The synthesis and properties of some dithiosemicarbazones[1]

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A series of new compounds has been prepared by reacting aliphatic and aromatic aldehydes with ethylene dithiosemicarbazide. The nature of these new dithiosemicarbazones has been deduced from their infrared spectra, from the products of the ferric chloride induced oxidation of two of them, and from the formation of 1:1 copper complexes of several of them. Since the copper complexes are paramagnetic, the copper must be present in the cupric oxidation state. A structure has therefore been proposed for the complexes which involves bonding between copper and both thiocarbonyl groups in the dithiosemicarbazone molecule.

Several of the compounds prepared in this work exhibit an antifungal action against the cellulolytic microorganism *Chaetomium globosum*.

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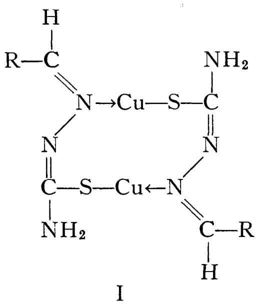
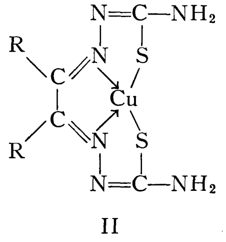
INTRODUCTION

Interest in compounds of the thiosemicarbazone type has arisen for several reasons. For example, the reaction between thiosemicarbazide and carbonyl compounds can be used to synthesize a wide variety of thiosemicarbazones (1, 2), many of which form definite copper complexes and are of interest as potential fungicides. Infrared absorption measurements, the use of a variety of *N*-methyl substituted thiosemicarbazides to make thiosemicarbazones (3), and other measurements (4) have been useful in the elucidation of the structure of copper complexes of thiosemicarbazones (I). The synthesis of thiosemicarbazones from dicarbonyl compounds has been reported (3). Some of the "di"-thiosemicarbazones form 1:1 complexes with copper; these are, in effect, 2:1 complexes in the sense of the thiocarbonyl group – copper ratio (II).



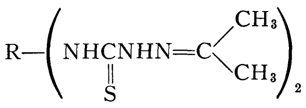
I



II

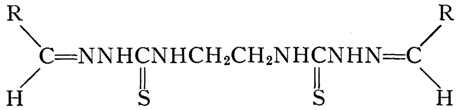
Lieber and Slutkin (5) have reported the preparation of a series of diisothiocyanates from diamines, and the subsequent conversion of the former into dithiosemicarbazides. To characterize these, they reacted them with acetone to prepare a series of acetone thiosemicarbazones having the general structure shown by III.

The present work describes the preparation and some properties of dithiosemicarbazones. The preparation involves reacting ethylene diisothiocyanate with hydrazine hydrate to form ethylene dithiosemicarbazide, and then reacting this with a series of aliphatic and aromatic aldehydes. These dithiosemicarbazones should presumably be referred to as ethylene di(aldehyde thiosemicarbazones). This is a new set of compounds, similar to those described by Lieber and Slutkin but quite different from the dithiocarbonyl-containing compounds II prepared from diketones and reported previously (3). The structure IV of the dithiosemicarbazones described in the present work has been deduced from infrared measurements, from the products of a subsequent cyclization reaction, and from copper complex formation. Compounds believed to be of type IV, and their copper complexes, have been tested as potential fungicides.



$$R\left(NH\underset{\underset{S}{\|}}{C}NHN{=}C\begin{smallmatrix}CH_3\\ CH_3\end{smallmatrix}\right)_2$$

III



$$\begin{smallmatrix}R\\ H\end{smallmatrix}C{=}NNH\underset{\underset{S}{\|}}{C}NHCH_2CH_2NH\underset{\underset{S}{\|}}{C}NHN{=}C\begin{smallmatrix}R\\ H\end{smallmatrix}$$

IV

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TABLE I

Ethylene di(aliphatic and aromatic aldehyde thiosemicarbazones)

Compound	Aldehyde	Melting point (°C)	Yield (%)	Formula	Calculated (%)	Found (%)
1	*n*-Heptanal	157	52*	$C_{18}H_{36}N_6S_2$	C 54.00	C 53.88
					H 9.00	H 8.98
					N 21.00	N 20.95
					S 16.00	S 16.09
2	*n*-Octanal	164	92*	$C_{20}H_{40}N_6S_2$	C 56.07	C 55.93
					H 9.37	H 9.71
					N 19.61	N 19.35
					S 14.95	S 14.75
3	*n*-Nonanal	147	64*	$C_{22}H_{44}N_6S_2$	C 57.89	C 57.16
					H 9.65	H 9.80
					N 18.42	N 18.00
					S 14.04	S 13.40
4	*n*-Decanal	161	86*	$C_{24}H_{48}N_6S_2$	C 59.50	C 59.77
					H 9.92	H 9.85
					N 17.36	N 17.90
					S 13.22	S 12.79
5	*n*-Undecanal	140	97*	$C_{26}H_{52}N_6S_2$	C 60.94	C 61.60
					H 10.16	H 10.13
					N 16.40	N 16.50
					S 12.50	S 12.12
6	9-Undecenal	127	68*	$C_{26}H_{48}N_6S_2$	C 61.42	C 61.58
					H 9.45	H 9.56
					N 16.54	N 16.60
					S 12.59	S 11.90
7	*n*-Dodecanal	125	41*	$C_{28}H_{56}N_6S_2$	C 62.22	C 62.45
					H 10.37	H 10.28
					N 15.56	N 15.45
					S 11.85	S 11.43
8	Benzaldehyde	240	86†	$C_{18}H_{20}N_6S_2$	C 56.25	C 56.93
					H 5.21	H 5.61
					N 21.88	N 21.61
9	*m*-Nitrobenzaldehyde	269	68‡	$C_{18}H_{18}N_8O_4S_2$	C 45.57	C 45.52
					H 3.79	H 4.12
					N 23.63	N 23.60
					S 13.50	S 13.50
10	*o*-Chlorobenzaldehyde	250	65†	$C_{18}H_{18}N_6S_2Cl_2$	C 47.68	C 47.81
					H 3.97	H 4.20
					N 18.54	N 18.76
					S 14.13	S 13.62
					Cl 15.67	Cl 15.20
11	*p*-Chlorobenzaldehyde	258	62‡	$C_{18}H_{18}N_6S_2Cl_2$	C 47.68	C 48.19
					H 3.97	H 4.06
					N 18.54	N 18.55
					S 14.13	S 14.20
					Cl 15.67	Cl 15.40
12	2,4-Dichlorobenzaldehyde	257	66‡	$C_{18}H_{16}N_6S_2Cl_4$	C 41.38	C 40.95
					H 3.07	H 3.12
					N 16.09	N 16.75
					S 12.26	S 12.33
					Cl 27.20	Cl 26.90
13	Anisaldehyde	261	47†	$C_{20}H_{24}N_6O_2S_2$	C 54.05	C 54.54
					H 5.41	H 5.44
					N 18.92	N 18.63
					S 14.42	S 14.30
14	*trans*-Cinnamaldehyde	263	50‡	$C_{22}H_{24}N_6S_2$	C 60.55	C 60.76
					H 5.50	H 5.58
					N 19.27	N 18.78
					S 14.68	S 14.30

*Recrystallized from ethanol.
†Recrystallized from ethyl acetate; *n*-hexane added until the onset of incipient precipitation.
‡Recrystallized from *N*,*N*-dimethylformamide; water added until the onset of incipient precipitation.

EXPERIMENTAL

Ethylene diisothiocyanate was prepared by the method of Klöpping and Vander Kerk (6), and purified by fractional distillation.

Ethylene dithiosemicarbazide was prepared in the following way. Hydrazine hydrate (0.04 mole) was added dropwise to ethylene diisothiocyanate (0.02 mole) dissolved in 50 ml of ethanol. The mixture was heated gently on a steam bath, and a white precipitate was obtained after 15 min. The precipitate was separated by filtration, washed with water, dried, and purified by repeated recrystallization from *N*,*N*-dimethylformamide–water, m.p. 229 °C (lit. (5) m.p. 225 °C).

Preparation of Ethylene Di(aldehyde thiosemicarbazones)

The solution of aldehyde (0.0048 mole) in 25 ml of ethanol was added dropwise to the solution of ethylene dithiosemicarbazide (0.0024 mole) in 25 ml of *N*,*N*-dimethylformamide. Glacial acetic acid (1 ml) was then added and the resulting mixture was heated for 15 min on a steam bath. The precipitate which formed when the mixture was cooled was collected, washed with 50% aqueous ethanol solution, dried, and recrystallized until pure. The ethylene dithiosemicarbazones reported in this paper are listed in Table I together with the yield, melting point, solvent used in recrystallization, and elemental analysis.

Oxidation of Ethylene Di(aldehyde thiosemicarbazones) with Ferric Chloride

Two of the dithiosemicarbazones listed in Table I were subjected to ferric chloride oxidation according to the method described by Ramachander and Srinivasan (7). Specifically, the cyclization reaction was carried out with ethylene di(*n*-decanal thiosemicarbazone) and with ethylene di(*n*-undecanal thiosemicarbazone). The data for the resulting ethylene di(substituted-1,3,4-thiadiazoles) are as follows.

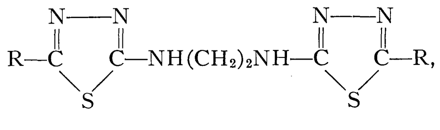
Ethylene di(2-amino-5-nonyl-1,3,4-thiadiazole): m.p. 144 °C, 91% yield, recrystallized from benzene.

Anal. Calcd. for $C_{24}H_{44}N_6S_2$: C, 60.00; H, 9.17; N, 17.50; S, 13.33. Found: C, 60.68; H, 8.91; N, 17.15; S, 13.15.

Ethylene di(2-amino-5-decyl-1,3,4-thiadiazole): m.p. 140 °C, 89% yield, recrystallized from benzene.

Anal. Calcd. for $C_{26}H_{48}N_6S_2$: C, 61.42 H, 9.46; N, 16.53; S, 12.59. Found: C, 61.65; H, 9.10; N, 16.35; S, 12.59.

The general structure for these two compounds is considered to be



where R is nonyl or decyl, as given above.

Copper Complexes of Ethylene Di(aldehyde thiosemicarbazones)

Copper complexes of all the ethylene di(aldehyde thiosemicarbazones) listed in Table I were prepared. The general procedure involved the addition of a solution of cupric acetate in ethanol to a warm solution containing an equimolar amount of dithiosemicarbazone in ethanol or *N*,*N*-dimethylformamide. The copper complexes precipitated immediately, and were filtered off and washed repeatedly with ethanol, acetone, and water. Because of their insolubility, however, the complexes could not be purified by recrystallization. Two were obtained in an acceptable degree of purity, except for the sulfur analysis, and they are listed here.

Ethylene di(*o*-chlorobenzaldehyde thiosemicarbazone) – Cu: m.p. 193 °C.

Anal. Calcd. for $C_{18}H_{16}N_6S_2Cl_2$–Cu: C, 41.98; H, 3.11; N, 16.33; S, 12.44; Cl, 13.79; Cu, 12.34. Found: C, 41.77; H, 3.46; N, 16.15; S, 9.31; Cl, 13.82; Cu, 12.30.

Ethylene di(*p*-chlorobenzaldehyde thiosemicarbazone) – Cu: m.p. 212 °C.

Anal. Found: C, 42.85; H, 3.52; N, 16.10; S, 9.40; Cl, 14.15; Cu, 12.10.

The magnetic properties of these two copper complexes (as finely divided solids) were determined at room temperature with Varian V-4502-15 electron spin resonance equipment. The spectra obtained were compared qualitatively with the signal from powdered $CuSO_4 \cdot 5H_2O$.

The copper analysis figures were acceptable for two more copper complexes, for which one or more of the other elemental analysis figures was unsatisfactory.

Ethylene di(benzaldehyde thiosemicarbazone) – Cu: m.p. 203 °C; % Cu required 14.3, % Cu found 14.9.

Ethylene di(*m*-nitrobenzaldehyde thiosemicarbazone) – Cu: m.p. 220 °C; % Cu required 12.4, % Cu found 12.6.

The correlation between the amount of copper required for a 1:1 complex (based on the ratio of Cu to dithiosemicarbazone) and the amount that is actually found by analysis implies that definite complexes are in fact formed in each case. It has been assumed that copper complex formation occurs with the loss of two hydrogen atoms from each dithiosemicarbazone molecule. This and other possibilities will be discussed later.

Preparation of Polymers of Ethylene Dithiosemicarbazide

An attempt was made to prepare condensation polymers of ethylene dithiosemicarbazide and a dialdehyde. An aqueous solution of the dialdehyde (0.0144 mole in 25 ml) was added dropwise to a solution of ethylene dithiosemicarbazide (0.0144 mole) in dimethyl sulfoxide (50 ml). After the addition of glacial acetic acid (1 ml), the resulting mixture was heated on a steam bath for 1 h and then cooled. The addition of water caused the polymer to precipitate as a sticky solid. The product was recrystallized once from an aqueous solution of dimethyl sulfoxide. After this, however, the polymers were no longer soluble, presumably because of cross-linking, and further purification was not feasible. Two examples, showing the elemental analyses, are given here.

Poly(ethylene dithiosemicarbazone glutaraldehyde): melting range 160–180 °C.

TABLE II

Infrared absorption bands for ethylene di(aldehyde thiosemicarbazones)

1	2	3	4	5	6	7	8	9	10	11	12	13	14
3 360 m	3 360 m	3 400 m	3 380 m	3 380 m	3 400 w	3 380 w	3 400 br	3 360 w	3 400 br	3 400 br	3 400 w	3 400 vw	3 400 w
3 170 s	3 160 s	3 200 s	3 160 m	3 160 m	3 180 m	3 160 w	3 160 m	3 200 w	3 200 vw	3 200 vw	3 200 vw	3 200 w	3 160 w
2 940 s	2 930 s	2 960 s	2 930 s	2 930 s	2 960 s	2 930 s	3 000 w	3 000 vw	3 000 w	3 000 w	3 000 vw	2 995 w	3 000 w
2 860 w	2 860 w	2 870 w	2 860 vw	2 860 vw	2 880 vw	2 860 vw							
								1 660 w				1 660 w	1 660 vw
1 635 w	1 630 vw	1 635 w	1 625 w	1 635 w	1 650 w	1 635 w	1 610 vw	1 625 vw	1 600 w	1 600 w	1 595 m	1 610 s	1 630 m
1 550 vs	1 550 vs	1 550 s	1 550 s	1 550 s	1 550 s	1 550 s	1 545 s	1 535 s	1 535 s	1 535 s	1 535 s	1 550 s	1 535 s
1 520 w	1 515 m	1 515 m	1 515 m	1 515 w	1 515 w	1 515 vw			1 475 w	1 495 m		1 515 s	
1 475 w	1 475 w	1 475 w	1 475 w	1 475 w	1 475 w	1 475 w	1 460 w	1 450 w	1 450 w		1 475 m	1 425 vw	1 465 vw
1 405 vw	1 405 w	1 405 w	1 405 w	1 405 w	1 405 w	1 405 w				1 410 w	1 395 w		1 400 w
1 385 vw		1 335 w		1 335 w				1 360 s					
1 335 vw													
1 300 m	1 300 s	1 300 s	1 300 m	1 300 s	1 300 s	1 300 m	1 300 m	1 300 w	1 290 w	1 300 m	1 300 w	1 305 m	1 300 m
							1 235 w	1 270 w	1 255 w				
								1 250 w	1 225 w		1 225 w	1 250 s	
1 215 s	1 215 s	1 210 s	1 215 s	1 210 s	1 210 s	1 215 s	1 210 m	1 200 m	1 200 w	1 200 m	1 200 w	1 205 w	1 210 m
	1 150 vw										1 145 vw	1 175 m	1 165 vw
1 105 s	1 105 s	1 105 s	1 105 m	1 105 m	1 105 s	1 105 m	1 120 m	1 120 m	1 120 m	1 120 w	1 105 m	1 105 m	1 110 m
		1 060 br			995 vw				1 060 m	1 095 m			
									1 035 w	1 020 w	1 055 w	1 030 m	
920 w	930 w	950 vw		925 w	965 w	950 br	950 m	945 m	945 br	930 w	930 w	950 w	970 s
												925 w	
890 w		910 w	910 w	895 vw	910 s	910 vw							
		845 vw					875 m	845 m	875 m	875 w	875 m	875 w	850 w
												835 m	
810 m	810 m	810 m	810 m	805 m	810 m	800 m	800 w	810 w	800 w	825 m	815 br	800 w	800 w
780 vw	775 w	770 vw		775 w	775 w		760 m	740 m	765 m	780 w	750 w		750 m
725 w	725 w	720 m	725 w	720 m	720 w	725 vw	695 m	675 w	710 w	710 vw			690 m

Anal. Calcd. for $C_9H_{16}N_6S_2$: C, 39.71; H, 5.88; N, 30.88; S, 23.53. Found: C, 38.27; H, 6.27; N, 30.80; S, 27.82.

Poly(ethylene dithiosemicarbazone α-hydroxyadipaldehyde): melting range 180–200 °C.

Anal. Calcd. for $C_{10}H_{18}N_6OS_2$: C, 39.74; H, 5.96; N, 27.81; S, 21.19. Found: C, 41.14; H, 6.66; N, 22.40; S, 22.57.

The infrared spectra of the new compounds described in this work were obtained from KBr pellets with a model 21 Perkin–Elmer double-beam spectrophotometer (NaCl prism) over the frequency range 3 500 to 650 cm^{-1}.

Because of the antimicrobial activity which has been reported for thiosemicarbazones (8) and some substituted thiosemicarbazones (9), the ethylene di(aldehyde thiosemicarbazones), the copper complexes of some of them, and the two thiadiazoles referred to above were tested for potential antifungal activity. The test organism was *Chaetomium globosum*, strain USDA 1042.4; the testing period was 2 weeks. The screening procedures involved the tube dilution method described previously (8) and concentrations of the compounds being tested of 10, 100, and 1 000 p.p.m.

RESULTS AND DISCUSSION

The bands in the infrared spectra of the 14 new ethylene di(aldehyde thiosemicarbazones) prepared in this work are shown in Table II. The spectra of the seven di(aliphatic aldehyde thiosemicarbazones) are very similar to one another and show absorption bands which are compatible with the proposed structure IV. For example, there are strong bands in the 3 200 to 3 500 cm^{-1} region characteristic of NH stretching vibrations, and in the 800 to 810 cm^{-1} region associated with the thiocarbonyl group (10). There are two bands in the 1 550 to 1 650 cm^{-1} region, where both C=N and CNH vibrations would be expected to absorb. It may be assumed that the band at higher frequency, i.e. 1 625 to 1 650 cm^{-1}, arises from the former (cf. ref. 3).

The absorption bands in the spectra of the seven di(aromatic aldehyde thiosemicarbazones) shown in Table II are analogous to, but not as well resolved as, those for compounds 1 to 7. Peaks in the NH stretching region are present, of course, but are frequently broadened and weakened. In addition, there is more variation in the C=N and CNH regions than was observed for compounds 1 to 7, and the assignment of ν(C=S) is not as straightforward.

Finally, attention may be drawn to the medium-strong band which occurs at 1 105 cm^{-1} in the spectra of the first seven compounds. There is good evidence that this band may be due to N—C—N stretching vibrations coupled, to a small extent, with C=S vibrations (10). The corresponding band in the spectra of compounds 8 to 14 seems to vary between 1 105 and 1 120 cm^{-1} and to be of a lower intensity, on the average. It is to be expected that the di(aldehyde thiosemicarbazones) containing phenyl and substituted phenyl groups will have infrared spectra which are more difficult to interpret, but there is, nevertheless, no obvious reason to doubt the validity of structure IV.

The oxidation by ferric chloride of two of the di(aldehyde thiosemicarbazones) was carried out for two reasons in particular: to provide additional evidence in support of the proposed structure IV of this type of dithiosemicarbazone, and to see whether the cyclization which was observed (7, 11) in simpler thiosemicarbazones would occur quantitatively at both "ends" of dithiosemicarbazone molecules. The absorption bands in the infrared spectra of the two substituted thiadiazoles obtained in the present work are shown in Table III. Compared with the parent dithiosemicarbazones (compounds 4 and 5), the thiadiazoles should have half the number of NH bonds and twice the number of C=N groups (all cyclic). The latter compounds, in addition, have no C=S groups and no exocyclic N—C—N bonds. Compared with Table II, Table III shows a band missing and intensity changes in the 3 200 to 3 500 cm^{-1} region, which would be consistent with a reduction in the NH content. The 800 to 810 cm^{-1} region indicates virtually no contribution from C=S stretching vibrations in the thiadiazole spectra. This and the lack of N—C—N vibrations are indicated by the almost complete disappearance of the important peak at 1 105 cm^{-1} in going from dithiosemicarbazone to thiadiazole. Finally, the strong bands at 1 470 and 1 605 cm^{-1} in the spectra of the latter may be indicative of cyclic C=N groups (7). Thus, the infrared data shown in Table III are consistent with

TABLE III

Infrared absorption bands for derivatives of ethylene di(aldehyde thiosemicarbazones)

Cu complex of compound 8	Cu complex of compound 9	Cu complex of compound 10	Cu complex of compound 11	Nonyl thiadiazole*	Decyl thiadiazole†
3 450 br	3 480 br	3 400 br	3 450 br		
				3 260 w	3 265 w
	2 960 vw	2 960 vw	2 960 vw	2 960 s	2 960 m
				2 880 w	2 880 w
			1 650 m		
1 620 w	1 625 w	1 600 w	1 600 w	1 605 s	1 605 s
1 525 br	1 535 s	1 525 br	1 525 br		
1 460 vw		1 445 w	1 495 vw	1 470 s	1 470 s
			1 400 w		
	1 360 s		1 325 vw	1 335 s	1 335 s
		1 290 vw			
		1 235 w	1 275 vw	1 280 w	1 280 m
1 215 vw		1 215 vw	1 215 w	1 220 w	1 220 w
				1 150 m	1 150 m
	1 100 w	1 135 vw	1 090 w	1 120 vw	1 120 vw
		1 060 m		1 050 w	1 055 w
					1 010 vw
950 w	950 w	950 w			
875 vw	840 w	875 w			
	810 vw		810 vw	800 vw	800 vw
760 m	740 w	760 s			
		725 vw		725 m	725 s
695 m	675 w	695 vw		665 w	665 m

*Ethylene di(2-amino-5-nonyl-1,3,4-thiadiazole).
†Ethylene di(2-amino-5-decyl-1,3,4-thiadiazole).

the structure IV proposed for ethylene di(aldehyde thiosemicarbazones) and indicate the general susceptibility of the thiosemicarbazone entity to cyclization by ferric chloride.

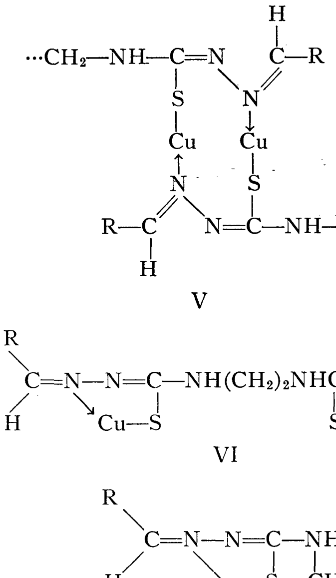
Since the analysis figures for the thiadiazoles are close to those for the corresponding dithiosemicarbazone parent compounds, additional evidence was obtained that oxidation with cyclization had, in fact, occurred. The mixture melting points of the thiadiazoles and the dithiosemicarbazones from which they were prepared were measured, and were found to be considerably lower than that of either the thiadiazole or the relevant dithiosemicarbazone. Finally, it should be noted that the thiadiazoles did not chelate with copper. This observation supports the contention that these compounds have cyclized at both "ends," i.e. no thiocarbonyl groups remain.

It has been pointed out in the Experimental why difficulty was experienced in purifying the copper complexes of the dithiosemicarbazones. The analyses for two of them were adequate for establishing the elemental composition. Two others have been included because the satisfactory copper analyses indicated that definite complexes had been obtained. In this context, the infrared data are considered to be meaningful as a basis for comparison with those for the uncomplexed parent compounds. The bands in the infrared spectra of the 1:1 copper complexes of the four di(aromatic aldehyde thiosemicarbazones) are shown in Table III. For the most part, the copper complexes show broader, less intense peaks which are less well resolved. There seems to be one less peak at approximately 3 200 cm^{-1}, in the region characteristic of NH stretching vibrations. This might be expected by analogy with the formation of copper complexes of monothiosemicarbazones, which involves a change of CNH to C=N (4).

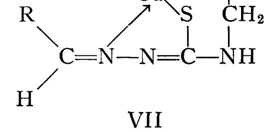
It can be seen in Table III that there is no particularly striking change in the 1 500 to 1 700 cm^{-1} region resulting from copper complex formation. Perhaps only small frequency shifts, peak broadening, and intensity changes occur in this region, because the CNH and C=N vibrations absorbing in this region are strongly coupled. If this were the case, then an increase in the number of C=N bonds and a decrease in the number of NH bonds would not be expected to alter the absorption drastically.

The spectra of compounds 8 to 11 show absorptions in the 800 to 825 cm^{-1} region, which are characteristic of C=S stretching vibrations. The formation of copper complexes of these compounds results in the disappearance or weakening and shifting of these bands. The band at 1 120 cm^{-1} in the spectra of dithiosemicarbazones has a lower intensity and a slightly different frequency in the corresponding spectra of the copper complexes. These observations are entirely consistent with the analogous effects of copper complex formation on the infrared spectra of the thiosemicarbazones (10).

There are at least three obvious possibilities for the structure of 1:1 copper complexes of di(aldehyde thiosemicarbazones). Both structures V and VI involve the conversion of one of the two C=S entities into C—S and the conversion of only one of the CNH units in the dithiosemicarbazone molecule into C=N. The possible justification for the dimeric nature of structure V arises because an analogous kind of dimer (structure I) has been found to exist in benzene solutions of some copper complexes of thiosemicarbazones. Structure VII has very nearly the same stoichiometry as the other two, but has one less hydrogen atom (one additional C=N) per dithiosemicarbazone molecule and, of course, no C=S group.



V



VI

VII

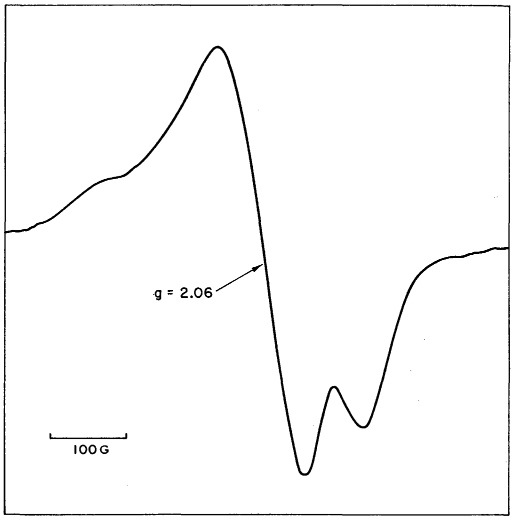


FIG. 1. The electron spin resonance spectrum of the copper complex of ethylene di(*o*-chlorobenzaldehyde thiosemicarbazone).

The most easily detectable difference, however, between structure VII and structures V or VI is that, in the former, copper is in the cupric, paramagnetic oxidation state and is presumably linked tetrahedrally to the two nitrogen and two sulfur atoms by bonds involving sp^3 hybrid orbitals of the copper. On the other hand, copper in structures V or VI is in the cuprous oxidation state, is diamagnetic, and is bonded by means of linear sp hybrid orbitals. The copper complexes of both the ethylene di(*o*-chlorobenzaldehyde thiosemicarbazone) and the *p*-chlorobenzaldehyde analogue are strongly paramagnetic. The signal obtained in either case (e.g. see Fig. 1) is similar to that from $CuSO_4 \cdot 5H_2O$, and has an intensity which is lower by an order of magnitude.

This is convincing evidence that these copper complexes exist in a form similar to that shown by structure VII (cf. structure II). It is reasonable to assume that all the copper complexes prepared from the dithiosemicarbazones in this work can be described in this way.

Some work has been reported (12, 13) on the preparation of polythiosemicarbazides by the reaction of *N*,*N'*-diaminopiperazine with a variety of diisothiocyanates. The use of methylenebis(4-phenylisothiocyanate), for example, resulted in the formation of a polymer which was soluble in dimethyl sulfoxide, could be used to form colorless films or fibers, and formed colored chelates with various metal ions. On the other hand, the polymers produced with hexamethylene diisothiocyanate, for example, were insoluble in common solvents and were not tested for chelating ability.

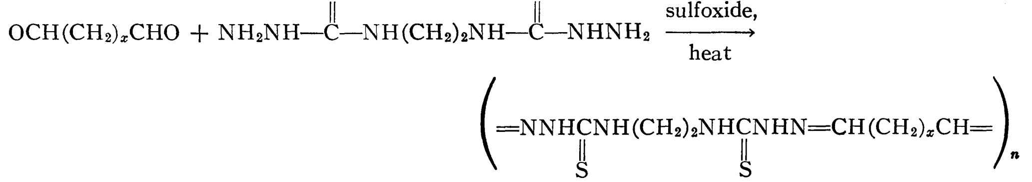
The poly(ethylene dithiosemicarbazone glutaraldehyde) and the poly(ethylene dithiosemicarbazone α-hydroxyadipaldehyde) described in the present work are examples of polydithiosemicarbazones which, although not reported previously, are formed in a way analogous to that used to prepare polythiosemicarbazides (12). The former reaction may be envisaged as shown in eq. [1]. The occurrence of backbone unsaturation presumably accounts for the swelling but lack of solubility of these polymers in common solvents by giving rise to rapid cross-linking. The light-brown polymers have infrared spectra characteristic of polymeric materials, i.e. with relatively broad and featureless absorption bands. The peaks to be expected for the vibrations of the NH (3 200 – 3 500 cm^{-1}), C=N (1 600 – 1 700 cm^{-1}), CNH ($\sim$1 550 cm^{-1}), N—C—N ($\sim$1 100 cm^{-1}), and C=S ($\sim$810 cm^{-1}) groups are present, although they are not particularly well defined. Condensation polymerizations were also carried out with hexamethylene dithiosemicarbazide and a dialdehyde, thus suggesting the considerable scope of this method of polymer synthesis.

The addition of cupric acetate solution to the solutions of polydithiosemicarbazones in dimethyl sulfoxide (before isolation, hence before cross-linking) caused the precipitation of dark-brown solids. This presumably indicates the formation of copper–polymer chelates analogous to those described by Campbell and Tomic (12), although no additional work has been carried out with these systems.

Many of the new compounds reported in this paper were tested for antifungal activity against the cellulolytic fungus *Chaetomium globosum*. The results of this screening, on a growth or no-growth basis, are as follows (compound numbers refer to Table I). (*a*) Compounds 3 to 6, 8, and 10 and the copper complexes of compounds 10 and 12 were effective at a concentration of 10 p.p.m.; both substituted thiadiazoles (Table III) also prevented growth at this concentration. (*b*) Compounds 1 and 2 and the copper complex of compound 13 were effective at 100 p.p.m.; compound 14 was effective at 1 000 p.p.m. (*c*) Compounds 9 and 11 to 14 and the copper complex of compound 9 were all ineffective at concentrations up to 1 000 p.p.m.

These data are obviously not sufficient to permit a contribution to the theory of the antimicrobial action of thiosemicarbazone-type fungistatic compounds. Nevertheless, it is considered to be significant that the copper complexes of compounds 12 to 14 are effective against *C. globosum* whereas the corresponding parent dithiosemicarbazones are not. There are several possible ways to account for this unexpected observation. For example, some of the dithio-

[1]



$$\mathrm{OCH(CH_2)_xCHO + NH_2NH{-}\overset{S}{\overset{\|}{C}}{-}NH(CH_2)_2NH{-}\overset{S}{\overset{\|}{C}}{-}NHNH_2 \xrightarrow[\text{heat}]{\text{dimethyl sulfoxide,}} \left(=NNH\underset{\underset{S}{}}{\underset{\|}{C}}NH(CH_2)_2NH\underset{\underset{S}{}}{\underset{\|}{C}}NHN{=}CH(CH_2)_xCH{=}\right)_n}$$

semicarbazones may, like copper oxinate, be effective only in the form of copper complexes. On the other hand, the solubility of fungistatic compounds and their rate of permeation through the microorganism cell wall (9) are likely to be important considerations. Such factors may be affected by the change in size and geometry of some dithiosemicarbazones which occurs on copper complex formation, e.g. in changing from structure IV to structure VII.

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