Some New Chalcones[1]

In connection with the study of the antifungal activity of organic compounds, we have prepared fourteen new chalcones. Except as noted, these were made by the condensation of substituted benzaldehydes and acetophenones at 0–10° in ethanol–water mixture using sodium hydroxide as a catalyst,[2] the duration of the reaction being about eighteen hours.

CHALCONES

Substituents	M. p.,[a] °C.	Formula	Analyses,[b] % Calculated C	H	Found C	H
2,3-Dimethoxy[c]	.....[d]	$C_{17}H_{16}O_3$	76.10	6.01	75.95	5.59
2,4'-Dichloro[e]	82–83	$C_{15}H_{10}OCl_2$	65.00	3.64	64.83	3.74
3,4-Diethoxy	128	$C_{19}H_{20}O_3$	77.00	6.80	76.64	6.55
3,4-Dichloro	112–113[f]	$C_{15}H_{10}OCl_2$	65.00	3.64	64.64	3.58
4-Methoxy-2'-chloro	80–81	$C_{16}H_{13}O_2Cl$	70.46	4.80	70.37	4.72
4-Isopropyl-4'-methoxy	69–70[g]	$C_{19}H_{20}O_2$	81.40	7.19	81.08	7.35
2,4,2'-Trichloro[e]	109–110	$C_{15}H_9OCl_3$	75.82	2.91	57.90	3.06
2,4-Dichloro-4'-methoxy	134	$C_{16}H_{12}O_2Cl_2$	62.56	3.94	62.61	4.18
3,4'-Dimethoxy-4-hydroxy[h]	158–159[i]	$C_{17}H_{16}O_4$	71.81	5.67	71.81	5.79
3-Methoxy-4-hydroxy-4'-chloro	101[i]	$C_{16}H_{13}O_3Cl$	66.56	4.54	66.56	4.46
3,4-Diethoxy-4'-methoxy-[j]	72–74[k]	$C_{20}H_{22}O_4$	73.60	6.80	73.35	6.83
3,4-Diethoxy-4'-methyl	96	$C_{20}H_{22}O_3$	77.39	7.15	77.65	7.29
3,4-Methylenedioxy-2'-chloro	97–98[k]	$C_{16}H_{11}O_3Cl$	67.02	3.87	67.20	4.09
3,4-Methylenedioxy-2'-hydroxy-5'-chloro	145–146[l]	$C_{16}H_{11}O_4Cl$	63.48	3.66	63.35[m]	3.70

[a] Except as noted, all compounds were crystallized from ethanol. [b] Except as noted, all analyses are by the Clark Microanalytical Laboratory. [c] Chemical Abstracts numbering. [d] Yellow liquid, b. p. 198–199° (2 mm.). [e] Reaction time four hours. [f] Recrystallized from acetone–ethanol. [g] Recrystallized from ethanol–benzene. [h] Reaction time three hours. [i] Reaction temperature 20–30°. [j] Reaction time two weeks. [k] Recrystallized from methanol. [l] Reaction temperature 30–40°. [m] Analysis by Micro-Tech Laboratories.

The results of the biological tests will be reported elsewhere.

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[1] This paper consists of a report of work done under contract with the Medical Division, Chemical Corps, U. S. Army.

[2] *Cf.* "Organic Syntheses," John Wiley & Sons, Inc., New York, N. Y., Coll. Vol. I, p. 78.

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Mercaptomethylthiazole Derivatives

2-Methyl-4-mercaptomethylthiazole.—In a 250-ml. three-neck flask fitted with a sealed stirrer, reflux condenser and drying tube, and dropping funnel was placed 16 g. (0.11 mole) of 2-methyl-4-chloromethylthiazole,[1] 10.5 g. (0.14 mole) of thiourea and 32 ml. of anhydrous ethanol. The solution was refluxed with stirring for two hours, cooled, treated with a solution of 8 g. (0.2 mole) of sodium hydroxide in 75 ml. of water and refluxed for an additional hour. To the cooled mixture was added enough 10% hydrochloric acid to show slight acidity to litmus and then 10% sodium carbonate solution to slight basicity. The mixture was extracted four times with 100 ml. of ether, and the solvent phase was dried with anhydrous calcium sulfate. The desiccant was removed by filtration, the volatiles removed from the filtrate by distillation, finally at reduced pressure and the residue distilled at 89–91° (3 mm.) to give 10.3 g. (64% yield) of a colorless oil.

Anal.[2] Calcd. for $C_6H_7NS_2$: N, 9.64. Found: N, 9.34.

2-Methyl-4-benzylthiomethylthiazole.—In a 250-ml. three-neck flask fitted with a sealed stirrer, reflux condenser and drying tube, dropping funnel and thermometer, was placed 4.6 g. (0.08 mole) of potassium hydroxide and 100 ml. of anhydrous ethanol. Stirring and refluxing was initiated and continued until solution was complete, after which time the heater was replaced by an ice-bath until the temperature dropped to 5°, when 8.7 g. (0.07 mole) of benzyl mercaptan in 20 ml. of absolute ethanol was added dropwise (fifteen minutes) at that temperature. At the end of that time, 10 g. (0.07 mole) of freshly prepared 2-methyl-4-chloromethylthiazole in 20 ml. of ethanol was added during ten minutes, causing an immediate precipitation of potassium chloride. The mixture was stirred and refluxed for one hour, cooled, diluted with 700 ml. of water and extracted four times with 200 ml. of ether. The ethereal solution was washed with a total of 200 ml. of water and then dried with calcium sulfate. After separation of the desiccant, the solvent was removed by distillation and the residue distilled at 131–135° (0.75 mm.) to give 12.1 g. (75% yield) of a colorless oil.

Anal. Calcd. for $C_{12}H_{13}NS_2$: N, 5.86. Found: N, 5.35.

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[1] Hooper and Johnson, THIS JOURNAL, **56**, 470 (1934).

[2] Analyses by Mr. H. Soloway of this Laboratory.

[3] Present address: Oxford Products, Inc., Cleveland, Ohio.

Thiol Esters

During work on compounds containing the thiophene-2-methyl group, it became desirable to prepare a series of thiol esters derived from thiophene-2-methyl mercaptan.[1] It was found that the mercaptan reacted in the usual manner with acyl halides and with acid anhydrides to give the desired esters in acceptable yields. The new products and their properties are tabulated in Table I.

Experimental

All of the compounds were prepared by the interaction of molar quantities of the appropriate acyl halide or anhydride with the mercaptan in excess pyridine, and worked up in the usual manner.

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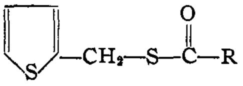
[1] Prepared *via* the isothiouronium salt from thienyl chloride.

TABLE I

THIOPHENE-2-METHYL THIOL ESTERS



R	B. p.,[a] °C.	Mm.	Yield, %	Formula	Analyses,[b] % Calculated C	Calculated H	Found C	Found H
CH_3	56–60	2	80	$C_7H_8OS_2$	48.80	4.68	49.06	4.92
C_2H_5	79–83	2	53	$C_8H_{10}OS_2$	51.58	5.41	51.68	5.74
C_6H_5	155	2.5	81	$C_{12}H_{10}OS_2$	61.50	4.30	62.17	4.50
C_4H_3O (furyl)	[c]		78.5	$C_{10}H_8O_2S_2$	53.55	3.59	52.93	3.91

[a] Boiling points are uncorrected. [b] Analyses by Oakwold Laboratories, Alexandria, Virginia. [c] M. p. 55°, recrystallized from aqueous methanol.

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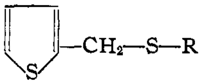
2-Thenyl Sulfides

During work on compounds containing the 2-thenyl grouping, it became desirable to prepare a series of sulfides bearing that loading. Certain of these compounds were obtained in good yields from the interaction of 2-thenyl chloride and the appropriate potassium mercaptide, while 2-(2′-thenylmercapto)-ethyl cyanide and the corresponding mercaptopropionic ester were synthesized by the addition of 2-thenyl mercaptan to the respective acylic compounds in the presence of a trace of alkaline catalyst.[1] The new compounds are listed in Table I.

TABLE I

2-THENYL SULFIDES



R	Yield, %	B. p., °C.[a]	Mm.	Formula	Analyses,[b] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Sulfur Calcd.	Sulfur Found
C_2H_5–	76	66–69	3	$C_7H_{10}S_2$	53.12	53.35	6.37	6.71	40.52	39.75
i-C_4H_9–	70	89–91	3.5	$C_9H_{14}S_2$	58.01	57.43	7.57	7.59	34.41	34.92
n-C_6H_{13}–	65.5	106–109	2	$C_{11}H_{18}S_2$	61.62	61.09	8.46	8.17	29.91	30.19
$C_6H_5CH_2$–	79.5	120–121	1.5	$C_{12}H_{12}S_2$	65.41	65.34	5.49	5.70	29.10	29.21
$C_4H_3SCH_2$–[c]	78	129–131	1.5	$C_{10}H_{10}S_3$	53.06	52.91	4.45	4.49	42.49	42.98
C_2H_5OCO–$(CH_2)_2$–	40	126	1	$C_9H_{12}O_2S_2$					29.64	29.79
NC–$(CH_2)_2$–	47	127–130	2.5	$C_8H_9NS_2$					34.99	34.27

[a] Boiling points are uncorrected. [b] Analyses by Oakwold Laboratories, Alexandria, Virginia. [c] Thiophene-2-methyl.

***i*-Butyl-2-thenyl Sulfide.**—In a 250-ml. 3-neck flask fitted with a sealed Hershberg stirrer, reflux condenser, thermometer and dropping funnel, was dissolved 6.6 g. (0.1 mole) of 85% potassium hydroxide in 100 ml. of absolute ethanol with stirring and heating. After solution was complete, the temperature was allowed to drop to about 25° and 10 g. (0.11 mole) of *i*-butyl mercaptan was added from the dropping funnel during ten minutes, the temperature being maintained constant. At the end of this time, 13.2 g. (0.1 mole) of 2-thenyl chloride[2] was added dropwise at the same temperature (fifteen minutes). The precipitation of potassium chloride began almost immediately, and the mixture was stirred and refluxed for three hours, after which time further heating did not increase the yield. The cooled mixture was poured into 900 ml. of water, causing separation of an oil which was removed by extraction with a total of 400 ml. of ether. The solvent layer was dried with calcium sulfate, filtered from the desiccant, stripped (finally at reduced pressure) and then fractionated through a 30-cm. Vigreux column to give 13 g. (70% yield) of a colorless oil boiling at 89–91° (3.5 mm.).

2-(2′-Thenylmercapto)-ethyl Cyanide.—In a 250-ml. 3-neck flask fitted as above was placed 26 g. (0.2 mole) of 2-thenyl mercaptan,[3] 0.05 g. (0.0022 mole) of sodium and 100 ml. of anhydrous benzene. The mixture was stirred and refluxed until the sodium had reacted completely. The mixture was cooled to 5° and 11.1 g. (0.21 mole) of freshly distilled acrylonitrile in 50 ml. of benzene was added dropwise during five minutes, the temperature rising to 40°.[4] The solution was refluxed for one hour, cooled, acidified with glacial acetic acid and the volatiles removed from the steam-bath at reduced pressure. The residue was fractionated at 127–130° (2.5 mm.) to give 17.3 g. (47% yield) of a colorless oil.

The thenylmercaptopropionic ester was prepared in a similar manner using methyl acrylate instead of acrylonitrile.

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[1] Rapoport, Smith and Newman, THIS JOURNAL, **69**, 693 (1947); Gershbein and Hurd, *ibid.*, **69**, 241 (1947); Hurd and Gershbein, *ibid.*, **69**, 2328 (1947).

[2] Blicke and Leonard, *ibid.*, **68**, 1934 (1946).

[3] From 2-thenyl chloride and thiourea, followed by treatment of the isothiouronium salt with alkali.

[4] The reaction could be performed in the absence of solvent, but it proceeded with almost explosive violence.

[5] Present address: Oxford Products, Inc., Cleveland, Ohio.

Thiofuroic Acid

Sixteen and four-tenths grams of furoyl chloride was added with agitation to 75 ml. of 10% aqueous sodium hydrosulfide. The reaction proceeded smoothly in the cold (4°). The reaction mixture was acidified to liberate the thioacid and then extracted with ether. The ether solution was dried with anhydrous sodium sulfate and the solvent