action of the sulfuric acid—was evident. The boiling mixture was filtered immediately, and the filtrate cooled by aspirating the solvent with the water pump. The sulfenyl chloride I precipitated as a yellow, crystalline solid; wt. 17.0 g. (65%).

In other runs, in which the wt. of III was below 15 g., the chlorinolysis was complete in 4 to 6 min. The yields of I could be raised to *ca.* 75% by charging the reaction mixture with the mother liquor from a previous chlorinolysis in which the same weight of III was employed.

The analytical sample was prepared by two recrystallizations from ethylene chloride. It melted with decomposition (darkening at temperatures above 140°) at 183–185°.

Anal. Calcd. for $C_7H_4ClNO_4S$: C, 35.98; H, 1.73; Cl, 15.18; N, 5.97. Found: C, 36.02; H, 1.89; Cl, 15.37; N, 6.17.

The infrared spectrum revealed the presence of a carbonyl function by the characteristic absorption at 5.9 μ.[14]

Treatment of I (0.9527 g.) with potassium iodide liberated iodine, equivalent to 4.20 meq. of thiosulfate solution. This corresponds to an equivalent weight of 228.0 (theoretical, 233.5). The procedure used for the titration has been described previously.[15]

2-Chlorocyclohexyl 2'-Nitro-4'-carboxyphenyl Sulfide.—To 3.0 g. (0.013 mole) of I, dissolved in 100 ml. of dry ethylene chloride was added 10 ml. of redistilled cyclohexene ($n^{22}D$ 1.4445). The mixture was heated on the steam-bath for 10 min. and let stand. After 12 hr., the starch-iodide test was negative, and the yellow product was collected; wt., 4.0 g. (98%). The product melted at 205–212° dec. It was also noted that in the range of 145–155°, the crystals appeared to explode mildly, but no melt could be observed. Recrystallization from ethyl acetate gave a pale-yellow material which now melted at 217–219° dec.; and the same behavior again was noted at 145–155°.

Anal. Calcd. for $C_{13}H_{14}ClNO_4S$: C, 49.45; H, 4.47; Cl, 11.23. Found: C, 49.76; H, 4.66; Cl, 11.09.

Additions of I to *cis*- and *trans*-2-Butenes.—The diastereomeric racemates were obtained by the procedure previously described.[10] The addition to the *trans*-2-butene was carried out in 200 ml. of ethyl acetate, using 6.0 g. of I, and an initial butene pressure of 1.2 atm. The pressure was maintained at this level during the addition by manual adjustment of the mercury level. The reaction was complete (negative starch-iodide test) after 3 hr. The solvent was aspirated, while heating on the steam-bath, the residue taken up in chloroform, and product precipitated by adding Skellysolve F. The product weighed 5.6 g. (75%), m.p. 175–177°. Recrystallization from a mixture of benzene and chloroform gave a sample melting at 171–173°.

Anal. Calcd. for $C_{11}H_{12}ClNO_4S$: C, 45.60; H, 4.18; Cl, 12.24. Found: C, 45.61; H, 4.46; Cl, 12.33.

After keeping a few days, samples of the above materials increased in m.p. to 181–184°, but still gave a correct elemental analysis for the 1:1 adduct. Such a behavior has been noted previously in certain other sulfenyl halide-2-butene adducts.[10]

The addition of I to *cis*-2-butene was carried out in chloroform as solvent; 6.3 g. of I gave 6.5 g. (83%) of adduct; m.p. 166–168° after recrystallization from benzene.

Anal. Calcd. for $C_{11}H_{12}ClNO_4S$: C, 45.60; H, 4.18; Cl, 12.24. Found: C, 45.82; H, 4.03; Cl, 12.17.

The adducts to the *cis*- and *trans*-2-butenes differ not only in melting behavior, but also in the solubilities in methanol and infrared spectra (*cf.* footnote 14 and ref. 10).

Neutralization Equivalents of the Adducts of I to Alkenes.—The adducts were dissolved in acetone-water mixtures and titrated with standard sodium hydroxide, using 0.5% phenol red indicator. The end-point was taken as the first change of color from yellow to red which lasted 30 sec. or longer. The values were 286 and 292, respectively, for the adduct to the *cis*- and *trans*-2-butenes (calcd. 290); and 316 for the adduct to cyclohexene (calcd. 315). Under similar conditions, titration of the adduct[16] of 2,4-dinitrobenzenesulfenyl chloride to cyclohexene required only the same small amount of standard base as found for the blank in the case of the adduct of I to cyclohexene, showing that only the carboxyl group was involved in the titration of the latter.

(14) The full spectrum of this product and of the 2-butene adducts (see below) will be included in a later paper which will summarize the data on a considerable number of sulfenyl halides and related substances.

(15) N. Kharasch and M. M. Wald, *Anal. Chem.*, in press.

(16) N. Kharasch, H. L. Wehrmeister and H. Tigerman, THIS JOURNAL, **69**, 1612 (1947).

LOS ANGELES, CALIFORNIA

[CONTRIBUTION FROM THE CHEMICAL AND BIOLOGICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

Experimental Chemotherapy of Tuberculosis. III. Ethyl Mercaptan and Related Compounds in Tuberculosis

BY S. KUSHNER, H. DALALIAN, F. L. BACH, JR., D. CENTOLA,[1] J. L. SANJURJO AND J. H. WILLIAMS

RECEIVED SEPTEMBER 17, 1954

A series of mercaptans and esters have been compared for antituberculous activity. A study of the tuberculostatic action of these compounds, many of which are ethylthiol esters, indicates that activity resides in ethyl mercaptan itself. These active compounds are more effective than pyrazinamide in animal assays.

Utilizing the mouse test as an assay method for antituberculous agents, we showed in 1948,[2] the role of nicotinamide and its derivatives in the chemotherapy of tuberculosis. As a sequence to the study of pyridine derivatives, many pyrazine analogs were synthesized which led ultimately to the discovery of pyrazinamide[3a] (Aldinamide[3b]), an effective, clinical, chemotherapeutic agent. Pyrazinamide in combination with isoniazid now appears probably destined to be a protocol[4] of choice. While investigating various methods of preparing pyrazinaldehyde for the purpose of synthesizing a tibione-like analog, we prepared ethyl thiolpyrazinoate as an intermediate. Routine screening showed this compound[5] to be highly active both subcutaneously and orally in the mouse and guinea pig. This was a new and undeveloped lead in tuberculosis chemotherapy.

A series of thiolpyrazinoates was prepared, as indicated in Table I, for comparative studies. The

(1) At present in the Armed Forces.

(2) S. Kushner, H. Dalalian, R. T. Cassell, J. L. Sanjurjo, D. McKenzie and Y. SubbaRow, *J. Org. Chem.*, **13**, 834 (1948).

(3) (a) S. Kushner, H. Dalalian, J. L. Sanjurjo, F. L. Bach, Jr., S. R. Safir, V. K. Smith, Jr., and J. H. Williams, THIS JOURNAL, **74**, 3617 (1952). (b) Trade mark American Cyanamid Co.

(4) W. S. Schwartz and R. E. Moyer, *Am. Rev. Tuberc.*, **70**, No. 3, 413 (1954).

(5) H. P. Dalalian and S. Kushner, U. S. Patent 2,646,431, July 21, 1953.

TABLE I

THIOLPYRAZINOATES

Substituent	Method of prepn.	Yield, %	M.p. or b.p., °C.	Mm.	Empirical formula	Analyses, % Calcd. C	H	N	S	Found C	H	N	S	T.B. activity[a]
$-CH_3$[d]	A	70	65–66		$C_8H_8N_2OS$			18.2	20.8			17.9	21.0	—
$-C_2H_5$[b]	A	46	95–98	1	$C_7H_8N_2OS$	50.0	4.8	16.7	19.1	49.8	4.7	16.4	19.0	+++
n-C_3H_7	A, B	18	131	3	$C_8H_{10}N_2OS$	52.7	5.5			52.3	5.8			—
i-C_3H_7	A	35	90	2	$C_8H_{10}N_2OS$	52.7	5.5	15.4	17.6	52.4	5.6	15.3	17.6	+
n-C_4H_9	A	80	122–123	2	$C_9H_{12}N_2OS$	55.1	6.1	14.2	16.4	55.3	6.4	14.2	16.7	—
i-C_4H_9	A	72	101	3	$C_9H_{12}N_2OS$	55.1	6.1	14.2	16.4	54.8	6.3	14.3	16.6	—
t-C_4H_9	A	66	87–88	2	$C_9H_{12}N_2OS$	55.1	6.1	14.2	16.4	55.3	6.5	14.0	16.8	—
n-C_5H_{11}	B	20	114–118	2	$C_{10}H_{14}N_2OS$	57.1	6.7		13.3	56.8	6.9	12.8		—
n-$C_{10}H_{21}$[d]	A	84	45–46		$C_{16}H_{24}N_2OS$	64.3	8.6	10.0		64.7	8.7	9.9		—
$-C_{19}H_{27}O$[c,f]	A	10	263–265		$C_{24}H_{30}N_2O_2S$			6.8				6.5		—
$-CH_2COOC_2H_5$[d,i]		14	65–68		$C_7H_6N_2O_3S$	47.6	4.9	12.3	14.1	47.9	4.6	12.7	14.2	—
$-SCOC_2H_5$[h,i]		18	65–67		$C_8H_8N_2O_2S_2$	42.0	3.5	12.3		41.9	3.8	12.3		—
$-CH_2C_6H_5$[d]	A	65	56–57		$C_{12}H_{10}N_2OS$			12.2	14.0			11.9	14.0	—
$-C_6H_5$[e]	B	66	149–151		$C_{11}H_8N_2OS$	61 1	3.7	13.0	14.9	61.6	4.1	12.4	15.1	—
o-$COOHC_6H_4$[d]	B	26	185–186		$C_{12}H_8N_2O_3S$	55.4	3.1	10.8	12.3	55.3	3.5	10.5		—
p-$CH_3C_6H_4$[d]	B	56	132–133		$C_{12}H_{10}N_2OS$	62.6	4.4	12.2	14.0	62.9	4.6	12.0	14.4	—
p-ClC_6H_4[g]	B	27	120–121		$C_{11}H_7N_2OSCl$	52.7	2.8	11.2	12.8	52.4	3.2	11.3	12 9	—

[a] A standardized mouse test using survival as a criterion was used to evaluate activity. These compounds were tested subcutaneously. 4+ indicates maximum survival time. [b] H. P. Dalalian and S. Kushner, U. S. Patent 2,646,431 (July 21, 1953); see *C. A.*, **48**, 7652[b] (1954). [c] Dehydroisoandrosteryl (the dehydroisoandrosteryl mercaptan was prepared according to the procedure of S. Bernstein and K. Sax, *J. Org. Chem.*, 16, 679 (1951)). [d] Recrystallized from ethanol. [e] Recrystallized from acetone. [f] Recrystallized from chloroform. [g] Recrystallized from benzene. [h] Compound recrystallized from petroleum ether (20–40°). [i] See Experimental.

only compound other than ethyl thiolpyrazinoate to show activity was the isopropylthiol ester which was decidedly less active. This tended to shift the seat of activity from the pyrazine nucleus to the ethylthiol moiety. Ethyl thiolacetate was then prepared and when tested *in vivo* its activity was designated as 3+.[6] These developments initiated a study which included 36 mono- and dimercaptan derivatives whose activities are reported in Table II. Ethyl mercaptan was found to be the most active compound tested in this program. Of the compounds described in Table II the only other showing activity was 2,3-dimercaptopropanol-1 (B.A.L.).

TABLE II

ANTITUBERCULOUS ACTIVITY OF VARIOUS MERCAPTANS AND MERCAPTIDES

Substituent	T.B. activity[a]	Substituent	T.B. activity	Substituent	T.B. activity
$-CH_3$[c]	—[b]	n-$C_{12}H_{25}$	—	$-C_{10}H_7$[f]	—
$-C_2H_5$	++++	i-$C_{12}H_{25}$	—	o-C_6H_4COOH	—
$-C_2H_5$[c]	++[b]	n-$C_{16}H_{33}$	—	$-CH_2COOH$	—
n-C_3H_7	—	i-$C_{16}H_{33}$	—	$-C_4H_3N_2$[g]	—
i-C_3H_7	—	n-$C_{18}H_{37}$	—	$-CH{=}CH-$	—
i-C_3H_7[c]	—[b]	$-CH_2CH_2NH_2$[i]	—	$-CH_2CH_2-$	—
n-C_4H_9	—	$-CH_2CH_2OH$	—	$-(CH_2)_4-$	—
i-C_4H_9	—	$-CH_2CH_2OC_2H_5$[h]	—	$-(CH_2)_5-$	—
t-C_4H_9	—	$-CH_2C_6H_5$	—	$-CH_2CHCOOH$	—
n-C_5H_{11}	—	$-CHCOOH$	—	|	
n-C_6H_{13}	—	|		CH_2CHCH_2OH	+
i-C_6H_{13}	—	CH_2COOH		|	
n-C_7H_{15}	—	p-ClC_6H_4[d]	—	$-CH_2CHCH_2OH$[c]	—[b]
n-$C_{10}H_{21}$	—	$-C_6H_5O$[e]	—	|	

[a] See criterion in Table I for subcutaneous dosage. [b] These compounds also were tested orally at 0.2% of diet, fed *ad libitum* (8 mg./day). [c] Lead salt of mercaptan. [d] R. Adams and C. S. Marvel, "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., p. 504. [e] Furfuryl. [f] β-Naphthyl. [g] 2-Pyrazinyl. [h] L. C. Swallen and C. E. Boord, THIS JOURNAL **52**, 651 (1930). [i] E. J. Mills and M. T. Bogert, *ibid.*, **62**, 1177 (1940).

Although it is not improbable that the tuberculostatic activity of isopropyl thiolpyrazinoate may be due to the pyrazine residue, since the corresponding isopropyl mercaptan is inactive, our belief is that the high activity of ethyl thiolpyrazinoate is due to its ability to release ethyl mercaptan. (The activity of the ethyl mercaptan corresponds to the activity of streptomycin by the subcutaneous route.) This theory has been substantiated recently in a communication[7] to the editor by Brown, *et al.*, who independently have reached similar conclusions.

Among the miscellaneous compounds in Table IV are included several derivatives having ethyl thiol groups much less vulnerable to cleavage than the simple thiol esters. As ancillary experiments, several acetylmercapto amines were prepared to determine the extent of activity in this type of substituted mercaptan. As in the work of H. D. Brown[7] and co-workers the sulfone and sulfoxide of ethyl mercaptan are reported inactive. None of the compounds in this group exhibit tuberculostatic activity.

Since ethylthiol esters, by their nature, are usually oils with disagreeable odors, it was necessary to make a derivative more convenient for testing. All the compounds in Table III other than ethylthiol acetate were synthesized toward this goal. Ethyl thiol-*p*-acetamidobenzoate, a colorless, odorless solid, although less active than ethyl mercaptan, was selected for further investigation. Toxicity studies[8] in the mouse revealed enlarged and cyanotic

(6) See footnote *a*, Table I.

(7) H. D. Brown, A. R. Matzuk, H. J. Becker, J. P. Conbere, J. M. Constantin, M. Solotorovsky, S. Winstein, E. Ironson and J. H. Quastel, THIS JOURNAL, **76**, 3860 (1954).

(8) J. S. Kiser, L. C. Malone, A. H. Schurr, H. F. Lindh, D. B. Hewell, F. Burger and F. I. Dessau, to be published elsewhere.

TABLE III

ETHYLTHIOL ESTERS $RCSC_2H_5$ (O (S))

Substituent	Method of prepn.	Yield, %	M.p. or b.p., °C.	Mm.	Empirical formula	Analyses, % Calcd. C	H	N	S	Found C	H	N	S	T.B. activity[a]
$-CH_3$	A	29	115–116	760	C_4H_8OS				30.8				31.2	+++
$-CH_2CH_2Cl$	A	47	75–78	15	C_6H_9ClOS	39.3	5.9		20.9	39.5	6.1		21.5	+++
$CH_3CHOC_6H_5$ |	A	74	128	11	$C_{11}H_{14}O_2S$	62.8	6.7			62.7	6.5			—
$-OC_2H_5$[d]		35	200	760										—
$-CH_2C_6H_5$	A	41.5	102–104	3	$C_{10}H_{12}OS$	66.6	6.6		17.8	66.5	6.6		18.2	++
$-C_6H_{11}$ (cyclo)	A	32.3	81–82	6	$C_9H_{16}OS$	62.8	9.3		18.7	62.7	9.3		19.1	++
$-C_6H_5$	A	89	97–98	4	$C_9H_{10}OS$	65.0	6.0		19.3	64.9	6.1		19.3	++
o-ClC_6H_4	A	52	97	11	C_9H_9ClOS	54.1	4.5	17.5[b]	16.0	53.8	4.7	17.6[b]	16.1	+[i]
o-IC_6H_4	A	33	143–145	3	C_9H_9IOS	37.0	3.1	43.5[c]	11.0	36.9	3.3	43.3[c]	11.1	+[i]
m-$NO_2C_6H_4$	A	45	135		$C_9H_9O_3NS$	51.2	4.4	6.6	15.2	51.0	4.4	6.5	15.8	+[i]
p-$NO_2C_6H_4$[e]	A	50	67–68		$C_9H_9O_3NS$									++[i]
p-$CH_3CONHC_6H_4$	A	30	124–125		$C_{11}H_{13}O_2NS$	59.4	5.8	6.3	14.4	59.3	6.0	6.4	14.6	++
$-C_6H_5$-o-OH-p-$NHCOCH_3$[f]	A	37	156.5–157.5											—
$-CH{=}CHC_6H_5$	A	37	150–152	11	$C_{11}H_{12}OS$	68.7	6.3		16.7	68.6	6.5		16.9	+
$-C_5H_4N$[g]	A	24	138–140	2	C_9H_9ONS	57.5	5.4	8.4	19.2	57.4	5.7	8.3	19.2	+++
$-C_5H_9O$[h]	A	90	240–245	760	$C_8H_{14}O_2S$	56.2	8.1			54.9	8.3			+++
$-C_{10}H_8ClO_3$[i]														—

[a] Criterion of activity same as Table I, subcutaneous dosage. [b] Chloride analysis. [c] Iodide analysis. [d] H. Debus, *Ann.*, **75**, 127 (1850); ethyl ethylxanthate. [e] H. L. Hansen and L. S. Fosdick, THIS JOURNAL, **55**, 2872 (1933). [f] W. Hückel and K. Janecka, *Arch. Pharm.*, **284**, 341 (1951). [g] β-Pyridyl. [h] 4-Tetrahydropyranyl. [i] S. Kushner, J. Morton, II, J. H. Boothe and J. H. Williams, THIS JOURNAL, **75**, 1097 (1953). [j] These compounds tested orally as described in Table II.

spleens. Since concurrent experiments with ethyl mercaptan resulted in the same pathological conditions, these compounds were withheld from clinical evaluation because the treatment of tuberculosis entails prolonged medication.

The thiolpyrazinoates were prepared in the classical manner by treating pyrazinoyl chloride with the appropriate lead mercaptide or the free mercaptan. These compounds, in general, were distillable oils with the expected disagreeable odors. An attempt to prepare pyrazinylisothiourea was unsuccessful; instead dipyrazinyl sulfide was obtained. The structure was proved by direct synthesis of this compound from the sodium salt of 2-pyrazinethiol and 2-chloropyrazine. An admixture of these two products showed no depression of melting point.

A full evaluation of the experimental animal studies will be presented elsewhere.[8]

TABLE IV

MISCELLANEOUS COMPOUNDS

Compound	T.B. activity[a]	Compound	T.B. activity
Diethyl sulfoxide[b]	–	2-Ethylmercapto-6-oxy-pyrimidine[g]	–
Diethyl sulfone[c]	–	2-Ethylmercapto-6-chloro-pyrimidine[g]	–
Diethylthiolmethane[d]	–	Diaminoethyl disulfide·2HCl[h]	–
p-Acetamidobenzaldehyde dithioethylmercaptal[e]	–	2-Acetylthioethylacetamide[i]	–
S-Ethylisothiourea·HCl[f]	–	2-Acetylthioethylamine·HCl[i]	–[k]
		Dibenzyl disulfide[j]	

[a] Oral dosage as described in Table II, unless otherwise indicated. [b] A. E. Wood and E. G. Travis, THIS JOURNAL, **50**, 1226 (1928). [c] S. F. Birch, W. S. Gowan and P. Norris, *J. Chem. Soc.*, **127**, 1934 (1925). [d] Bayer and Co., German Patent, 97,207. [e] See Experimental. [f] H. P. Stevens, *J. Chem. Soc.*, **81**, 80 (1902). [g] H. L. Wheeler and T. B. Johnson, *Amer. Chem. J.*, **29**, 496 (1903). [h] J. W. Barnett, *J. Chem. Soc.*, 5 (1944). [i] J. Baddiley and E. M. Thain, *ibid.*, 2253 (1951). [j] M.p. 73–74°; ref. m.p. 71–72°; E. Fromm and P. Schmoldt, *Ber.*, **40**, 2870 (1907). [k] This compound tested both orally and subcutaneously.

Acknowledgment.—We wish to thank L. Brancone and staff for the analyses contained within.

Experimental[9]

Thiolesters.—These products were prepared by treating an acid chloride with an appropriate lead mercaptide suspended in benzene or ether as described in method A, or by treating the acid chloride directly with the various mercaptans as in method B.

Method A. 1. Ethyl Thiolpyrazinoate.—To a stirred solution of 18 g. (0.13 mole) of freshly prepared pyrazinoyl chloride in 300 cc. of dry ether was added 23 g. (0.07 mole) of lead ethyl mercaptide. After five hours, the yellow-brown suspension which had taken on a purplish-red color was filtered and the filter cake was washed several times with dry ether. After the filtrate was washed with two 200-cc. portions of cold, 5% sodium hydroxide solution and one portion of water, it was treated with Norit, filtered, dried over anhydrous magnesium sulfate and then fractionated to give 9.8 g. of the desired product.

2. Benzyl Thiolpyrazinoate.—A mixture consisting of 25 g. (0.20 mole) of lead benzyl mercaptan, 12 g. (0.08 mole) of freshly prepared pyrazinoyl chloride and 250 cc. of dry benzene was refluxed for three hours. After the reflux period the benzene was decanted and the residual material was extracted with an additional volume of hot benzene (three 100-cc. portions). The combined benzene solutions were treated in a manner similar to that described in method A and the crude, oily material obtained was fractionated to yield 22.0 g. of the ester.

Lead mercaptides were treated in benzene with the exception of lead methyl mercaptan where ether was used. The conditions were varied as indicated in Table V.

TABLE V

$Pb(SR)_2$	Synthesis Temp., °C.	Time, hr.	$Pb(SR)_2$	Synthesis Temp., °C.	Time, hr.
$-CH_3$	25	16	t-C_4H_9	65–70	1
n-C_3H_7	25	15	i-C_4H_9	65–70	2
i-C_3H_7	65–70	1	n-$C_{10}H_{21}$	25	4
n-C_4H_9	65–70	1	$-C_{13}H_{27}O$	65–70	1

Various ethylthiol esters were prepared in the same general manner using the acid chlorides and conditions listed in Table VI.

Method B. Phenyl Thiolpyrazinoate.—Nineteen grams (0.13 mole) of pyrazinoyl chloride, 15 g. (0.14 mole) of thiophenol and 300 cc. of benzene were refluxed for one-half hour at the steam-bath. The benzene was decanted and the residue was extracted with three 100-ml. portions of hot benzene. The solvent was removed leaving a crude,

(9) The melting points are not corrected.

TABLE VI

RCOCl	Synthesis Temp., °C.	Time, hr.	RCOCl	Synthesis Temp., °C.	Time, hr.
$-CH_3$	70	0.75	$-O-IC_6H_4$	25	5
$-CH_2CH_2Cl$	25	15	$m-NO_2C_6H_4$	25	15
$-CHCH_3$	70	3	$p-NO_2C_6H_4$	25	48
OC_6H_5			$p-CH_3CONHC_6H_4$	25	17
$-CH_2C_6H_5$	25	3	$-CH=CHC_6H_5$	25	40
$-C_6H_{11}$ (cyclo)	25	15	$-C_6H_9O$ (tetrahydro-	25	20
$-C_6H_5$	70	1	pyran)		1
$-O-ClC_6H_4$	25	3	$-\beta-C_6H_4N$	65–70	

oily residue which weighed 29.0 g. This material solidified on standing and was recrystallized twice from acetone using Norit. The pure product was a cream-colored, crystalline material melting at 149–151°. Additional thiopyrazinoates were prepared in the same general manner with the exception of *n*-amylmercaptan which reacted in toluene. The free mercaptans and reaction conditions employed are listed in Table VII.

TABLE VII

RSH	Synthesis Temp., °C.	Time, hr.
$n-C_5H_{11}$	Reflux	72
$o-COOHC_6H_4$	Reflux	26
$p-CH_3C_6H_4$	Reflux	36
$p-ClC_6H_4$	Reflux	2
$n-C_3H_7$	25	15

Ethyl S-Pyrazinoyl Thioglycolate.—Sixteen grams (0.111 mole) of pyrazinoyl chloride in 75 cc. of ethyl acetate was added to a suspension of 22.4 g. (0.157 mole) of ethyl S-sodiothioglycolate (prepared from 6.6 g. of sodium methoxide and 14.5 g. of ethyl thioglycolate in 100 cc. of ethyl acetate After an initial exothermic reaction the purple-colored suspension was stirred overnight. The suspension was filtered and concentrated to a red oil containing a yellow solid. The oily material was taken up in ethanol and the insoluble material collected. The ethanolic solution was concentrated to an oil and the residue was fractionated yielding a material which was collected as a solid at 120–200° (18 mm.). This material was combined with the yellow solid obtained from the reaction and recrystallized from ethanol. The product obtained in this manner melted at 65–68°.

O-Ethyl S-Pyrazinoylxanthate.—Twelve grams (0.083 mole) of pyrazinoyl chloride was suspended in 50 cc. of dry benzene and chilled by means of an ice-bath to 10–15°. Potassium ethylxanthate (10.0 g., 0.062 mole) freshly prepared was added to the suspension and the mixture stirred for 3 hours at 10–15°. The insoluble material remaining was separated by filtration and the clear filtrate was treated with Norit, dried over anhydrous magnesium sulfate, and concentrated at room temperature under reduced pressure. The heavy, yellow, residual oil crystallized on standing and weighed 8.0 g., m.p. 65–67°.

***p*-Acetamidobenzaldehyde Dithioethylmercaptal.**—A mixture consisting of 16.3 g. (0.10 mole) of *p*-acetamidobenzaldehyde, 31.0 g. (0.50 mole) of ethyl mercaptan and 5.0 g. of anhydrous zinc chloride was cooled to 0–10° and then treated with dry hydrogen chloride gas until two layers separated. The volatile material was removed and the semi-solid material remaining was triturated with an acetone–water solution. The solid obtained was sublimed at 140–150° (0.2 mm.) and 1.0 g. of pure material was collected, m.p. 136–137.5°.

Anal. Calcd. for $C_{13}H_{19}NOS_2$: C, 57.9; H, 7.1; N, 5.2; S, 23.7. Found: C, 58.1; H, 7.3; N, 5.0; S, 23.2.

Dipyrazinyl Sulfide.—A mixture consisting of 2.0 g. (0.017 mole) of 2-chloropyrazine, 1.5 g. (0.02 mole) of isothiourea and 50 cc. of ethanol was autoclaved for 20 hours at 120°. The cooled, wine-colored solution, after treatment with Norit, was filtered and concentrated to approximately 5 cc. Upon the addition of 30 cc. of ether a brown, gummy material separated which crystallized when triturated with a minute amount of alcohol. The crude solid contained mostly ammonium chloride. The ethereal solution was concentrated to a semi-crystalline residue which yielded yellow needles, after trituration with ethanol. This material weighing 700 mg. was recrystallized once from butanol; m.p. 100–100.5°.

Anal. Calcd. for $C_8H_6N_4S$: C, 50.5; H, 3.2. Found: C, 50.4; H, 3.4.

Dipyrazinyl sulfide was prepared by the following procedure for structure proof: Three grams (0.0223 mole) of sodiomercaptopyrazine (prepared from 2-mercaptopyrazine with sodium methoxide in alcohol) was autoclaved at 150° for 20 hours with 2.5 g. (0.0718 mole) of 2-chloropyrazine in 30 cc. of ethanol. After treating the dark-brown residue with Norit, filtering and evaporating to dryness, a yellow, amorphous material was obtained. This material was recrystallized twice from ether, yielding 1.0 g., m.p. 100–102°. This product showed no melting point depression on admixture with the sample obtained above. Roblin[10] and Clapp report a melting point of 106–107.3° for the same compound prepared as a by-product in the synthesis of 2-pyrazinethiol.

PEARL RIVER, N. Y.

(10) R. O. Roblin, Jr., and J. W. Clapp, THIS JOURNAL, **72**, 4891 (1950).