiosalicylate, 75 g. (1.27 moles) of 85% hydrazine hydrate, and 15 ml. of isopropyl alcohol. The mixture was heated to reflux and held for 3½ hours. After cooling in an ice-bath, the yellow solution was diluted with 200 ml. of water and acidified to *p*H 6.5–7.0 with 6 *N* sulfuric acid. The light lemon-colored solid was collected and washed with 100 ml. of cold water. The weight of material, m.p. 112–116°, was 22 g. (74%). A sample was recrystallized twice from ten parts of water; m.p. 115–116°.

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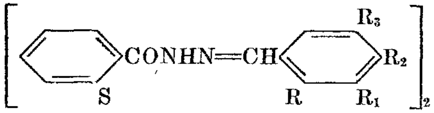
[3] All melting points are uncorrected.

[4] Microanalyses by the Clark Microanalytical Laboratory, Urbana, Illinois.

TABLE II

BIS-BENZALDITHIOSALICYLHYDRAZIDES



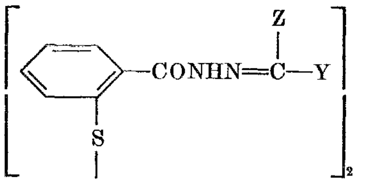
R	R_1	R_2	R_3	YIELD,[a] %	M.P., °C	EMPIRICAL FORMULA	ANALYSES[c]					
							Calc'd			Found		
							C	H	N	C	H	N
OH	H	H	H	93[b]	233–235[d]	$C_{28}H_{22}N_4O_4S_2$	61.99	4.06		61.47	3.98	
OCH_3	H	H	H	98	238–239[e]	$C_{30}H_{26}N_4O_4S_2$	63.16	4.56	9.80	63.20	4.86	9.42
OC_2H_5	H	H	H	94[b]	190–192[d, f]	$C_{32}H_{30}N_4O_4S_2$	64.43	4.70	9.38	64.46	5.12	9.42
$OCH_2CH_2CH_3$	H	H	H	97[b]	224–225[g]	$C_{34}H_{34}N_4O_4S_2$	65.15	5.46		65.30	5.47	
$OCH_2CH(CH_3)_2$	H	H	H	95[b]	227–228[e]	$C_{36}H_{38}N_4O_4S_2$	66.04	5.82	8.56	66.30	6.05	8.46
$OCH_2CH_2CH_2CH_3$	H	H	H	85[b]	226–227[d]	$C_{36}H_{38}N_4O_4S_2$	66.04	5.82		66.14	5.85	
$OCH(CH_3)CH_2CH_3$	H	H	H	86[b]	226–227[e]	$C_{36}H_{38}N_4O_4S_2$	66.04	5.82		66.47	5.80	
$OCH_2CH_2CH_2CH_2CH_3$	H	H	H	99[b]	204–205[e]	$C_{38}H_{42}N_4O_4S_2$	66.83	6.21		66.76	6.21	
$OCH_2CH_2CH(CH_3)_2$	H	H	H	99[b]	222–224[h]	$C_{38}H_{42}N_4O_4S_2$	66.83	6.21		66.55	5.88	
OCH_2CH_2Cl	H	H	H	99[b]	222–223[i]	$C_{32}H_{28}Cl_2N_4O_4S_2$	57.55	4.23		57.52	4.42	
$OCH_2CH_2N(C_2H_5)_2$	H	H	H	88[b]	156–158[j]	$C_{40}H_{50}Cl_2N_6O_4S_2$	64.86	6.48		64.59	6.34	
OCH_2CO_2H	H	H	H	97[b]	189–190[d]	$C_{32}H_{26}N_4O_8S_2$	58.36	3.95		58.12	4.61	
OH	H	H	Br	96[b]	259–260[d]	$C_{28}H_{20}Br_2N_4O_4S_2$	47.99	2.88		48.30	2.93	
H	OH	H	H	92[b]	243–244[d]	$C_{28}H_{22}N_4O_4S_2$	61.99	4.06		62.20	3.84	
H	OCH_3	OCH_3	H	98	206–207[d]	$C_{32}H_{30}N_4O_6S_2$	60.93	4.80		61.01	4.86	
H	H	OH	H	99	243–245[d]	$C_{28}H_{22}N_4O_4S_2$	61.99	4.06	10.31	61.67	4.07	10.12
H	H	OCH_3	H	97	252–253[d]	$C_{30}H_{26}N_4O_4S_2$	63.16	4.56	9.80	63.14	4.66	9.53
H	H	OCH_2CH_2Cl	H	93	237–238[i]	$C_{32}H_{28}Cl_2N_4O_4S_2$	57.55	4.23		57.49	4.27	
H	$CH_2N(CH_3)_2$	OH	H	99	214–216[d]	$C_{34}H_{36}N_6O_4S_2$	62.17	5.53	12.80	62.01	5.71	12.30
H	H	[o]	H	30	197–199[k]	$C_{40}H_{50}Cl_2N_6O_4S_2$	59.01	6.22	8.74	58.73	6.37	8.54
NO_2	H	H	H	88	240–241[e]	$C_{28}H_{20}N_6O_6S_2$	55.98	3.36		55.77	3.37	
H	NO_2	H	H	98	263–264[d]	$C_{28}H_{20}N_6O_6S_2$	55.98	3.36		55.89	3.30	

H	H	NO_2	H	88	257–258[e]	$C_{28}H_{20}N_6O_6S_2$	55.98	3.36		55.63	3.53	
H	Br	OH	H	91	229–231[e]	$C_{28}H_{20}Br_2N_4O_4S_2$	47.99	2.88		47.67	3.13	
H	H	OCH_2CO_2H	H	83[b]	237–239[d]	$C_{32}H_{26}N_4O_8S_2$	58.36	3.95		58.53	4.19	
H	[p]	[p]	H	98	250–252[e]	$C_{30}H_{22}N_4O_6S_2$	60.18	3.71		60.05	3.96	
Cl	H	H	H	94	243–244[e]	$C_{28}H_{20}Cl_2N_4O_2S_2$	58.03	3.45	9.66	58.03	3.51	8.78
Cl	H	Cl	H	89	267–268[l]	$C_{28}H_{18}Cl_4N_4O_2S_2$	51.86	2.80	8.63	51.89	3.24	8.46
H	H	Cl	H	88	240–241[e]	$C_{28}H_{20}Cl_2N_4O_2S_2$	58.03	3.45	9.66	58.01	3.51	9.01
H	Cl	Cl	H	93	220–222[m]	$C_{28}H_{18}Cl_4N_4O_2S_2$	51.86	2.80		52.25	2.58	
H	H	$N(CH_3)_2$	H	78	241–243[e]	$C_{32}H_{32}N_6O_2S_2$	64.43	5.37	14.05	64.44	5.37	13.41
H	H	$N^+(CH_3)_3I^-$	H	35	216–217[n]	$C_{34}H_{38}I_2N_6O_2S_2$	46.36	4.31		46.59	4.10	
H	H	$NHCOCH_3$	H	99	266–267[d]	$C_{32}H_{28}N_6O_4S_2$	61.53	4.48		61.29	4.76	
H	H	$SO_2C_2H_5$	H	90	262–263[d]	$C_{32}H_{30}N_4O_6S_4$	55.33	4.32	8.07	55.12	4.53	8.13
H	H	CO_2H	H	85	292–293[d]	$C_{30}H_{22}N_4O_6S_2$	60.20	3.67	9.35	60.18	3.75	9.33

[a], [b] This is the yield obtained when thiosalicylhydrazide was reacted with the respective aldehyde and in most instances represents the yield of free mercapto compound which on recrystallization changed to the dithio derivative. In those cases where the dithio derivative was prepared from the dithiosalicylhydrazide dihydrochloride a superscript [b] appears next to the yield percent figure. [c] During the early stages of this investigation we were plagued by the failure to obtain theoretical nitrogen values for compounds which analyzed correctly for carbon and hydrogen. For this reason some of the nitrogen values reported are not in agreement with the theoretical values. Due to the diligence of the Clark Microanalytical Laboratory this difficulty was surmounted by employing a modification of the regular Dumas procedure. Further information *re* this modification may be obtained from the Clark Microanalytical Laboratory. [d] Recrystallized from aqueous dimethylformamide. Material retained solvent of crystallization. [e] Recrystallized from aqueous Methyl Cellosolve. [f] This compound melted completely at 190–192° and then resolidified and melted again at 246–248°. Possibly another of the geometrical isomers was formed during the molten stage. [g] Recrystallized from aqueous ethanol. [h] Recrystallized from aqueous *n*-propanol. [i] Recrystallized from methanolic dimethylformamide. [j] Recrystallized poorly from chlorobenzene. [k] This compound was analyzed as the hydrochloride after one recrystallization from propanol-2. [l] Recrystallized from dimethylformamide. [m] Recrystallized from *n*-butanol. [n] Recrystallized from water. [o] 2-Diethylaminoethoxy at R_2. [p] R_1,R_2 = 3,4-Methylenedioxy.

TABLE II A

Miscellaneous Derivatives of Dithiosalicylhydrazide



Y	Z	YIELD, %	M.P., °C.	EMPIRICAL FORMULA	ANALYSES					
					Calc'd			Found		
					C	H	N	C	H	N
1-Naphthyl	H	92^b	207–208^c	$C_{36}H_{26}N_4O_2S_2$	70.80	4.29	9.18	70.79	4.39	9.34
2-Naphthyl	H	46^b	258–260^d	$C_{36}H_{26}N_4O_2S_2$	70.80	4.29	9.18	70.72	4.39	9.38
2-Furfuryl	H	91	261–262^e	$C_{24}H_{18}N_4O_4S_2$	58.77	3.70		58.45	3.53	
2-Thienyl	H	96	257–258^c	$C_{24}H_{18}N_4O_2S_4$	55.37	3.49		55.21	3.45	
2-Pyridyl	H	70^b	148–149^c	$C_{26}H_{20}N_6O_2S_2$	60.94	3.90		60.96	4.23	
3-Pyridyl	H	88^b	244–245^d	$C_{26}H_{18}N_6O_2S_2$	60.91	3.94		60.86	3.79	
4-Methoxystyryl	CH_3	90^b	220–221^d	$C_{36}H_{34}N_4O_4S_2$	66.26	5.03		66.26	5.03	
2-Hydroxyphenyl	CH_3	95^b	259–260^d	$C_{30}H_{26}N_4O_4S_2$	63.16	4.56		63.23	4.43	
2-Quinolyl	H	92^b	167–170^e	$C_{34}H_{24}N_6O_2S_2$	66.64	3.95		66.68	3.99	
4-Quinolyl	H	46^b	224–225^d	$C_{34}H_{24}N_6O_2S_2$	66.64	3.95		66.42	4.16	
5-Nitrofurfuryl	H	95^b	236–237^d	$C_{24}H_{16}N_6O_8S_2$	49.65	2.78		50.40	2.88	

[a], [b] See remarks under Table II. [c] Recrystallized from aqueous Methyl Cellosolve. [d] Recrystallized from aqueous dimethylformamide. [e] Recrystallized from Diethyl Carbitol [bis(2-ethoxyethyl) ether].

TABLE III

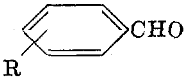
MICROBIOLOGICAL DATA[a] (Expressed in mcg/ml. for 100% inhibition)

ORGANISMS	COMPOUNDS			
	I	II	III	IV
Staph. aureus	6.25–12.5	25–50	125	25–50
Proteus vulgaris	12.5–25.0	25–50	125	25–50
Pseudomonas aerunginosa	50–125	125–250	250	250
Brucella abortus	1.25–2.5	25–50	5.0–12.5	5.0–12.5
Candida albicans	25–50	125–250	125	125
Trichophyton rubrum	5.0–12.5	12.5–25	2.5–5.0	5.0–12.5
Trichophyton shoenleini	2.5–5.0	12.5–25	1.25–2.5	2.5–5.0
Trichophyton mentagrophytes	5.0–12.5	12.5–25	12.5–25	5.0–12.5
Microsporum canis	5.0–12.5	25–50	12.5–25	12.5–25
Microsporum audouini	12.5–25	25–50	5.0–12.5	125–250
Microsporum gypseum	2.5–5.0	25–50	5.0–12.5	12.5–25
Histoplasma capsulatum	5.0–12.5	5.0–12.5	12.5–25	12.5–25

[a] *Acknowledgment.* The authors are indebted to Dr. F. Carvajal and Mr. R. Hill for the determination of microbiological data.

TABLE III A

ALKOXYBENZALDEHYDES



R	B.P., °C./MM.	YIELD, %	ANALYSES			
			Calc'd		Found	
			C	H	C	H
2-(2-Chloroethoxy)	103/0.15[a]	21	58.53	4.92	58.09	4.83
2-(2-Diethylaminoethoxy)	118/0.08	41				
Its hydrochloride	m.p. 144–145		60.54	7.82	60.80	7.69
2-*n*-Propoxy	87/0.3	61	73.17	7.32	73.39	7.29
2-*n*-Butoxy[b]	105/0.2	53				
2-Isobutoxy[c]	117/1–2	15				
2-*sec*-Butoxy[d]	78/0.05	28				
2-*n*-Amyloxy	112/0.4	52	74.96	8.38	74.82	8.21
2-Isoamyloxy[d]	94/0.1	35				
2-Carboxymethoxy[e]	m.p. 129°	71				
4-(2-Chloroethoxy)	110/0.1[f]	30	58.53	4.92	58.23	4.91
4-(2-Diethylaminoethoxy)	106/0.1	60				
Its hydrochloride	m.p. 116–118		60.54	7.82	60.68	7.79

[a] M.p. 46°. [b] Prepared by Buu-Hoï, *Compt. rend.*, **241**, 202 (1945), b.p. 158°/20 mm. [c] Prepared by Baumann and Fromme, *Ber.*, **24**, 1448 (1891), b.p. 265°/760 mm. [d] Referred to by Smith and Burnett, Jr., *J. Econ. Entomol.*, **42**, 439 (1949) but no physical constants were given. [e] Prepared by Rossing, *Ber.*, **17**, 2988 (1894) in poor yield, m.p. 132°. [f] M.p. 31°.

Anal. Calc'd for $C_7H_8N_2OS$: C, 50.00; H, 4.76; N, 16.66.
Found: C, 50.04; H, 4.60; N, 16.44.

Dimethyl dithiosalicylate. Into a 300-ml. round-bottomed flask equipped for refluxing were placed 51 g. (0.167 mole) of crude dithiosalicylic acid and 70 g. (0.64 mole) of thionyl chloride. This mixture was heated gently to reflux and maintained at reflux for three hours. The resultant clear solution was concentrated *in vacuo* to remove excess thionyl chloride, benzene being added in the last stages to facilitate removal. To the residue in the flask was added 100 ml. of methanol and after the initial vigorous reaction had subsided, the mixture was refluxed for one hour. The solution was chilled at 0–5° for 12 hours, and the crystals were separated by filtration and dried at 50°. The weight of material m.p. 129–131° (Lit. m.p. 131–133°) was 40.5 g. (73%).

Thiosalicylhydrazide from dimethyl dithiosalicylate. Into a 250-ml. three-necked flask equipped for stirring and refluxing were placed 30 g. (0.09 mole) of dimethyl dithiosalicylate and 30 g. (0.60 mole) of hydrazine hydrate. After refluxing the mixture for three hours the deep yellow solution was cooled, diluted with 100 ml. of 10% sodium chloride solution, and adjusted to *p*H 4–4.5 with 20 ml. of concentrated hydrochloric acid. The pale yellow crystals were collected and dried at 50° to yield 27.2 g. (90%) m.p. 99–105°. Recrystallization from water gave lemon-colored granules, m.p. 113–115°.

CONDENSATION OF THIOSALICYLHYDRAZIDE WITH CARBONYL COMPOUNDS

A. With salicylaldehyde. Because the procedures for the condensations were essentially the same several typical examples are cited. Into a 400-ml. beaker on a hot plate were placed 100 ml. of methanol, 2 ml. of glacial acetic acid, and 10 g. (0.0595 mole) of thiosalicylhydrazide. The mixture was heated to boiling and 7.59 g. (0.0615 mole) of salicylaldehyde was added to the clear solution. The mixture was boiled an additional five minutes and cooled to 10° whereupon shining crystals began to separate. The solid was collected, washed with 20% aqueous methanol, and dried at 60°. The weight of material, m.p. 172–176°, was 14.9 g. (92%).

B. With 2,4-dichlorobenzaldehyde. Employing the same reaction conditions and substituting isopropyl alcohol for methanol as the solvent a 93–96% yield of 2,4-dichlorobenzalthiosalicylhydrazide was realized; m.p. 211–216°. After several recrystallizations from aqueous dimethylformamide the melting point was constant at 265–267° due to conversion of thiol to disulfide.

C. With 4-ethylsulfonylbenzaldehyde. Essentially the same conditions were used as described above substituting 25% aqueous acetic acid for the methanol-acetic acid mixture.

D. With 4-carboxybenzaldehyde. The insolubility of the aldehyde in alcohol or acetic acid necessitated carrying out the condensation in Methyl Cellosolve (2-ethoxyethanol). Thus 3.36 g. (0.02 mole) of thiosalicylhydrazide was added to a boiling solution of 2.98 g. (0.02 mole) of 4-carboxybenzaldehyde in a solution of 100 ml. of Methyl Cellosolve and 5 ml. of glacial acetic acid. After boiling an additional five minutes, hot water was added to the cloud point and the mixture allowed to cool. There was obtained 5.1 g. (85%); m.p. 290–292°.

E. With L - (+)*arabinose.* L - (+)Arabinose (1.5 g., 0.01 mole) was dissolved in 5 ml. of hot water and added to a solution of 1.68 g. (0.01 mole) of thiosalicylhydrazide in 15 ml. of hot water. The hot clear solution soon deposited feathery needles and set to a solid mass upon cooling. The crystals were filtered off, washed with water, ethanol, and ether and dried at 60° to yield 3.0 g. (100%); m.p. 174–176°. Two recrystallizations from water raised the melting point to 175–176°.

(3-Dimethylaminomethyl-4-hydroxybenzal)thiosalicylhydrazide. Into a 250-ml. beaker were placed 12.2 g. (0.1 mole) of *p*-hydroxybenzaldehyde and 18.9 g. (0.105 mole) of 25% aqueous dimethylamine. The mixture was cooled to 20° and 11.2 ml. (0.15 mole) of 40% aqueous formaldehyde was added so that the temperature did not rise above 35°. After standing overnight the solution was heated on a steam-bath for two hours, 20 g. of sodium chloride was added, and the solution was cooled and extracted with three 150-ml. portions of benzene. The benzene extracts were dried with magnesium sulfate, the filtrate was concentrated to 200 ml. and dry hydrogen chloride was passed in. There was obtained 4.0 g. of a semi-solid.

This solid was condensed with 3.5 g. (0.02 mole) of thiosalicylhydrazide by boiling for 15 minutes in a solution of 2 ml. of glacial acetic acid and 100 ml. of water. The cooled solution was neutralized with a saturated sodium carbonate solution and the yellow gum which precipitated initially slowly crystallized. There was obtained 5.6 g.; m.p. 195–200°. A sample recrystallized from methanol-dimethylformamide melted at 205–207°, resolidified, and melted again above 250° dec.

Anal. Calc'd for $C_{17}H_{19}N_3O_2S$: C, 62.00; H, 5.77; N, 12.76.
Found: C, 62.01; H, 5.71; N, 12.30.

Dithiosalicylhydrazide. Thiosalicylhydrazide (13.4 g., 0.08 mole) was dissolved in 100 ml. of 50% methanol by warming. The solution was cooled to room temperature and 10.1 g. (.04 mole) of iodine was added in one portion while agitating vigorously. The iodine reacted as rapidly as it dissolved and a clear light yellow solution was obtained. Dilution of the solution with an equal quantity of water and the addition of sodium bicarbonate solution gave a white precipitate which was collected, washed with water, and dried at 50°. The yield was 10.5 g. (79%); m.p. 206–208°. The analytical sample after two recrystallizations from dimethylformamide-methanol had m.p. 214–215°.

Anal. Calc'd for $C_{14}H_{14}N_4O_2S_2$: C, 50.28; H, 4.22; N, 16.75.
Found: C, 50.51; H, 4.20; N, 16.54.

Dithiosalicylhydrazide dihydrochloride. Dithiosalicylhydrazide (5 g.) was slurried with 35 ml. of water and concentrated hydrochloric acid was added dropwise until a clear solution was obtained. The addition of an additional 25 ml. of concentrated hydrochloric acid caused the mixture to set to a thick mass of crystals. These crystals were collected, washed with isopropyl alcohol and ether, and dried. Recrystallization from methanol-ethyl acetate gave 5 g. (83%) of white needles, m.p. 220–222°.

Anal. Calc'd for $C_{14}H_{14}N_4O_2S_2 \cdot 2HCl$: Cl, 17.40. Found: Cl, 16.85.

Several attempts were made to prepare a sample for analysis which would contain the theoretical amount of halogen. Each time it appeared that some hydrogen chloride was lost during the drying operation.

Bis-(2,4-dichlorobenzal)dithiosalicylhydrazide. 2,4-Dichlorobenzaldehyde (500 mg.) was added to a hot solution of 334 mg. of dithiosalicylhydrazide in 5 ml. of glacial acetic acid. Crystals started to separate from the hot solution after a few minutes. The mixture was cooled and the crystals were collected and washed with acetic acid and methanol to yield 505 mg. (78%); m.p. 253–255°. After two recrystallizations from dimethylformamide-methanol the material melted at 266–267°, and was identical with the compound obtained by repeated crystallization of the condensation product from TSH with 2,4-dichlorobenzaldehyde.

Anal. Calc'd for $C_{28}H_{18}Cl_4N_4O_2S_2$: C, 51.86; H, 2.80.
Found: C, 51.60; H, 3.03.

Bis-(2,4-dichlorobenzal)dithiosalicylhydrazide. Pyridine and iodine oxidation. 2,4-Dichlorobenzalthiosalicylhydrazide (3.25 g.) was dissolved in 40 ml. of pyridine and a solution of 1.27 g. of iodine in 20 ml. of pyridine was added slowly at room temperature. The iodine was consumed immediately and crystals separated. After standing for one-half hour in an ice-bath, the white solid was collected, washed with methanol, and dried at 60° to yield 3 g.; m.p. 262–264°. The material melted at 265–267° after one recrystallization from dimethylformamide-methanol and did not depress the melting of material prepared in the preceding experiment.

Anal. Calc'd for $C_{28}H_{18}Cl_4N_4O_2S_2$: C, 51.86; H, 2.80.
Found: C, 51.99; H, 2.88.

Oxidation of 2,4-dichlorobenzalthiosalicylhydrazide with pyridine and hydrogen peroxide. 2,4-Dichlorobenzalthiosalicylhydrazide (2 g.) was dissolved in 25 ml. of pyridine by warming. The yellow solution was cooled to 25° and 5 ml. of 30% hydrogen peroxide was added. After standing overnight at room temperature, the solution had deposited crystals which were filtered off, washed with pyridine and methanol, and dried. The weight of material, m.p. 265–266°, was 1 g. One recrystallization from dimethylformamide raised the melting point to 266–267°. A mixture melting point with the disulfide obtained by repeated recrystallization of 2,4-dichlorobenzalthiosalicylhydrazide or that prepared from dithiosalicylhydrazide showed no depression.

N^2,$N^{2'}$-Di-(2,4-dichlorobenzyl)dithiosalicylhydrazide. Into a 1-l. beaker equipped with a mercury cathode and a carbon anode fitted with a fritted glass diaphragm was placed a solution of 5.0 g. of 2,4-dichlorobenzalthiosalicylhydrazide in 250 ml. of 50% aqueous piperidine. While stirring gently, reduction was accomplished by passing a one-half ampere current through the electrolyte for two hours. During this period the temperature did not exceed 55°. The clear yellow solution was neutralized with 6 *N* hydrochloric acid and allowed to stand at 0–5° for two hours. The solid was collected and dried at 60° to yield 4.3 g. (85%); m.p. 172–175°. This material was soluble in acetone or methanol. When recrystallization was attempted from aqueous methanol the melting point rose to 253–255°. Further recrystallization from aqueous dimethylformamide gave an analytically pure disulfide; m.p. 255–257°.

Anal. Calc'd for $C_{28}H_{22}Cl_4N_4O_2S_2$: C, 51.53; H, 3.37.
Found: C, 51.37; H, 3.13.

Preparation of thiosalicylic acids. Inasmuch as the procedure for the synthesis of the thiol acids was similar in all cases the preparation of 5-chlorothiosalicylic acid is cited as an example.

A solution of 94 g. (0.545 mole) of 5-chloroanthranilic acid (8), 23 g. (0.55 mole) of sodium hydroxide, and 37.5 g. (0.545 mole) of sodium nitrite in 650 ml. of water was added slowly and with good agitation to a mixture of 150 ml. of concentrated hydrochloric acid and 200 g. of ice in a 2-l. beaker surrounded by an ice-bath. The temperature was maintained at 0–5° by the addition of ice. After the completion of the addition of the nitrite solution the mixture was stirred an additional 30 minutes and neutralized to Hydrion paper with potassium acetate. The cold diazonium solution was run, in a thin stream, into a 4-l. beaker containing a vigorously stirred solution of 250 g. (1.55 moles) of potassium ethyl xanthate in 800 ml. of water which had been preheated to 75–80°. The temperature was maintained at 75–80° during the addition and a copious evolution of nitrogen occurred. Some oily material separated during the reaction. The reaction mixture was cooled, acidified to approximately *p*H 3 with concentrated hydrochloric acid, and the aqueous phase decanted from the resulting semi-solid sludge.

The sludge was dissolved in 400 ml. of 10% sodium hydroxide and heated on a steam-bath for two hours. In order to insure that the thiol compound was present 50 g. of sodium hydrosulfite was added at this point and the solution was held at 80–90° for ten minutes. Then the solution was filtered, cooled, acidified with concentrated hydrochloric acid to *p*H 4–5, and the solid collected quickly on a Büchner funnel. After washing the cake with three 100-ml. aliquots of water the cake was sucked as dry as possible with the aid of a rubber dam.

Because the thiol acids oxidized easily to the disulfide when drying, to eliminate water the following technique was devised: The moist cake was slurried or dissolved in 80 ml. of methanol and 1500 ml. of isopropyl ether was added. The aqueous phase was separated and the organic solution was dried over magnesium sulfate. Removal of the ether on a steam-bath yielded 88 g. (85%) of 5-chlorothiosalicylic acid; m.p. 192–194°.

The thiol acids prepared by this method are listed in Table IV.

5,5'-Dichlorodithiosalicylic acid. A 3-g. sample of 5-chlorothiosalicylic acid was oxidized in 50 ml. of methanol with iodine. A yield of 2.8 g., m.p. 326–328°, was isolated. Recrystallization from a mixture of Methyl Cellosolve, methanol, and water gave material melting at 330°.

Anal. Calc'd for $C_{14}H_8Cl_2O_4S_2$: C, 44.81; H, 2.15; Cl, 18.90.
Found: C, 44.78; H, 2.26; Cl, 18.74.

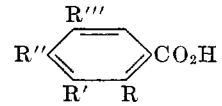
Preparation of methyl thiolbenzoates. The thiol acids were all esterified by the methanol-hydrogen chloride gas method and the technique is illustrated in the following procedure: A solution of 25.4 g. (0.109 mole) of 5-bromothiosalicylic acid in 250 ml. of absolute methanol was refluxed for 12 hours while passing in dry hydrogen chloride gas. The solution, from which some oil had separated, was cooled and poured into ice and water. The semi-solid oil was then taken up in ether, and the extract washed successively with saturated sodium bicarbonate solution and water, and dried over sodium sulfate. Evaporation of the ether yielded 26.5 g. (98%) of an oil which solidified upon cooling. This crude material was used directly for the preparation of the 5-bromothiosalicylhydrazide.

Most of the thiol esters were usually used directly in the formation of the respective hydrazide. Several of the methyl esters were characterized and their physical constants are contained in Table V.

m-Thiolbenzhydrazide. To 11 g. (0.065 mole) of crude methyl *m*-thiolbenzoate was added 30 ml. (0.6 mole) of 85% hydrazine hydrate. The mixture was refluxed 2½ hours, and the resulting solution was diluted with one volume of ice and water and made faintly acid to Hydrion paper with concentrated hydrochloric acid. The precipitate which formed slowly was filtered off, washed with water, and dried at room temperature to yield 3.5 g. (32%), m.p., 65–70°. Two recrystallizations from water and one from benzene gave needles; m.p. 120.5–121.5°.

TABLE IV

THIOL BENZOIC ACIDS



R	R′	R″	R‴	YIELD, %	M.P., °C.	EMPIRICAL FORMULA	ANALYSES			
							C		H	
							Calc'd	Found	Calc'd	Found
H	SH	H	H	85	145–146[a]					
H	H	SH	H	92	218–220[b]					
SH	H	Cl	H	85	195–196	$C_7H_5ClO_2S$	44.60	44.87	2.67	2.87
SH	H	H	Cl	86	193–194	$C_7H_5ClO_2S$	44.60	44.91	2.67	2.96
SH	Cl	H	Cl	93	196–198[c]					
SH	H	H	Br	86	210–211	$C_7H_5BrO_2S$	36.07	35.91	2.16	2.14
SH	Br	H	Br	97	221–222[d]	$C_7H_4Br_2O_2S$	26.95	27.61	1.29	1.43
SH	H	CH_3SO_2	H	59	180–181[e]	$C_8H_8O_4S_2$	41.40	41.48	3.47	3.47

[a] This compound was originally prepared by Hubner and Frerichs (22) by the reduction of *m*-chlorosulfonylbenzoyl chloride, m.p. 146–147. [b] Thompson (23) prepared this compound by reduction of 4,4′-dicarboxydiphenyl disulfide with iron and sodium carbonate, m.p. 212°. [c] Reported by Tarbell and McCall (24), m.p. 207–208°. [d] This material was slightly low in bromine as evidenced by the analysis. [e] The low yield is attributed to the water solubility.

Anal. Calc'd for $C_7H_8N_2OS$: C, 50.00; H, 4.76; S, 19.07.

Found: C, 50.06; H, 4.61; S, 18.85.

Another run using 26.5 g. (0.157 mole) of ester and 25 ml. (0.5 mole) of hydrazine hydrate gave a crude yield of 64%.

Bis-3,3′-dithiobenzhydrazide. The oxidation of *m*-thiolbenzhydrazide with iodine in methanol-water gave a 95% yield of the disulfide, m.p. 155–156° after two recrystallizations each from isopropyl alcohol and pyridine-water.

Anal. Calc'd for $C_{14}H_{14}N_4O_2S_2$: C, 50.28; H, 4.22.

Found: C, 50.62; H, 4.28.

Bis-3,3′-(2,4-dichlorobenzal)benzhydrazide disulfide. *m*-Thiolbenzhydrazide (2 g., 0.012 mole) was dissolved in 15 ml. of hot methanol and 0.5 ml. of acetic acid. Then (2.7 g., 0.012

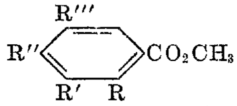
mole) of 2,4-dichlorobenzaldehyde in 15 ml. of hot methanol was added and the mixture was boiled for ten minutes. Water was slowly added to induce crystallization and the mixture was cooled. After filtration, washing with 50% methanol, and drying at 60°, 2.8 g. (73%) of material was obtained which, when treated with boiling *n*-butanol went into solution and then started to reprecipitate. The mixture was cooled, and the crystals were filtered off and washed with methanol. After recrystallization from dimethyl formamide-water, they melted at 285–287° and were insoluble in aqueous alkali.

Anal. Calc'd for $C_{28}H_{18}Cl_4N_4O_2S_2$: C, 51.86; H, 2.80; N, 8.64.
Found: C, 52.15; H, 2.95; N, 8.39.

A sample prepared by the condensation of the *bis*-3,3′-dithiobenzhydrazide described above with 2,4-dichlorobenzaldehyde was identical with this material.

TABLE V

METHYL THIOL BENZOATES



R	R′	R″	R‴	YIELD, %	M.P., °C.	EMPIRICAL FORMULA	ANALYSES			
							C		H	
							Calc'd	Found	Calc'd	Found
H	SH	H	H	95						
H	H	SH	H	71	55–56[a]	$C_8H_8O_2S$	57.14	57.36	4.76	4.60
SH	H	Cl	H	75						
SH	H	H	Cl	85	44–45[b]	$C_8H_7ClO_2S$	47.41	47.71	3.48	3.56
SH	Cl	H	Cl	87						
SH	H	H	Br	98						
SH	Br	H	Br	86	88–89[c]	$C_8H_6Br_2O_2S$	29.47	30.43	1.86	1.94
SH	H	OCH_3	H	88						
SH	H	CH_3SO_2	H	60						

[a] Recrystallized from Skellysolve B. [b] Recrystallized from methanol-water. [c] Recrystallized from methanol.

4-Thiolbenzhydrazide. To 12 g. (0.071 mole) of crude methyl *p*-thiolbenzoate was added 50 ml. (1 mole) of hydrazine hydrate. The mixture was refluxed for three hours and the resulting clear solution was cooled, diluted with one volume of water, and made faintly acid to Hydrion paper with concentrated hydrochloric acid. The precipitate was filtered off, washed with water, and dried at 60°. The yield was 8.5 g. (71%); m.p. 140–146°. Two recrystallizations from water raised the melting point to 152–153°.

Anal. Calc'd for $C_7H_8N_2OS$: C, 50.00; H, 4.76.
Found: C, 50.52; H, 4.54.

Bis-4,4′-dithiobenzhydrazide. A solution of iodine in methanol was added dropwise to 10 g. of 4-thiolbenzhydrazide dissolved in 300 ml. of 50% methanol, until no more was consumed. A slight excess of iodine was removed with sodium thiosulfite solution and the mixture was filtered from a small amount of insoluble matter. Dilution with an equal volume of water and the addition of a saturated potassium bicarbonate solution precipitated the product. The solid was collected and recrystallized once from isopropyl alcohol and four times fron Cellosolve[5]-water; m.p. 196–197°.

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[5] 2-Ethoxyethanol.

Anal. Calc'd for $C_{14}H_{14}N_4O_2S_2$: C, 50.28; H, 4.22.
Found: C, 50.20; H, 4.45.

(2,4-Dichlorobenzal)-4-mercaptobenzhydrazide. This material was prepared from 4-thiolbenzhydrazide and 2,4-dichlorobenzaldehyde in 67% yield. After three recrystallizations from methanol it had m.p. 193–194°.

Anal. Calc'd for $C_{14}H_{10}Cl_2N_2OS$: C, 51.70; H, 3.10.
Found: C, 51.99; H, 3.07.

The disulfide was prepared by oxidation of the aforementioned benzal derivative with iodine in pyridine and was found to be identical with material prepared by the condensation of *bis*-4,4′-dithiobenzhydrazide with 2,4-dichlorobenzaldehyde in acetic acid; m.p. 295–296° after three recrystallizations from dimethyl formamide-water.

Anal. Calc'd for $C_{28}H_{18}Cl_4N_4O_2S_2$: C, 51.86; H, 2.80; N, 8.64.
Found: C, 52.15; H, 3.03; N, 8.64.

(3,4-Dichlorobenzal)-4-thiolbenzhydrazide. The condensation of 4-thiolbenzhydrazide with 3,4-dichlorobenzaldehyde gave this material in 98% yield; m.p. 204–205° after three recrystallizations from ethanol.

Anal. Calc'd for $C_{14}H_{10}Cl_2N_2OS$: C, 51.70; H, 3.10; N, 8.61.
Found: C, 51.90; H, 3.03; N, 8.41.

The disulfide was prepared by oxidation with iodine in pyridine and was found to be identical with material prepared from *bis*-4,4′-dithiobenzhydrazide, m.p. 238–240° after three recrystallizations from dimethylformamide-methanol.

Anal. Calc'd for $C_{28}H_{18}Cl_4N_4O_2S_2$: C, 51.86; H, 2.80.
Found: C, 52.31; H, 3.10.

4,4′-Dichlorodithiosalicylhydrazide. Methyl 4-chlorothiosalicylate (20 g.) was refluxed for two hours with 20 ml. of 85% hydrazine hydrate. After acidifying the reaction mixture to *p*H 5, 17 g. (85%) of material was obtained, m.p. 142–143° after one recrystallization from water. Further purification, however, converted more and more of the material to the disulfide. Analytical results therefore are given for the pure disulfide which was prepared by oxidation of the crude thiol and recrystallization from dimethylformamide-methanol; m.p. 229–230°.

Anal. Calc'd for $C_{15}H_{12}Cl_2N_4O_2S_2$: C, 41.70; H, 3.00.
Found: C, 42.12; H, 2.77.

Bis-(2,4-dichlorobenzal)-4,4′-dichlorodithiosalicylhydrazide. Recrystallization from dimethylformamide of the condensation product from crude 4-chlorothiosalicylhydrazide and 2,4-dichlorobenzaldehyde gave the disulfide. This was identical with samples prepared by deliberate oxidation with iodine of the condensation product or by the condensation of 4,4′-dichlorodithiosalicylhydrazide with the aldehyde; m.p. 260–261°.

Anal. Calc'd for $C_{28}H_{16}Cl_6N_4O_2S_2$: C, 46.93; H, 2.25.
Found: C, 47.18; H, 2.17.

5,5′-Dichlorodithiosalicylhydrazide. Methyl 5-chlorothiosalicylate (60 g.) was refluxed with 60 ml. of 85% hydrazine hydrate for three hours. The reaction mixture was chilled, acidified to *p*H 5 with concentrated hydrochloric acid, and the crystals were collected by filtration and dried at 60–70°. Yield, 56 g. (93%) of solid, m.p. 240–245°. This material was substantially the disulfide inasmuch as further treatment with methanolic iodine and subsequent recrystallization gave an analytically pure sample; m.p. 249–250°.

Anal. Calc'd for $C_{14}H_{12}Cl_2N_4O_2S_2$: C, 41.70; H, 3.00.
Found: C, 42.20; H, 3.28.

Bis-2,4-dichlorobenzal)-5,5′-dichlorodithiosalicylhydrazide. The condensation of crude 5-chlorothiosalicylhydrazide with 2,4-dichlorobenzaldehyde in isopropyl alcohol gave a 90% yield of the benzal derivative. Recrystallization of the crude product from Methyl Cellosolve resulted in complete conversion to the disulfide; m.p., 245–247°.

Anal. Calc'd for $C_{28}H_{16}Cl_6N_4O_2S_2$: C, 42.93; H, 2.25.
Found: C, 47.29; H, 2.39.

This material was identical with the compound formed from 5,5′-dichlorodithiosalicylhydrazide and the aldehyde.

3,3′,5,5′-Tetrachlorodithiosalicylhydrazide. Methyl 3,5-dichlorothiosalicylate (47.5 g.) was refluxed with 50 ml. of hydrazine hydrate for three hours. The yield of crude hydrazide was 43.5 g. (91%), m.p. 162–169°. Recrystallization attempts converted the thiol derivative to the disulfide. Complete oxidation was accomplished with iodine in methanol. Two recrystallizations from methanolic dimethylformamide gave pure material; m.p. 223–225°.

Anal. Calc'd for $C_{14}H_{10}Cl_4N_4O_2S_2$: C, 35.60; H, 2.12.
Found: C, 35.73; H, 2.16.

Bis-(2,4-dichlorobenzal)-3,3′,5,5′-tetrachlorodithiosalicylhydrazide. This derivative separated from methanol in 80% yield upon reacting 2,4-dichlorobenzaldehyde with the 3,3′,5,5′-tetrachlorodithiosalicylhydrazide. The melting point was 258–260° after four recrystallizations from aqueous dimethylformamide.

Anal. Calc'd for $C_{28}H_{14}Cl_8N_4O_2S_2$: C, 42.72; H, 1.78.
Found: C, 42.46; H, 1.83.

Bis-(2-methoxybenzal)-3,3′,5,5′-tetrachlorodithiosalicylhydrazide. This derivative separated from methanol in 73% yield after reacting *o*-methoxybenzaldehyde with the above 3,3′,5,5′-tetrachlorodithiosalicylhydrazide. The melting point was 237–240° after three recrystallizations from aqueous dimethylformamide.

Anal. Calc'd for $C_{30}H_{22}Cl_4N_4O_4S_2$: C, 50.82; H, 3.12.
Found: C, 51.16; H, 3.41.

5-Bromothiosalicylhydrazide. To 11 g. (0.045 mole) of crude methyl 5-bromothiosalicylate was added 10 ml. (0.2 mole) of hydrazine hydrate and the mixture was refluxed three hours to give a clear solution. The solution was treated with Darco (charcoal), filtered, and made faintly acid to Hydrion paper with concentrated hydrochloric acid. The precipitated hydrazide was collected, washed with water, and dried at 60°. The yield was 8.5 g. (77%) softening at 160° and melting at 215–220°. A sample recrystallized from ethanol softened at 165–170°, melted and resolidified at 215–220° and melted again at 240–245°. This material was soluble in aqueous alkali, indicating the presence of a free sulfhydryl group, and gave the correct analysis for the desired compound. The indefinite melting point was undoubtedly due to formation of the disulfide at the high temperature.

Anal. Calc'd for $C_7H_7BrN_2OS$: C, 34.02; H, 2.86; N, 11.34.
Found: C, 33.87; H, 2.70; N, 10.89.

5,5′-Dibromodithiosalicylhydrazide. This dithiosalicylhydrazide was prepared in 80% yield by oxidation of the corresponding thiol compound with iodine in aqueous pyridine. After two recrystallizations from methanolic dimethylformamide the melting point was 249–250°.

Anal. Calc'd for $C_{14}H_{12}Br_2N_4O_2S_2$: C, 34.15; H, 2.45.
Found: C, 34.65; H, 2.22.

Bis-(2,4-Dichlorobenzal)-5,5′-dibromodithiosalicylhydrazide. This compound was prepared by the condensation of 5-bromothiosalicylhydrazide with 2,4-dichlorobenzaldehyde. The intermediate sulfhydryl was converted to the disulfide on recrystallization from dioxane-water. The yield was 94%; m.p. 227–229°.

Anal. Calc'd for $C_{28}H_{16}Br_2Cl_4N_4O_2S_2$: C, 41.61; H, 2.24; N, 6.93.
Found: C, 41.76; H, 2.45; N, 6.41.

A sample prepared by the condensation of the 5,5′-dibromodithiosalicylhydrazide described above with 2,4-dichlorobenzaldehyde in acetic acid was identical with this material.

3,3′,5,5′-Tetrabromodithiosalicylhydrazide. To 10 g. (0.033 mole) of methyl 3,5-dibromothiosalicylate was added 15 ml. (0.3 mole) of hydrazine hydrate and the mixture was refluxed for 2¾ hours. The clear solution was cooled, treated with Darco, filtered, diluted with one volume of ice and water, and made faintly acid to Hydrion paper with concentrated hydrochloric acid. The precipitated hydrazide was filtered off, washed with water, and dried at 60°. The yield was 7.5 g. (75%), m.p. 170–175°. This crude hydrazide was difficult to crystallize and was therefore oxidized directly to the dihydrazide with iodine in methanol. After three recrystallizations from aqueous Methyl Cellosolve the material melted at 233–234°.

Anal. Calc'd for $C_{14}H_{10}Br_4N_4O_2S_2$: C, 25.87; H, 1.55.
Found: C, 26.50; H, 1.54.

Bis-(2,4-dichlorobenzal)-3,3',5,5'-tetrabromodithiosalicylhydrazide. The condensation of the above benzhydrazide disulfide with 2,4-dichlorobenzaldehyde in acetic acid, afforded the *bis*-benzal derivative in 67% yield. The melting point was 252–253°, after three recrystallizations from Methyl Cellosolve.

Anal. Calc'd for $C_{28}H_{14}Br_4Cl_4N_4O_2S_2$: C, 34.85; H, 1.45.
Found: C, 35.81; H, 1.77.

As indicated previously it is evident from the analyses that there was insufficient bromine in the original 3,5-dibromoanthranilic acid.

2-Nitro-4-methoxybenzonitrile. The procedure used was essentially the one devised by Bogert and Hand (25) for the preparation of *o*-nitrobenzonitrile, except that the reaction mixture was not filtered after the addition of the diazonium salt to the cyanide solution but was cooled directly and the solid collected. One mole (168 g.) of 2-nitro-4-methoxyaniline gave 175 g. (95%) of crude nitrile, m.p. 134–136°. After five recrystallizations from methanol the dark brown crystals melted at 136–137°.

Anal. Calc'd for $C_8H_6N_2O_2$: C, 53.93; H, 3.37.
Found: C, 54.13; H, 3.10.

2-Nitro-4-methoxybenzoic acid. 2-Nitro-4-methoxybenzonitrile (170 g.) and 1700 ml. of 65% sulfuric acid (by weight) were charged into a 3-l. flask fitted with a stirrer and heated on the steam-bath for 72 hours. After cooling, the dark brown solution was poured into ice and the precipitated solid was collected and washed with water. This crude brown material was taken up into 1.5 liters of diluted ammonia water and 20 g. of unchanged nitrile was filtered off. The filtrate was treated with Darco and acidified with concentrated hydrochloric acid. The almost white crystals were collected, washed with water, and dried in the oven to yield 135 g. (81% based on unrecovered nitrile), m.p. 194–196° [Lit. (16) m.p. 200° corr.].

4-Methoxyanthranilic acid. A two-liter flask fitted with a stirrer and reflux condenser was charged with 80 g. of iron powder, 500 ml. of water, and 4 ml. of concentrated hydrochloric acid. This mixture was heated to reflux and 67.5 g. of 2-nitro-4-methoxybenzoic acid was added portionwise during the course of one hour. The reaction was exothermic and very little external heat was required to maintain reflux. After an additional hour of heating the mixture was made alkaline with 5 *N* sodium hydroxide and filtered to remove excess iron. The filtrate upon neutralization with sulfuric acid deposited small glistening crystals of amino acid. After one hour at 0–5° the crystals were separated by filtration to yield 53 g. (92%), m.p. 174–176° [Lit. (16) m.p. 175°].

4,4'-Dimethoxydithiosalicylhydrazide. The requisite 4-methoxythiosalicylic acid was prepared in 72% yield by the usual method employing methyl ethyl ketone for extraction. The thiol was very susceptible to air oxidation and was therefore converted directly to the corresponding methyl ester, hydrazide, and thence to the dihydrazide. After three recrystallizations from methanol-Methyl Cellosolve analytically pure material was obtained; m.p. 229–230°.

Anal. Calc'd for $C_{16}H_{18}N_4O_4S_2$: C, 48.73; H, 4.60.
Found: C, 49.05; H, 4.58.

Bis-(2,4-dichlorobenzal)-4,4'-dimethoxydithiosalicylhydrazide. The condensation of 4,4'-dimethoxydithiosalicylhydrazide with 2,4-dichlorobenzaldehyde in acetic acid afforded this material in almost quantitative yield. After three recrystallizations from dimethylformamide the yellow needles melted at 230–231°.

Anal. Calc'd for $C_{30}H_{22}Cl_4N_4O_4S_2$: C, 50.90; H, 3.13.
Found: C, 51.14; H, 3.13.

Methyl p-tolyl sulfide. This material was prepared from *p*-thiocresol in 70% yield according to the procedure of Auwers and Arndt (11).

Methyl p-tolyl sulfone. Oxidation of the corresponding sulfide in the manner of Otto (12) afforded the sulfone in 75% yield. Permanganate oxidation (26) gave quantitative yields of material, m.p. 88–89°, lit. (16) m.p. 86–89°.

3-Nitro-p-tolyl methyl sulfone. Into a 250-ml. flask equipped for stirring and heating were placed 55 g. (0.5 mole) of concentrated sulfuric acid and 11.0 g. (0.12 mole) of nitric acid (*d.* 1.4). The solution was cooled to 45° and 17.1 g. (0.1 mole) of *p*-tolyl methyl sulfone was added portionwise in the course of 15 minutes. During this time the temperature was maintained at 45–50°. After the completion of the addition the amber-colored solution was heated to 70° and held at 70–75° for one-half hour and at 75–80° for one-half hour. The mixture was poured onto 100 g. of ice and 100 g. of 5 *N* sodium carbonate from which the white solid was separated by filtration. After drying at 80°, 20.0 g. of material (93%) was obtained; m.p. 115–117°. A sample purified by recrystallization from ethanol melted at 118–119°.

Anal. Calc'd for $C_8H_9NO_4S$: C, 44.65; H, 4.18.
Found: C, 45.02; H, 4.25.

4-Methylsulfonyl-2-nitrobenzoic acid. This oxidation was carried out precisely as described by Leonard and Boyd (14). From 12.5 g. of 3-nitro-*p*-tolyl methyl sulfone 7.5 g. of starting material and 2.8 g. (49%) of light yellow granules, m.p. 208–211°, were obtained. A sample recrystallized three times from hot water melted at 212–213°, softening at 205°.

Anal. Calc'd for $C_8H_7NO_6S$: C, 39.18; H, 2.86; Neut. equiv., 245.
Found: C, 39.18; H, 2.89; Neut. equiv., 249 ± 1.

4-Methylsulfonyl-2-aminobenzoic acid. Into a 500-ml. flask equipped for refluxing, stirring, and heating were placed 125 ml. of water, one ml. of concentrated hydrochloric acid, and 20 g. of iron dust. This mixture was stirred vigorously and heated to 90–95°. At this temperature 20.0 g. (0.082 mole) of 4-methylsulfonyl-2-nitrobenzoic acid was added at 15-minute intervals over a period of two hours. After an additional one hour at 90–95° the reaction mixture was made alkaline with 5 *N* sodium hydroxide and filtered hot through a bed of Super-Cel. The filtrate was chilled to 5° and acidified to a faint Congo Red test with 6 *N* hydrochloric acid. The slurry was chilled in an ice-bath for one hour and the solid was collected by filtration. The yield of cream-colored material, m.p. 238–240°, was 15.0 g. (84%). A sample recrystallized three times from water melted at 245–246° and had a faint blue fluorescence in aqueous solution.

Anal. Calc'd for $C_8H_9NO_4S$: C, 44.65; H, 4.18.
Found: C, 44.85; H, 4.46.

In order to establish the amino acid as an anthranilic acid derivative 1.95 g. (0.009 mole) of the acid, 1.6 g. (0.009 mole) of 2-chlorobenzthiazole, 7 ml. of glacial acetic acid, and 7 ml. of *n*-butanol were refluxed for one hour. During the course of the reaction a crystalline precipitate began to separate. The reaction mixture was chilled and the solid was collected by filtration to give 1.8 g. of material, m.p. 235–240°. Three recrystallizations from Methyl Cellosolve raised the melting point to 256°.

Anal. Calc'd for $C_{15}H_{10}N_2O_3S_2$: C, 54.54; H, 3.03.
Found: C, 54.71; H, 3.26.

4-Methylsulfonylthiosalicylhydrazide. The ester was prepared in the usual manner and was converted directly to the hydrazide in 58% over-all yield. The melting point after three recrystallizations from water was 180–181°.

Anal. Calc'd for $C_8H_{10}N_2O_2S_2$: C, 39.01; H, 4.09.
Found: C, 39.46; H, 4.24.

4,4'-Di-(methylsulfonyl)dithiosalicylhydrazide. Oxidation of 4-methylsulfonylthiosalicylhydrazide with iodine in aqueous methanol gave the disulfide in 85% yield. The melting point was 219–220° after three recrystallizations from aqueous Methyl Cellosolve.

Anal. Calc'd for $C_{16}H_{18}N_4O_6S_4$: C, 39.20; H, 3.70.
Found: C, 39.59; H, 3.85.

Bis-(2,4-dichlorobenzal)-4,4'-di-(methylsulfonyl)dithiosalicylhydrazide. The condensation of *bis*-4,4'-di-(methylsulfonyl)dithiosalicylhydrazide in acetic acid with 2,4-dichlorobenzaldehyde gave the benzal derivative in 93% yield. After three recrystallizations from dimethylformamide the yellow needles melted at 260–261°.

Anal. Calc'd for $C_{30}H_{22}Cl_4N_4O_6S_4$: C, 44.80; H, 2.76.
Found: C, 44.65; H, 2.61.

S-Methylthiosalicylhydrazide. Into a 100-ml. flask were charged 13.0 g. (0.07 mole) of methyl S-methylthiosalicylate (21), 15 ml. (0.3 mole) of hydrazine hydrate, and 30 ml. of ethanol. After refluxing for two hours the clear light yellow solution was cooled and diluted with 250 ml. of water. When the aqueous solution was acidified to *p*H 6–7 with 6 *N* hydrochloric acid, a white solid was formed which was collected and dried, weight 1.5 g., m.p. 66–68°. This was starting ester.

The aqueous filtrate was extracted with three 200-ml. portions of 50% ethylene chloride-ethyl acetate. The extracts were combined, dried, and evaporated to dryness. The residual oil slowly crystallized to give 8.0 g. of solid (70%, based on unrecovered ester). A sample was recrystallized from benzene four times, m.p. 103–104°.

Anal. Calc'd for $C_8H_{10}N_2OS$: C, 52.75; H, 5.49; N, 15.38.
Found: C, 52.95; H, 5.24; N, 15.18.

4-Chlorobenzal-S-methylthiosalicylhydrazide. A mixture of 3.6 g. (0.02 mole) of S-methylthiosalicylhydrazide, 2.9 g. (0.021 mole) of *p*-chlorobenzaldehyde, and 30 ml. of methanol containing one ml. of glacial acetic acid was heated on a hot plate for 15 minutes. The clear solution was diluted with warm water to the cloud point and allowed to crystallize. The solid was collected and dried at 60° to yield 5.4 g. (88%), m.p. 156–158°. A sample recrystallized three times from methanol-water melted at 159–160°.

Anal. Calc'd for $C_{15}H_{13}ClN_2OS$: C, 59.11; H, 4.27.
Found: C, 59.01; H, 4.24.

2-Methylsulfonylbenzhydrazide. Methyl 2-methylsulfonyl benzoate (27) (30.5 g.), prepared from the sulfide by permanganate oxidation (26), was refluxed for three hours with 30 ml. of hydrazine hydrate. The cooled reaction mixture was poured into 200 ml. of ice and water and the clear solution was extracted with ethylene chloride. Evaporation of the solvent after drying with magnesium sulfate afforded 12.0 g. of oil which partially crystallized on cooling. On recrystallization from methanol-ether, 5 g. of pure material, m.p. 147–148° was obtained. The aqueous phase undoubtedly contained more hydrazide since it was appreciably water-soluble but no attempt was made to increase the recovery. After two recrystallizations from methanol-ether, white, stout rods, m.p. 148–149°, were obtained.

Anal. Calc'd for $C_8H_{10}N_2O_3S$: C, 44.82; H, 4.71.
Found: C, 45.01; H, 4.74.

2,4-Dichlorobenzal-2-methylsulfonylbenzhydrazide. This derivative was prepared in 96% yield by reacting equimolar portions of 2-methylsulfonylbenzhydrazide with 2,4-dichlorobenzaldehyde in 20 volumes of methanol. It was necessary in this instance to evaporate the mixture to dryness and treat the residue with ether to obtain a crystalline solid. Three recrystallizations from 95% ethanol gave stout, colorless needles or rods melting at 211–212°.

Anal. Calc'd for $C_{15}H_{12}Cl_2N_2O_3S$: C, 48.56; H, 3.25.
Found: C, 48.51; H, 3.33.

Reaction of thiosalicylhydrazide with formaldehyde. In a 100-ml. beaker were mixed 4.2 g. (0.025 mole) of TSH, 2.2 ml. of 40% formalin solution, 10 ml. of water, and 0.1 g. of potassium carbonate. When this mixture was heated to 60° a heavy gum formed which solidified upon heating and stirring manually an additional ten minutes. The solid was collected and dried at 65° to yield 4.5 g. (98%) of material, m.p. 195–198°. A sample recrystallized three times from aqueous dimethylformamide was submitted for analysis; m.p. 204–206°.

Anal. Calc'd for $C_8H_8N_2OS$: C, 53.33; H, 4.44; N, 15.55.
Found: C, 53.24; H, 4.24; N, 15.24.

The molecular weight[6] determined ebullioscopically in acetic acid was 183; Calc'd, 180. Active hydrogen by Zerewitinoff[6] determination gave two active hydrogen atoms at room temperature.

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[6] Analyses by the Clark Microanalytical Laboratory, Urbana, Illinois.

SUMMARY

Methods have been described for the synthesis of a large number of bis-benzaldithiosalicylhydrazides whose progenitors were the requisite anthranilic acids. Diazotization of the acids, replacement of the diazonium chloride group by the sulfhydryl group, esterification of the thiosalicylic acid, treatment of the ester with hydrazine hydrate, and subsequent oxidation afforded substituted dithiosalicylhydrazides which, in turn, were caused to react with a variety of carbonyl components. These derivatives exhibited pronounced microbiological activity against bacteria and fungi, maximum activity being attained when 2,4- or 3,4-dichlorobenzaldehyde, 2-alkoxybenzaldehyde, or quinoline-4-aldehyde was the carbonyl reactant.

The reaction of formaldehyde with thiosalicylhydrazide resulted in a compound thought to be 2,3,4-trihydro-1,3,4-benzothiadiazepinone-5.

LAWRENCEBURG, INDIANA

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