

pentabromophenyl methacrylate from isopropyl alcohol gave colorless needles with the constant m.p. 138–140°.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF J. T. BAKER CHEMICAL CO.]

Some New Thiol Esters. Preparation of DithioLFumarates

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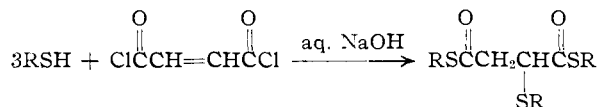
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A number of new thiol esters have been prepared using a variety of methods. These new esters include six dithioLFumarates, the first compounds in this series to be reported. The fact that some of these compounds are colored, thus possessing a chromophoric grouping, is discussed.

We have prepared a number of new thiol esters. Current interest in the antifungal properties of similar compounds makes it desirable to report our work at this time.^{2–4}

Of particular interest among the compounds prepared by us are several dithioLFumarates. As far as we are aware, compounds in this series have not been reported in the literature.⁵ The fact that esters of fumaric acid in general have achieved their present industrial importance renders it desirable to know something of the properties of the sulfur analogs of these compounds.

Diphenyl and bis-(4-chlorophenyl) dithioLFumarate were readily prepared by the addition of fumaryl chloride to a solution of the appropriate thiophenol in a slight excess of aqueous 5% sodium hydroxide. The solubility of alkyl mercaptans in aqueous alkali allowed an attempt to extend this method to the preparation of the dialkyl dithioLFumarates. The attempt was successful in the case of *t*-butyl mercaptan, giving a 37% yield of di-*t*-butyl dithioLFumarate, which separated from the reaction mixture as a solid. When the reaction was carried out with methyl, ethyl and isopropyl mercaptan, oils resulted. Attempts to purify these by fractionation failed because of their high boiling points and a tendency to decompose. Simple distillation at reduced pressure gave materials which, judging from their sulfur analyses, evidently contained 50% or more of the product formed by addition of a mole of mercaptan to the double bond of the dialkyl dithioLFumarate



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(2) See K. Miyaki and S. Yamagishi, *J. Pharm. Soc. (Japan)*, **76**, 436, 1196, 1200 (1956); *C. A.*, **51**, 3490 (1957).

(3) A. M. Shah, Ph.D. Thesis, State University of Iowa; *C. A.*, **52**, 4501 (1958).

(4) The antifungal and antibacterial properties of the compounds described in this paper are being reported elsewhere.

(5) While our manuscript was in the hands of the referees a paper appeared by C. S. Marvel and J. F. Porter, *J. Org. Chem.*, **24**, 137 (1959), describing the synthesis of dimethyl dithioLFumarate, m.p. 78–79°, by a several-step method. They report failure to obtain a homopolymer from this material, and also that no copolymerization with vinyl chloride could be achieved. We likewise were unable to obtain a homopolymer from dimethyl dithioLFumarate, or a copolymer with vinyl chloride. We thank Mr. Carl Miller for carrying out the latter experiments.

Dimethyl, diethyl and diisopropyl dithioLFumarate were successfully prepared by a method involving the reaction of the mercaptan and acid chloride using 1,2-dimethoxyethane as a solvent and pyridine as a hydrogen chloride acceptor. All of the dithioLFumarates reported here proved to be crystalline solids except the diethyl compound. This yellow oil crystallized readily on cooling, however, and melted at 14°.

It is surprising that some of these compounds proved to be distinctly yellow. While benzil and similar compounds, including those with one or more conjugated double bonds between the keto groups are colored, diphenyl oxalate and related compounds are colorless. Also, bis-(4-chlorophenyl) dithioLFumarate and phenyl thiolcinnamate (see Experimental) proved to be colorless solids. However, bis-(4-chlorophenyl) dithioLFumarate proved to be deep yellow. Similarly diphenyl and bis-(4-chlorophenyl) dithioLFumarate are also yellow solids. Even more surprising was the fact that di-*t*-butyl dithioLFumarate was yellow, though distinctly lighter in shade than the aryl dithioLFumarates. The remaining dialkyl dithioLFumarates were colorless in the solid state.

Marvel and co-workers have presented infrared spectral data indicating that the carbonyl group in a thioLFumarate has more of the character of a ketone carbonyl than does the carbonyl group in a normal ester.⁶ The color noted in the bis-aryl dithioLFumarates is further evidence along this line for thiol esters in general. However, the question of the color in these compounds seems to be somewhat more complex. Pentachlorophenyl thioLFumarate, previously reported from these laboratories,⁷ is a yellow crystalline solid. Pentachlorophenyl thioacetate is also yellow (see Experimental). We have no explanation at present as to why these compounds are colored, whereas a more complexly conjugated system such as that in phenyl thiolcinnamate is colorless. Evidently the highly electronegative pentachlorophenyl group plays a role.

In addition to the thiol esters mentioned above, we are describing in the Experimental section of this paper the preparation of a number of thiol esters of various aliphatic acids, along with several

(6) C. S. Marvel, S. L. Jacobs, W. K. Taft and B. G. Labbe, *J. Polymer Sci.*, **19**, 59 (1956).

(7) G. Sumrell, G. E. Ham and E. D. Hornbaker, *THIS JOURNAL*, **80**, 2509 (1958).

TABLE I

Acid chloride	R	Formula	Yield, %	M.p., °C.	NEW DITHIOL ESTERS, $\text{RSC}(=\text{O})\text{X}(\text{O})\text{CSR}$				Found			
					Calculated			Cl	Found			Cl
			C	H	S	C	H		S	C	H	
Fumaryl	Methyl	$\text{C}_6\text{H}_8\text{O}_2\text{S}_2$	90	81-82	40.89	4.58	36.38		40.96	4.51	36.25	
Fumaryl	Ethyl	$\text{C}_8\text{H}_{12}\text{O}_2\text{S}_2$	61	14	47.03	5.92	31.39		47.28	6.09	31.50	
Fumaryl	Isopropyl	$\text{C}_{10}\text{H}_{16}\text{O}_2\text{S}_2$	40	41-42	51.69	6.94	27.60		51.94	6.92	27.40	
Fumaryl	<i>t</i> -Butyl	$\text{C}_{12}\text{H}_{20}\text{O}_2\text{S}_2$	37	98-99	55.35	7.74	24.62		55.14	7.75	24.92	
Fumaryl	Phenyl	$\text{C}_8\text{H}_8\text{O}_2\text{S}_2$	50	137-138	63.97	4.03	21.35		64.22	4.01	21.54	
Fumaryl	4-ClPh	$\text{C}_{16}\text{H}_{10}\text{Cl}_2\text{O}_2\text{S}_2$	45	181-183	52.04	2.73	17.36	19.20	52.14	2.70	17.27	19.28
Succinyl	4-ClPh	$\text{C}_{16}\text{H}_{12}\text{Cl}_2\text{O}_2\text{S}_2$	85	117-119	51.76	3.26	17.27	19.10	51.91	3.22	17.11	19.18
Oxlyl	4-ClPh	$\text{C}_{14}\text{H}_8\text{Cl}_2\text{O}_2\text{S}_2$	88	206-208	48.99	2.34	20.66	18.68	48.99	2.33	20.35	18.35

TABLE II

Acid chloride	R	Formula	Yield, %	M.p., °C.	NEW THIOL ESTERS, $\text{R}'\text{C}(=\text{O})\text{CSR}$				Found			
					Calculated			Halo-gen	Found			Halo-gen
			C	H	S	C	H		S	C	H	
Acetyl	C_6Cl_5	$\text{C}_8\text{H}_7\text{Cl}_5\text{OS}$	100 ^a	118-119	29.61	0.93	9.88	54.64	29.73	0.96	9.77	54.60
Clacetyl	4-ClPh	$\text{C}_8\text{H}_6\text{Cl}_2\text{OS}$	73	79-82	43.46	2.74	14.50	32.07	43.60	2.82	14.44	31.94
DiClacetyl	4-ClPh	$\text{C}_8\text{H}_5\text{Cl}_3\text{OS}$	78 ^a	61-62	37.60	1.97	12.55	41.62	37.58	1.99	12.40	41.50
Crotonyl	C_6H_5	$\text{C}_{10}\text{H}_{10}\text{OS}$	59		67.38	5.66	17.99		67.35	5.68	18.10	
Isobutyryl	C_6H_5	$\text{C}_{10}\text{H}_{12}\text{OS}$	77		66.66	6.71	17.76		66.61	6.82	17.71	
Isobutyryl	4-ClPh	$\text{C}_{10}\text{H}_{11}\text{ClOS}$	50				14.93				14.75	
Cinnamoyl	C_6H_5	$\text{C}_{12}\text{H}_{12}\text{OS}$	84	92-92	74.97	5.03	13.34		74.73	4.85	13.16	
2-Ethylcinnamoyl	C_6H_5	$\text{C}_{17}\text{H}_{18}\text{OS}$	64		76.08	6.01	11.95		76.31	5.96	12.20	
4-Clbenzoyl	C_6H_5	$\text{C}_{12}\text{H}_9\text{ClOS}$	84	82-84	62.77	3.65	12.89	14.26	62.90	3.64	12.91	14.29
4-Clbenzoyl	4-ClPh	$\text{C}_{12}\text{H}_8\text{Cl}_2\text{OS}$	46	136-138	55.14	2.85	11.32	25.04	55.34	2.80	11.27	25.03
2-Clbenzoyl	4-ClPh	$\text{C}_{12}\text{H}_8\text{Cl}_2\text{OS}$	72	95-96	55.14	2.85	11.32	25.04	45.20	2.83	11.20	24.99
3-Brbenzoyl	4-ClPh	$\text{C}_{11}\text{H}_8\text{BrClOS}$	67	107-108	47.65	2.46	9.78	35.21	47.77	2.43	9.63	35.46
Furoyl	C_6H_5	$\text{C}_{11}\text{H}_9\text{O}_2\text{S}$	50 ^a	50-53	64.69	3.95	15.70		64.85	3.90	15.59	
Furoyl	4-ClPh	$\text{C}_{11}\text{H}_7\text{ClO}_2\text{S}$	40	106-107			13.43				13.65	
Furoyl	C_6Cl_5	$\text{C}_{11}\text{H}_5\text{Cl}_5\text{O}_2\text{S}$	^b	156-158				47.09				46.95

^a Crude yields; remaining values are for recrystallized or distilled product. ^b Mechanical loss; 10% yield of recrystallized product isolated.

thiofuroates, substituted thiolbenzoates, and other miscellaneous thiol esters. The methods used are amply described in the procedures.

Experimental

Analyses for the products are given in Tables I and II. Boiling points and melting points are uncorrected. Unless otherwise indicated, distillations were carried out through an 80-cm. Podbielniak-type column with heated jacket and partial reflux head similar to that described by Cason and Rapoport.⁸

Starting Materials.—The mercaptans were commercial materials and were used without purification. Similarly, all of the acid chlorides were purchased and used without purification except 2-ethylcinnamoyl chloride, the preparation of which is described below.

Diphenyl Dithiofumarate (Illustrating Method A).—Two moles of benzenethiol were dissolved in 2000 ml. of 5% aqueous sodium hydroxide. The mixture was chilled to -5° with an ice-acetone bath. Then, with stirring, one mole of fumaryl chloride was added dropwise at such a rate that the temperature did not rise above 5° . The mixture was stirred an additional hour, then the product was filtered and washed thoroughly with water. Recrystallization from acetone gave 150 g. (50%) of yellow blades of m.p. 137-138°.

Bis-(4-chlorophenyl) dithiofumarate was prepared on a 0.4-mole scale by method A. Some tarry material formed, but was easily removed from the product by washing with acetone, in which the product was sparingly soluble. The crude yield was 33 g. (45%), m.p. 175-182°. Recrystallization of 10 g. of this material from 150 ml. of benzene gave 8 g. of fine yellow needles with the constant m.p. 181-183°.

(8) J. Cason and H. Rapoport, "Laboratory Text in Organic Chemistry," Prentice-Hall, Inc. New York, N. Y., 1950, p. 238.

Di-*t*-butyl dithiofumarate was prepared on a 2-mole scale by method A. The crude wet solid was recrystallized from 500 ml. of methanol, yielding 97 g. (37%) of fine light yellow needles of m.p. 96-98°. Further recrystallization from methanol or acetone gave a constant value of 98-99°.

Diisopropyl Dithiofumarate (Illustrating Method B).⁹ A mixture of 1 mole of isopropyl mercaptan and 0.5 mole of fumaryl chloride in 100 ml. of 1,2-dimethoxyethane was maintained at $0-5^\circ$ while 1 mole of pyridine was added dropwise. After an hour of additional stirring, the mixture was diluted with water and the organic phase was extracted into ether. Distillation through a Claisen head gave 46 g. (40%) of a light yellow oil at $105-107^\circ$ (0.2 mm.), n_D^{20} 1.5385. This material crystallized on standing and had m.p. 36-39°. Two recrystallizations from a mixture of isopropyl alcohol and water gave colorless platelets with the constant m.p. 41-42°.

Diethyl dithiofumarate was prepared on a 0.25-mole scale by method B. Distillation yielded 31 g. (61%) of a yellow oil at $95-97^\circ$ (0.2 mm.), n_D^{20} 1.5596. The material crystallized on chilling, giving colorless needles of m.p. 14°.

Dimethyl Dithiofumarate.⁵—Methyl mercaptan was bubbled into 100 ml. of ice-cold anhydrous 1,2-dimethoxyethane until the weight increased 48 g. (1 mole). This mixture was added to 76.5 g. (0.5 mole) of fumaryl chloride. The temperature was maintained at 0° while 1 mole of pyridine was added dropwise. After 0.5 hour of additional

(9) An attempt to prepare this compound on a 1-mole scale by method A gave a tarry oil which exhibited decomposition and a pressure rise when an attempt was made to fractionate it at 1 mm. of pressure. Distillation through a simple head gave 34 g. of yellow oil at $130-150^\circ$ (0.2 mm.), n_D^{20} 1.5240. Analysis for sulfur gave a value of 29.77%; theory for the addition compound, 31.18%. Similar results were obtained when this procedure was tried with methyl and ethyl mercaptan. For the reaction of methyl mercaptan and methacrylyl chloride under similar conditions, see ref. 7.

stirring, 500 ml. of water was added. The mixture was chilled back to 0° and filtered, and the solid was washed with water. Drying gave 79 g. (90%) of material of m.p. 75–79°. Recrystallization from acetone, or from a mixture of isopropyl alcohol and water, gave long colorless needles of m.p. 81–82°.

Bis-(4-chlorophenyl) Dithiolsuccinate.—A mixture of 0.4 mole of 4-chlorobenzenethiol, 0.2 mole of succinyl chloride and 100 ml. of 1,2-dimethoxyethane was surrounded by a pan of cold water while 0.4 mole of pyridine was added rapidly dropwise. The temperature rose from 20 to 90° and yellowish solid began separating immediately. Stirring was continued for one hour, then 100 ml. of water was added and mixture chilled to 0°. The solid was filtered and washed with water. Drying gave 63 g. (85%) of material of m.p. 110–115°. Two recrystallizations from acetone gave colorless needles with the constant m.p. 117–119°.

Bis-(4-chlorophenyl) Dithioloalate.—To a stirred solution of 0.6 mole of 4-chlorobenzenethiol in 150 ml. of 1,2-dimethoxyethane (cooled with a pan of cold water) was added dropwise 0.3 mole of oxalyl chloride. An exothermic reaction occurred accompanied by a vigorous evolution of hydrogen chloride. The reaction mixture soon set up from the formation of yellow solid. The mixture was allowed to stand for several hours, then was filtered and the solid washed with 1,2-dimethoxyethane. After drying, it amounted to 91 g. (88%), m.p. 204–208°. This material was sparingly soluble in most organic solvents including ethanol, acetone, ethyl acetate, dimethyl sulfoxide and dimethylformamide. A sample of 5 g. was recrystallized from 200 ml. of benzene, yielding 4 g. of bright yellow needles of m.p. 206–208°.

Pentachlorophenyl Thioloacetate.—A mixture of 0.05 mole of pentachlorobenzenethiol, 0.1 mole of acetyl chloride, 0.1 mole of pyridine and 100 ml. of 1,2-dimethoxyethane was refluxed for 5 hours. The reaction mixture was then poured into a beaker of water. The solid was filtered, washed with water and dried, giving a quantitative yield of crude pentachlorophenyl thioloacetate melting at 114–118°. Two recrystallizations of the yellow solid from acetone gave the constant m.p. 118–119°.

Phenyl Thiol-(2-Methylpropionate) (Illustrating Method C).—To a stirred solution of 0.5 mole of benzenethiol in 500 ml. of 5% sodium hydroxide was added dropwise 0.5 mole of isobutyryl chloride while maintaining at 15–20° by cooling. Stirring was continued for 1 hour, then the organic layer was extracted with ether and dried over sodium sulfate. Fractionation gave 69 g. (77%) of the thiol ester at 108–109° (7 mm.), n_D^{20} 1.5453.

4-Chlorophenyl Thiol-(2-methylpropionate).—A mixture of 0.1 mole each of 4-chlorobenzenethiol and isobutyryl chloride, and 35 ml. of pyridine was maintained at 70–90° for 1 hour. It was then poured into water. The oil was separated, dried, and distilled, yielding 10.7 g. (50%) of the thiol ester, b.p. 147–148° (13 mm.).

Phenyl thiocrotonate was prepared on a 0.14-mole scale by method C. Fractionation gave 15 g. (59%) of the thiol ester at 152–154° (15 mm.).

4-Chlorophenyl Thioloacetate (Illustrating Method D).—A mixture of 0.53 mole of 4-chlorobenzenethiol, 0.53 mole of chloroacetyl chloride and 150 ml. of dimethoxyethane was maintained below 20° by cooling while 45 ml. of pyridine was slowly added. Stirring was continued for 1 hour, then 500 ml. of water was added and the oil was extracted into chloroform. The extract was washed with 5% sodium hydroxide, then with water, and dried over sodium sulfate. The product crystallized on evaporation of the chloroform. Recrystallization from methanol gave 85 g. (73%) of colorless needles of m.p. 79–81°. Further recrystallization raised the m.p. to 82–83°.

4-Chlorophenyl thiodichloroacetate was prepared on a 0.25-mole scale by method D, yielding 50 g. (78%) of crude material of m.p. 58–61°. Recrystallization from methanol gave colorless needles of m.p. 61–62°.

Phenyl thiocinnamate was prepared on a 0.1-mole scale by method D, except that the product separated as a solid

on addition of water to the reaction mixture. The solid was filtered, washed with water and dried, giving a quantitative yield of material of m.p. 90–93°. Recrystallization from 200 ml. of ethanol gave 20 g. (84%) of colorless blades of m.p. 92–93°.

Phenyl Thiol-(2-ethylcinnamate).—A mixture of 35.2 g. (0.2 mole) of 2-ethylcinnamic acid, 31 g. (0.26 mole) of thionyl chloride and 50 ml. of 1,2-dimethoxyethane was closed with a calcium chloride tube and allowed to stand overnight. It was then boiled briefly to remove hydrogen chloride. After cooling, the mixture was transferred to a dropping funnel and added dropwise with stirring and cooling to a solution of 0.2 mole of benzenethiol in 400 ml. of 10% sodium hydroxide. Stirring was continued for 1 hour, then the dark mixture was extracted with ether. Fractionation gave a forerun, followed by 34.4 g. (64%) of a reddish colored oil at 253–254° (23 mm.), n_D^{20} 1.6290.

Phenyl Thiol-(4-chlorobenzoate) (Illustrating Method E).—Phenyl thiol-(4-chlorobenzoate) was prepared on a 0.2-mole scale in a similar manner to that described as method C, except that the reaction mixture was allowed to stand overnight after addition of the acid chloride. The product separated as a solid. It was filtered, washed with water, and dried, yielding 48 g. (96%) of material of m.p. 77–84°. Recrystallization from 150 ml. of isopropyl alcohol gave 42 g. of colorless platelets of m.p. 82–84°, unchanged by further recrystallization.

4-Chlorophenyl Thiol-(4'-chlorobenzoate) was prepared on a 0.2-mole scale by method E, yielding 38 g. (67%) of material of m.p. 132–135°. Recrystallization from 350 ml. of acetone gave 26 g. of small colorless blades of m.p. 136–138°.

4-Chlorophenyl Thiol-(2-chlorobenzoate) was prepared on a 0.2-mole scale by method E, giving a quantitative yield of material of m.p. 91–94°. Recrystallization from 200 ml. of acetone gave 20.5 g. (72%) of colorless needles of m.p. 95–96°.

4-Chlorophenyl thiol-(3'-bromobenzoate) was prepared on a 0.2-mole scale by method E, giving a quantitative yield of material of m.p. 102–106°. Recrystallization from 450 ml. of acetone gave 43.5 g. (67%) of clusters of fine needles of m.p. 107–108°.

Phenyl thioufoate was prepared on a 0.15-mole scale by method E, yielding 15.8 g. (50%) of material of m.p. 50–53°, which analyzed correctly for the thiol ester without recrystallization.

4-Chlorophenyl Thioufoate.—A mixture of 0.1 mole each 4-chlorobenzenethiol and furoyl chloride, and 25 ml. of benzene was heated under reflux for several hours. The solution was then reduced in volume and chilled, yielding 9.6 g. (40%) of crystalline solid of m.p. 106–107°.

Pentachlorophenyl Thioufoate.—To a solution of 0.1 mole of pentachlorobenzenethiol in 50 ml. of pyridine was added 0.1 mole of furoyl chloride. The mixture was slowly warmed to boiling, then allowed to cool and poured into water. The solid was recrystallized from ethanol, yielding 3.3 g. of crystals of m.p. 156–158°.

O-Ethyl S-(4-Chlorophenyl)-thiolcarbonate.—To a solution of 0.5 mole of 4-chlorobenzenethiol in 500 ml. of 5% sodium hydroxide at 0° was added dropwise 0.55 mole of ethyl chloroformate. Stirring was continued for 1 hour at room temperature. The lower layer was then separated, washed with water and dried over sodium sulfate. Fractionation gave 85 g. (78%) of product at 142–143° (10 mm.), n_D^{20} 1.5542.

Anal. Calcd. for $C_9H_9ClO_2S$: C, 49.89; H, 4.19; Cl, 16.36; S, 14.80. Found: C, 50.15; H, 4.11; Cl, 16.49; S, 14.69.

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