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STUDIES IN FUNGITOXICITY. V.*—Fungicidal Activity of Certain Dithiocarbamates

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Forty-nine derivatives of dimethyldithiocarbamic acid: dimethyldithiocarbamoylamides, *N*-(dimethyldithiocarbamoylalkyl)-amides, -acid esters and -ethers and related compounds were synthesised and tested for fungitoxicity. Of the amides, only those compounds that readily split off the dimethyldithiocarbamate ion, detected by a brown colour with copper acetate, had high activity against *Venturia inaequalis*. Of six ethylenebis-*S*-alkanamidoalkyl dithiocarbamates, all of which readily yielded the ethylenebisdithiocarbamate ion, only those with a trichloromethyl substituent had high activity. Of the other new condensation products of *N*-(1,2,2,2-tetrachloroethyl)amides with various nucleophiles, only the 8-oxinate was highly active

Introduction

Davies & Sexton¹ found *S*-methyl dimethyldithiocarbamate to have low fungicidal activity. Klöpping & van der Kerk² confirmed this finding and tentatively suggested that 'the dimethyldithiocarbamate (i.e. dimethylthiocarbamoylthio) group is highly toxic only if present in the ionic state or, alternatively, in such a structural form that ion formation, for example by means of an oxidation-reduction system of the cell, can be brought about.' Ludwig & Thorn,³ in their review on dithiocarbamate fungicides, regard this suggestion with caution, since certain other esters, e.g. the allyl ester, are highly active.¹

In order to test van der Kerk's suggestion several new derivatives of dimethyldithiocarbamic acid have been prepared, from which the dimethyldithiocarbamate radical would be expected to split off more or less readily. Correlation was sought between fungicidal activity and the ease with which the dimethyldithiocarbamate radical was liberated. For this purpose we synthesised and tested variously substituted dimethyldithiocarbamoylamides (I), dimethyldithiocarbamoylmethyl derivatives (II, III, V), *N*-(dimethyldithiocarbamoylmethyl)- (IV) and *N*-(1-dimethyldithiocarbamoyl-

2,2,2-trichloroethyl)- (VI) amides, (dimethyldithiocarbamoyl)-methyl esters (VII), ethers (VIII, IX), ethylenebis-[*S*-alkanamidoalkyl]dithiocarbamates (X) and other related compounds (XI).

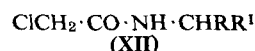
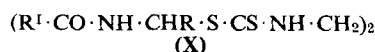
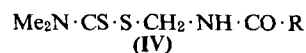
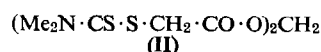
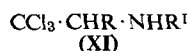
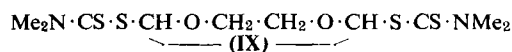
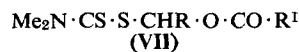
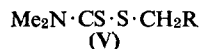
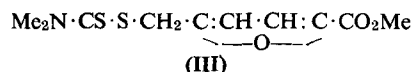
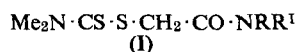
Preparative methods

Chlorocarboxamides, chloro-ethers, chloromethylheterocycles, chloromethyl-*N*-(1,2,2,2-tetrachloroethyl)amides and chloromethyl and substituted chloromethyl acid esters were prepared and condensed with sodium dimethyldithiocarbamate and sometimes with disodium ethylenebisdithiocarbamate and other nucleophiles.

Chlorocarboxamides

N-Methylchloroacetamide,⁴ *NN*-dimethylchloroacetamide⁴ and *N*-isopropylchloroacetamide were prepared by the method of Weaver & Whaley⁵ by adding chloroacetyl chloride (1 mole), in ethylene dichloride, to the appropriate amine (2 moles) in ethylene dichloride, at -10° with stirring. *N*-Isopropylchloroacetamide was obtained as white crystals (from xylene), m.p. $58.5-60.5^{\circ}$ (lit.,⁶ m.p. 42°) (Found: C, 43.7; H, 7.9; Cl, 27.0; N, 10.0. Calc. for $C_5H_{10}ClNO$ C, 44.3; H, 7.4; Cl, 26.2; N, 10.3%).

* Part IV: *J. Sci. Fd Agric.*, 1963, **14**, 55



N-Methoxymethylchloroacetamide

N-Hydroxymethylchloroacetamide⁷ (10 g), dissolved in a mixture of methanol (60 ml) and conc. hydrochloric acid (2 ml), was set aside for 18 h at room temperature, neutralised with sodium bicarbonate (8.6 g), filtered and the oil distilled. The compound (XII; R = H, R¹ = OMe) was obtained (4.1 g; 36.8%) as a colourless oil, b.p. 108°/6 mm, n_D^{24} 1.4738 (Found: Cl, 26.2. C₄H₈ClNO₂ requires Cl, 25.8%). It solidified to deliquescent, thick, long white needles (from propan-2-ol), m.p. 30–30.5°.

N-Ethanethiomethylchloroacetamide

N-Hydroxymethylchloroacetamide (37 g), ethanethiol (21 g), conc. hydrochloric acid (5 ml) and ether (500 ml) were shaken occasionally for 4 days at room temperature. The ether layer was separated, dried (sodium sulphate) and the ether evaporated off. The compound (XII; R = H, R¹ = SEt), obtained (50.2 g; 67%) as a white solid, m.p. 46–57° (from di-isopropyl ether), was used for further condensation.

Chloroethers

2,3-Dichloro-1,4-dioxan was prepared by the method of Kucera & Carpenter.⁸ *sym*-Dichlorodimethyl ether and *sym*-dichlorodimethyl sulphide were of commercial grade.

Chloromethyl heterocycles

Methyl 5-chloromethyl-2-furoate⁹ and 3-(chloromethyl)-benzoxazolone¹⁰ were prepared by known methods.

N-Chloromethyl- and N-(1,2,2,2-tetrachloroethyl)-amides were prepared by the chlorination of crude N-hydroxymethyl- and N-(1-hydroxy-2,2,2-trichloroethyl)-amides.

N-Hydroxymethyl p-chlorobenzamide (crude)

p-Chlorobenzamide (5.8 g), in 50% aqueous ethanol (20 ml), potassium carbonate (0.2 g) and 4.5 ml of aqueous formaldehyde (37.5% w/v) were gently warmed for 30 min. The compound crystallised out on cooling. It was obtained (5.6 g) as white crystals, m.p. 137–138.5°.

N-(1-Hydroxy-2,2,2-trichloroethyl)chloroacetamide (crude)

Anhydrous chloral (1 mole) was added to a stirred boiling solution of chloroacetamide (1 mole) in chloroform (250 ml). After the addition the reaction mixture was heated under reflux for 3 h. The compound (XII; R = CCl₃, R¹ = OH) crystallised out on cooling. It was obtained (94%) as white crystals, m.p. 139–140°.

N-(1-Hydroxy-2,2,2-trichloroethyl)crotonamide (crude)

This compound (XI; R = OH; R¹ = CO·CH:CH·CH₃)

was prepared similarly from anhydrous chloral and crotonamide in 92% yield, m.p. 156°.

N-(1-Hydroxy-2,2,2-trichloroethyl)-2-furoamide (crude)

The preparation followed the method of Diels & Seib.¹¹ α-Furoamide (1 mole), anhydrous chloral (3 moles) and fuming hydrochloric acid (16 ml) were heated for 2 h (steam bath). The compound (XI; R = OH, R¹ = 2-furoyl) crystallised out on cooling. It was obtained (96%) as white crystals, m.p. 152°.

n-Dodecyl N-(1-hydroxy-2,2,2-trichloroethyl) carbamate (crude)

n-Dodecyl carbamate (1 mole) and anhydrous chloral (1 mole) were heated for 3 h on a steam bath. The product was crystallised from petroleum.* The compound (XI; R = OH, R¹ = CO₂·C₁₂H_{25-n}) was obtained (73%) as white glistening plates, m.p. 58–60° (from petroleum).

N-Chloromethyl- and N-(1,2,2,2-tetrachloroethyl)-amides

The chlorination of the hydroxy-compounds was carried out with thionyl chloride by one of three methods. Method (I) involved heating under reflux the hydroxy-compound and thionyl chloride (10 equivalents) until the evolution of gases ceased, removing the excess thionyl chloride under reduced pressure and recrystallising the solid residue. Method (II) involved heating under reflux, with stirring, the hydroxy-compound and thionyl chloride (1.1 equivalent), adding petroleum to the well-stirred hot reaction mixture after the evolution of gases had ceased and filtering off the solid that crystallised out. In Method (III) the hydroxy-compound was treated with thionyl chloride (1.1 equivalent) at 20° and the excess of thionyl chloride removed with gentle warming under reduced pressure after the reaction had subsided.

The compounds thus obtained (Table I) were, with the exception of the two before the last one, white crystalline solids.

With the exception of N-(1,2,2,2-tetrachloroethyl)propionamide and ethyl N-(1,2,2,2-tetrachloroethyl)carbamate, these compounds were not purified for analyses and were freshly prepared when required.

Chloromethyl and substituted chloromethyl acid esters

These compounds were used in the crude state for further condensations. The chloromethyl esters were prepared by known methods²¹ the following being new: *chloromethyl*

* Unless otherwise stated petroleum refers to the fraction b.p. 60–80°

TABLE I

Chloromethylamides $\text{ClCHR}\cdot\text{NH}\cdot\text{CO}\cdot\text{R}^1$ obtained by chlorination of *N*-hydroxymethylamides

Name of chloro-compound	R	R ¹	Obtained from	Method	M.p., °C	Solvent for crystallisation	Yield, %
<i>N</i> -(Chloromethyl)chloroacetamide ¹²	H	CH ₂ Cl	<i>N</i> -Hydroxymethylchloroacetamide	III	44-45*	Not recrystallised	97
<i>N</i> -(Chloromethyl)benzamide ^{12, **}	H	Ph	<i>N</i> -Hydroxymethylbenzamide ⁷	III	87-88	Not recrystallised	
<i>N</i> -(Chloromethyl)- <i>p</i> -chlorobenzamide	H	<i>p</i> -ClC ₆ H ₄	<i>N</i> -Hydroxymethyl <i>p</i> -chlorobenzamide	III	Solid	Not recrystallised	
<i>N</i> -(1,2,2,2-Tetrachloroethyl)formamide ^{13***}	CCl ₃	H	<i>N</i> -(1-Hydroxy-2,2,2-trichloroethyl) formamide ¹⁴	II	95-97***	Petroleum	93
<i>N</i> -(1,2,2,2-Tetrachloroethyl)acetamide ^{15***}	CCl ₃	Me	<i>N</i> -(1-Hydroxy-2,2,2-trichloroethyl) acetamide ¹⁶	II	130-132†	Ligroin	97
<i>N</i> -(1,2,2,2-Tetrachloroethyl)propionamide	CCl ₃	Et	<i>N</i> -(1-Hydroxy-2,2,2-trichloroethyl) propionamide ¹⁶	I	98-99††	Petroleum	73
<i>N</i> -(1,2,2,2-Tetrachloroethyl)isobutyramide	CCl ₃	Pr ¹	<i>N</i> -(1-Hydroxy-2,2,2-trichloroethyl)isobutyramide ¹⁷	I	139-140	Benzene	75
<i>N</i> -(1,2,2,2-Tetrachloroethyl)chloroacetamide	CCl ₃	CH ₂ Cl	<i>N</i> -(1-Hydroxy-2,2,2-trichloroethyl)chloroacetamide	II	74-75	Petroleum	78
<i>N</i> -(1,2,2,2-Tetrachloroethyl)acrylamide	CCl ₃	CH : CH ₂	<i>N</i> -(1-Hydroxy-2,2,2-trichloroethyl) acrylamide ¹⁸	II	118-122	Ligroin	47
<i>N</i> -(1,2,2,2-Tetrachloroethyl)crotonamide	CCl ₃	CH : CH : CH ₃	<i>N</i> -(1-Hydroxy-2,2,2-trichloroethyl) crotonamide	II	138-139	Ligroin	93
<i>N</i> -(1,2,2,2-Tetrachloroethyl)benzamide ¹⁸	CCl ₃	Ph	<i>N</i> -(1-Hydroxy-2,2,2-trichloroethyl) benzamide ¹⁹	I	125††††	Ligroin	78
<i>N</i> -(1,2,2,2-Tetrachloroethyl) α -furoamide	CCl ₃	α -Furyl	<i>N</i> -(1-Hydroxy-2,2,2-trichloroethyl) α -furoamide	I	95	Ligroin	71
Methyl <i>N</i> -(1,2,2,2-Tetrachloroethyl)carbamate	CCl ₃	OMe	Methyl <i>N</i> -(1-hydroxy-2,2,2-trichloroethyl)carbamate ¹⁴	I	90-91	Petroleum	70
Ethyl <i>N</i> -(1,2,2,2-tetrachloroethyl)carbamate	CCl ₃	OEt	Ethyl <i>N</i> -(1-hydroxy-2,2,2-trichloroethyl)carbamate ¹¹ (compound No. 56)	I	62.5-63†††	Petroleum, b.p. 40-60°	65
<i>n</i> -Butyl <i>N</i> -(1,2,2,2-tetrachloroethyl)carbamate	CCl ₃	OBu ⁿ	<i>n</i> -Butyl <i>N</i> -(1-hydroxy-2,2,2-trichloroethyl)carbamate ²⁰	I	44-45	Petroleum, b.p. 40-60°	82
<i>n</i> -Hexyl <i>N</i> -(1,2,2,2-tetrachloroethyl)carbamate	CCl ₃	O·C ₆ H ₁₃	<i>n</i> -Hexyl <i>N</i> -(1-hydroxy-2,2,2-trichloroethyl)carbamate ²⁰	I	—	Not purified	92
<i>n</i> -Dodecyl <i>N</i> -(1,2,2,2-tetrachloroethyl)carbamate	CCl ₃	O·C ₁₂ H ₂₅ ⁿ	<i>n</i> -Dodecyl <i>N</i> -(1-hydroxy-2,2,2-trichloroethyl)carbamate	I	—	Not purified	
2-Chloroethyl <i>N</i> -(1,2,2,2-tetrachloroethyl)carbamate	CCl ₃	O·CH ₂ ·CH ₂ Cl	2-Chloroethyl <i>N</i> -(1-hydroxy-2,2,2-trichloroethyl)carbamate ²⁰	I	56-58	Petroleum	60

* Böhme *et al.*¹² reported this compound as an undistillable oil** The workers quoted in references^{12,13} used phosphorus pentachloride as the chlorinating agent*** Feist¹³ reported m.p. 94-95°† Meldrum & Vad¹⁵ used dry chlorine for chlorination and reported m.p. 128°†† Found: Cl, 59.6. C₅H₇Cl₄NO requires Cl, 59.0%††† Found: Cl, 55.6. C₅H₇Cl₄NO₂ requires Cl, 55.7%†††† Böhme *et al.*¹⁸ reported m.p. 121-122°

esters of lauric, acrylic, crotonic, cinnamic and *p*-nitrobenzoic acid. By the same method²¹ also 1-chloro-1-(3-nitrophenyl)methyl acetate was prepared from acetyl chloride, *m*-nitrobenzaldehyde and zinc chloride.

Condensations of chloro-compounds with nucleophiles

(1) Condensations with sodium dimethyldithiocarbamate

The sodium dimethyldithiocarbamate used contained 2½ moles of water of crystallisation. The condensations were carried out by one of three methods. Method Ia involved heating for 1.5 h under reflux a solution of the chloro-compound (0.05 mole) and sodium dimethyldithiocarbamate (0.05 mole) in acetone (50-100 ml), filtering the mixture, concentrating the filtrate, filtering off the crystallised solid and recrystallising it from a suitable solvent. Method Ib was similar to Method Ia, but the reaction mixture was not heated; it was set aside at room temperature for 19 h. Method II involved the rapid addition of a solution of the chloro-compound (0.05 mole) in acetone (100 ml) to a well-stirred solution of sodium dimethyldithiocarbamate (0.05 mole) in water (40 ml), filtering off the solid after 2 h and recrystallising it. Method IIIa involved the addition of a solution of sodium dimethyldithiocarbamate (0.05 mole) in water (10 ml) to a well-stirred solution of the chloro-compound (0.05 mole) in acetone (20 ml) at -60°, evaporating the reaction mixture to dryness under reduced pressure, triturating the residual solid with water and recrystallising it. Method IIb was similar to Method IIIa, but the reaction mixture instead of being evaporated to dryness, was filtered, the acetone was removed from the filtrate under reduced pressure, the residue was extracted with chloroform, the chloroform extract was washed with water, dried (sodium sulphate) and concentrated, and the solid that crystallised out was filtered off and recrystallised. Method IIIc comprised the addition of an aqueous solution of sodium dimethyldithiocarbamate to a well-stirred solution of the crude chloromethyl ester in acetone at -60° (as for Method IIIa), stirring the reaction mixture at room temperature for 1½ h, filtering off the precipitate where formed (this

was Compound No. 47, which arose from a condensation of sodium dimethyldithiocarbamate with *sym*-dichlorodimethyl ether, a contaminant of the crude chloromethyl acid esters), removing the acetone from the filtrate under reduced pressure, diluting the residue with water, extracting with chloroform, drying (sodium sulphate), removing the chloroform and distilling the residue or recrystallising it from a suitable solvent. Method IV involved heating for 1 h under reflux a solution of the chloro-compound (0.05 mole) and sodium dimethyldithiocarbamate (0.05 mole) in acetone (115 ml), filtering the reaction mixture, evaporating the filtrate to dryness under reduced pressure, extracting the residue with chloroform, drying the chloroform extract (calcium chloride), evaporating off the solvent under reduced pressure and recrystallising the residual solid or distilling the oil. Tables II-V list the compounds, the methods of preparation and their physical characteristics.

Methylenebis(dimethyldithiocarbamoylacetate) (Compound No. 8)

Descudé²⁵ observed that when an acid chloride was heated with paraformaldehyde in the presence of zinc chloride, in addition to the chloromethyl ester, the methylene di(acrylate) was also formed. Crude chloromethyl chloroacetate would thus be expected to contain methylenedi(chloroacetate).

To a solution of crude chloromethyl chloroacetate (from 11.3 g of chloroacetyl chloride) in acetone, cooled to -60°, a solution of sodium dimethyldithiocarbamate (18.8 g) in water (80 ml) was added with vigorous stirring. The cooling bath was removed after 10 min., the reaction mixture was diluted with water and stirred at room temperature for 35 min. The solid that precipitated (3.4 g) was filtered off (*NN*-dimethyldithiocarbamoylacetamide). The filtrate was concentrated under reduced pressure. The solid that crystallised out was filtered off and crystallised twice from benzene, then chloroform. The compound (II) was obtained (2.25 g) as white plates, m.p. 153° (Found: N, 7.7. C₁₁H₁₈N₂O₄S₄ requires N, 7.6%).

TABLE II
Dimethyldithiocarbamoylcarboxamides, $\text{Me}_2\text{N} \cdot \text{CS} \cdot \text{S} \cdot \text{CH}_2 \cdot \text{CO} \cdot \text{NRR}^1$, prepared from the appropriate *N*-substituted acetamide and sodium dimethyldithiocarbamate

No. of compound	Method	Derivative obtained	R	R ¹	M.p., °C	Yield, %	Appearance	Formula	Nitrogen, % Found	% Required
1	Ia	Dimethyldithiocarbamoylacetamide ^a	H	H	126–128	98.5	White needles	$\text{C}_5\text{H}_{10}\text{N}_2\text{OS}_2$	15.7	15.7
2	Ia	Dimethyldithiocarbamoyl- <i>N</i> -methylacetamide ^a	H	Me	118–5*	87	White needles	$\text{C}_6\text{H}_{12}\text{N}_2\text{OS}_2$	14.6	Calc. 14.5
3	Ia	Dimethyldithiocarbamoyl- <i>NN</i> -dimethylacetamide ^{b,c}	Me	Me	70.5–71.5	87	White prisms	$\text{C}_7\text{H}_{14}\text{N}_2\text{OS}_2$	13.6	13.6
4	Ia	Dimethyldithiocarbamoyl- <i>N</i> -isopropylacetamide ^a	H	Pr ^d	125	82	Fluffy white needles	$\text{C}_8\text{H}_{16}\text{N}_2\text{OS}_2$	12.7	12.7
5	Ia	Dimethyldithiocarbamoyl- <i>N</i> -hydroxymethylacetamide ^a	H	CH_2OH	126–127	64.5	Large white needles	$\text{C}_6\text{H}_{12}\text{N}_2\text{O}_2\text{S}_2$	13.3	13.4
6	Ib	Dimethyldithiocarbamoyl- <i>N</i> -(methoxymethyl)-acetamide ^a	H	CH_2OMe	121–122	69	Short white needles	$\text{C}_7\text{H}_{14}\text{N}_2\text{O}_2\text{S}_2$	12.7	12.6
7	Ia	Dimethyldithiocarbamoyl- <i>N</i> -(ethanethiomethyl)-acetamide ^d	H	CH_2SEt	68.5–70	77	Large white needles	$\text{C}_8\text{H}_{16}\text{N}_2\text{OS}_3$	10.7	11.1

(fluoro compounds analogous to the above were described in an earlier paper²³)

Solvents for crystallisation: ^a acetone; ^b carbon tetrachloride–petroleum, b.p. 40–60°; ^c petroleum, b.p. 30–40°; ^d methanol; ^e carbon tetrachloride; ^f propan-2-ol
* Nachmias²² reported m.p. 125°

TABLE III
N-(Dimethyldithiocarbamoylmethyl)carboxamides, $\text{Me}_2\text{N} \cdot \text{CS} \cdot \text{SCH}_2 \cdot \text{NH} \cdot \text{CO} \cdot \text{R}$, prepared from the appropriate amide and sodium dimethyldithiocarbamate

No. of compound	Method	Derivatives obtained	R	M.p., °C	Yield, %	Appearance	Formula	Nitrogen, % Found	% Required
10	IIIb	<i>N</i> -(Dimethyldithiocarbamoylmethyl)fluoroacetamide ²³	CH_2F	89–91	72	White crystals	$\text{C}_6\text{H}_{11}\text{ClN}_2\text{OS}_2$	12.7	12.3
11	IIIa	<i>N</i> -(Dimethyldithiocarbamoylmethyl)chloroacetamide ^{e,f}	CH_2Cl						
12	IIIb	<i>N</i> -(Dimethyldithiocarbamoylmethyl)benzamide ^f	Ph	119–121	29	Fine white crystals	$\text{C}_{11}\text{H}_{14}\text{N}_2\text{OS}_2$	10.8	11.0
13	II	<i>N</i> -(Dimethyldithiocarbamoylmethyl)- <i>p</i> -chlorobenzamide ^d	$\text{C}_6\text{H}_4\text{Cl-p}$	> 220	29	Fine white crystals	$\text{C}_{11}\text{H}_{13}\text{ClN}_2\text{OS}_2$	9.3	9.7
14	Ia**	<i>N</i> -(Dimethyldithiocarbamoylmethyl)dimethyl-dithiocarbamoylacetamide ^a	$\text{CH}_2 \cdot \text{S} \cdot \text{CS} \cdot \text{NMe}_2$	163–164 (decomp.)	52	Thick white needles	$\text{C}_9\text{H}_{17}\text{N}_3\text{OS}_4$	13.7	13.5

(fluoro compounds analogous to the above were described in an earlier paper²³)

Solvents for crystallisation: ^a acetone; ^b carbon tetrachloride–petroleum, b.p. 40–60°; ^c petroleum, b.p. 30–40°; ^d methanol; ^e carbon tetrachloride; ^f propan-2-ol
** Two equivalents of sodium dimethyldithiocarbamate were used † Decomposed on storage

TABLE IV
N-(1-Dimethyldithiocarbamoyl-2,2,2-trichloroethyl)amides $\text{Me}_2\text{N} \cdot \text{CS} \cdot \text{S} \cdot \text{CH}(\text{CCl}_3) \cdot \text{NH} \cdot \text{CO} \cdot \text{R}$ prepared from the appropriate reagent and sodium dimethyldithiocarbamate

No. of compound	Method	Derivative obtained	R	M.p., °C	Yield, %	Appearance	Formula	Analysis, % Found	% Required
17	II	<i>N</i> -(1-Dimethyldithiocarbamoyl-2,2,2-trichloroethyl)formamide ^{a,b}	H	162	91	Short off-white needles	$\text{C}_6\text{H}_9\text{Cl}_3\text{N}_2\text{OS}_2$	Cl, 36.1	Cl, 36.0
18	II	<i>N</i> -(1-Dimethyldithiocarbamoyl-2,2,2-trichloroethyl)acetamide ^{c,d,e}	Me	150–151	82	Fine white needles	$\text{C}_7\text{H}_{11}\text{Cl}_3\text{N}_2\text{OS}_2$	N, 9.3	N, 9.1
19	II	<i>N</i> -(1-Dimethyldithiocarbamoyl-2,2,2-trichloroethyl)propionamide ^d	Et	177–178	82	Glistening short white needles	$\text{C}_8\text{H}_{13}\text{Cl}_3\text{N}_2\text{OS}_2$	N, 9.1	N, 8.7
20	II	<i>N</i> -(1-Dimethyldithiocarbamoyl-2,2,2-trichloroethyl)isobutyramide ^c	Pr ^d	184	87	Short white needles	$\text{C}_9\text{H}_{15}\text{Cl}_3\text{N}_2\text{OS}_2$	Cl, 31.3	Cl, 31.5
21	IIIa	<i>N</i> -(1-Dimethyldithiocarbamoyl-2,2,2-trichloroethyl)fluoroacetamide ²³	CH_2F						
22	IIIa	<i>N</i> -(1-Dimethyldithiocarbamoyl-2,2,2-trichloroethyl)chloroacetamide ^{a,e}	CH_2Cl	152–153	74	Short white needles	$\text{C}_7\text{H}_{10}\text{Cl}_4\text{N}_2\text{OS}_2$	N, 8.3	N, 8.1
23	Ib†	<i>N</i> -(1-Dimethyldithiocarbamoyl-2,2,2-trichloroethyl)thiocyanatoacetamide ^p	$\text{CH}_2 \cdot \text{SCN}$	141–142	40	Short off-white needles	$\text{C}_6\text{H}_9\text{Cl}_3\text{N}_2\text{OS}_3$	Cl, 11.9	Cl, 11.5
24	II	<i>N</i> -(1-Dimethyldithiocarbamoyl-2,2,2-trichloroethyl)acrylamide ^{b,d,i}	$\text{CH} : \text{CH}_2$	143–144	79	White prisms	$\text{C}_8\text{H}_{11}\text{Cl}_3\text{N}_2\text{OS}_2$	N, 8.2	N, 8.7
25	II	<i>N</i> -(1-Dimethyldithiocarbamoyl-2,2,2-trichloroethyl)crotonamide ^{a,m,d}	$\text{CH} : \text{CH} \cdot \text{CH}_3$	160(d.)	65	White plates	$\text{C}_9\text{H}_{13}\text{Cl}_3\text{N}_2\text{OS}_2$	{ Cl, 31.5 N, 8.5	{ Cl, 31.7 N, 8.4
26	II	<i>N</i> -(1-Dimethyldithiocarbamoyl-2,2,2-trichloroethyl)benzamide ^a	C_6H_5	135–136	77	Large white crystals	$\text{C}_{12}\text{H}_{13}\text{Cl}_3\text{N}_2\text{OS}_2$	{ Cl, 27.6 N, 7.2	{ Cl, 28.4 N, 7.5
27	II	<i>N</i> -(1-Dimethyldithiocarbamoyl-2,2,2-trichloroethyl)-2-furoamide ^f	2-Furyl	134–135	59	Small white rhombs	$\text{C}_{10}\text{H}_{11}\text{Cl}_3\text{N}_2\text{O}_2\text{S}_2$	Cl, 30.8	Cl, 30.5
28	IV	Methyl <i>N</i> -(dimethyldithiocarbamoyl-2,2,2-trichloroethyl)carbamate ^g	OMe	155–156	35	Fluffy white plates	$\text{C}_7\text{H}_{11}\text{Cl}_3\text{N}_2\text{O}_2\text{S}_2$	Cl, 32.5	Cl, 32.7
29	II	Ethyl <i>N</i> -(1-dimethyldithiocarbamoyl-2,2,2-trichloroethyl)carbamate ^{a,h,k}	OEt	113.5–115	79	White plates	$\text{C}_8\text{H}_{13}\text{Cl}_3\text{N}_2\text{O}_2\text{S}_2$	N, 8.3	N, 8.3
30	II	<i>n</i> -Butyl <i>N</i> -(1-dimethyldithiocarbamoyl-2,2,2-trichloroethyl)carbamate ^h	OBu ⁿ	90–93	79	Small buff rhombs	$\text{C}_{10}\text{H}_{17}\text{Cl}_3\text{N}_2\text{O}_2\text{S}_2$	Cl, 28.7	Cl, 29.0
31	II	<i>n</i> -Hexyl <i>N</i> -(1-dimethyldithiocarbamoyl-2,2,2-trichloroethyl)carbamate ^{l,d,n}	$\text{O} \cdot \text{C}_6\text{H}_{13-n}$	96–97	43	White plates	$\text{C}_{12}\text{H}_{21}\text{Cl}_3\text{N}_2\text{O}_2\text{S}_2$	{ Cl, 26.5 N, 6.8	{ Cl, 26.9 N, 7.1
32	II	<i>n</i> -Dodecyl <i>N</i> -(1-dimethyldithiocarbamoyl-2,2,2-trichloroethyl)carbamate ^l	$\text{O} \cdot \text{C}_{12}\text{H}_{23-n}$	70–71	66	White plates	$\text{C}_{18}\text{H}_{33}\text{Cl}_3\text{N}_2\text{O}_2\text{S}_2$	Cl, 22.9	Cl, 22.2
33	IV	2-Chloroethyl <i>N</i> -(1-dimethyldithiocarbamoyl-2,2,2-trichloroethyl)carbamate ^h	$\text{O} \cdot \text{C}_2\text{H}_4\text{Cl}$	112–113	24	White plates	$\text{C}_8\text{H}_{12}\text{Cl}_4\text{N}_2\text{O}_2\text{S}_2$	Cl, 37.7	Cl, 38.0
34	Ib	<i>N</i> -(1-dimethyldithiocarbamoyl-2,2,2-trichloroethyl)dimethyldithiocarbamoyl-acetamide ^{††}	$\text{CH}_2 \cdot \text{S} \cdot \text{CS} \cdot \text{NMe}_2$	146	58	Small white rhombs	$\text{C}_{10}\text{H}_{14}\text{Cl}_3\text{N}_3\text{OS}_4$	{ Cl, 24.6 N, 9.5	{ Cl, 24.8 N, 9.8

Solvents for crystallisation: ^a methanol; ^b acetone; ^c benzene; ^d propan-2-ol; ^e toluene; ^f carbon tetrachloride; ^g benzene–petroleum; ^h petroleum; ⁱ diethyl ether; ^j petroleum, b.p. 40–60°; ^k toluene–ligroin; ^l ethanol–ligroin; ^m toluene–propan-2-ol; ⁿ ligroin–propan-2-ol; ^p ethyl acetate; ^q ethanol
† From compound 22 and potassium thiocyanate †† From compound 22

TABLE V
(Dimethyldithiocarbamoylmethyl) esters, $\text{Me}_2\text{N} \cdot \text{CS} \cdot \text{S} \cdot \text{CHR} \cdot \text{O} \cdot \text{CO} \cdot \text{R}^1$
prepared from the appropriate chloroalkyl ester and sodium dimethyldithiocarbamate

No. of compound	Method	Derivative obtained	R	R ¹	M.p. or b.p./mm	Yield, %	Refractive index of oil or appearance of solid	Formula	Nitrogen, % Found Required	
36	IIIc	Dimethyldithiocarbamoylmethyl acetate ^a	H	Me	Not distilled	45	$n_D^{20} 1.5913$	$\text{C}_6\text{H}_{11}\text{NO}_2\text{S}_2$	7.6	7.3
37	IIIc	Dimethyldithiocarbamoylmethyl propionate	H	Et	122/0.02**	26		$\text{C}_7\text{H}_{13}\text{NO}_2\text{S}_2$	6.7	6.8
38	IIIc	Dimethyldithiocarbamoylmethyl <i>n</i> -butyrate	H	Pr ⁿ	119–120/0.02	16	$n_D^{20} 1.5550$	$\text{C}_8\text{H}_{15}\text{NO}_2\text{S}_2$	6.3	6.3
39	IIIc†	Dimethyldithiocarbamoylmethyl laurate ^a	H	$\text{C}_{11}\text{H}_{23}\text{-N}$	45–46	10	Long prisms	$\text{C}_{16}\text{H}_{31}\text{NO}_2\text{S}_2$	4.2	4.2
40	Ia††	Dimethyldithiocarbamoylmethyl <i>p</i> -chlorobenzoate†††	H	$\text{C}_6\text{H}_4\text{Cl-p}$	96–96.5(d.)	62	Long transparent prisms	$\text{C}_{11}\text{H}_{12}\text{ClNO}_2\text{S}_2$	Cl, 12.4	Cl, 12.4
41	Ib	Dimethyldithiocarbamoylmethyl <i>p</i> -nitrobenzoate ^b	H	$\text{C}_6\text{H}_4 \cdot \text{NO}_2\text{-p}$	148	98	White prisms	$\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_4\text{S}_2$	9.0	9.4
42	IIIc††††	Dimethyldithiocarbamoylmethyl acrylate ^c	H	$\text{CH} : \text{CH}_2$	118–125	86	White prisms	$\text{C}_7\text{H}_{11}\text{NO}_2\text{S}_2$	7.3	6.8
43	IIIc††††	Dimethyldithiocarbamoylmethyl crotonate ^d	H	$\text{CH} : \text{CHMe}$	51–52.5	16	Long white prisms	$\text{C}_8\text{H}_{13}\text{NO}_2\text{S}_2$	6.3	6.4
44	Ib	Dimethyldithiocarbamoylmethyl cinnamate ^{e, f}	H	$\text{CH} : \text{CHPh}$	109–110.5	21	White needles	$\text{C}_{13}\text{H}_{15}\text{NO}_2\text{S}_2$	5.0	5.0
45	IIIc††††	1-(Dimethyldithiocarbamoyl)ethyl acetate ^c	Me	Me	75	25	White needles	$\text{C}_7\text{H}_{13}\text{NO}_2\text{S}_2$	6.7	6.6
46	IIIc††††	(Dimethyldithiocarbamoyl)-(3-nitrophenyl)methyl acetate	$\text{C}_6\text{H}_4 \cdot \text{NO}_2\text{-m}$	Me	97–98	79	Yellowish needles	$\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_4\text{S}_2$	8.5	8.9
Dimethyldithiocarbamoylmethyl ethers, $(\text{Me}_2\text{N} \cdot \text{CS} \cdot \text{S} \cdot \text{CH}_2)_2\text{R}$, prepared from the appropriate chloro-ether and sodium dimethyldithiocarbamate										
47	Ia***	sym.-Bis(dimethyldithiocarbamoylmethyl) ether ^g	O	$\text{CH}_2 \cdot \text{S} \cdot \text{CS} \cdot \text{NMe}_2$	114–115	91	White needles	$\text{C}_8\text{H}_{16}\text{N}_2\text{OS}_4$	9.9	9.9
48	Ia***	sym.-Bis(dimethyldithiocarbamoylmethyl) sulphide ^h	S	$\text{CH}_2 \cdot \text{S} \cdot \text{CS} \cdot \text{NMe}_2$	91–91.5	81	Off-white needles	$\text{C}_8\text{H}_{16}\text{N}_2\text{S}_5$	9.2	9.3
49	Ia***	2,3-Bis(dimethyldithiocarbamoyl)-1,4-dioxan ^h	Formula (IX)		185–186	27	White plates	$\text{C}_{10}\text{H}_{18}\text{N}_2\text{O}_2\text{S}_4$	8.7	8.6

Solvents for crystallisation: ^a petroleum, b.p. 40–60°; ^b carbon tetrachloride; ^c ethyl acetate; ^d propan-2-ol; ^e di-isopropyl ether;

^f ethanol; ^g acetone; ^h benzene

* Rossi & Corradini²⁴ prepared the diethyl homologue

** This compound crystallised out. White needles, m.p. 42–43° (from petroleum)

*** One equivalent of the dichloro compound and 2 equivalents of sodium dimethyldithiocarbamate were used

† The compound crystallised out from the chloroform solution

†† The reaction mixture was heated for 10 min., then poured into excess water. The precipitated solid was filtered off and recrystallised from di-isopropyl ether

††† Rossi & Corradini²⁴ prepared dimethyldithiocarbamoylmethyl benzoate

†††† Oil that solidified on standing

Methyl 5-dimethyldithiocarbamoylmethyl-2-furoate (Compound No. 9)

Methyl 5-chloromethyl-2-furoate and sodium dimethyldithiocarbamate were condensed using Method Ib. The compound (III) was obtained (78%) as white needles (from methanol), m.p. 101.5–102.5° (Found: N, 5.4. $\text{C}_{10}\text{H}_{13}\text{NO}_3\text{S}_2$ requires N, 5.4%).

3-(Dimethyldithiocarbamoylmethyl)benzoxazol-2-one (Compound No. 16)

3-Chloromethylbenzoxazol-2-one and sodium dimethyldithiocarbamate were heated under reflux for 7 h in acetone and worked up by Method Ia. The compound (V; R = 3-benzoxazol-2-onyl) was obtained (40%) as white crystals (from benzene), m.p. 162–163° (Found: N, 10.1. $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_2\text{S}_2$ requires N, 10.4%).

N-(1-Dimethyldithiocarbamoyl-2,2,2-trichloroethyl)-ethoxydithioformylacetamide (Compound No. 35)

N-(1-Dimethyldithiocarbamoyl-2,2,2-trichloroethyl)chloroacetamide (6.9 g), in acetone (100 ml), and ethyl potassium xanthate (3.22 g), in water (20 ml), were heated under reflux for 10 min., then set aside for 24 h, at 20°. The acetone was removed from the reaction mixture and the residue extracted with chloroform. The extracts were washed with water, dried (calcium chloride) and concentrated leaving a residual oil. The oil was dissolved in ether (100 ml), from which the solid that crystallised out (2 g) was filtered off. The compound (VI; R = $\text{CH}_2 \cdot \text{S} \cdot \text{CS} \cdot \text{OEt}$) was obtained as white crystals (from propan-2-ol), m.p. 135–136° (Found: Cl, 24.5. $\text{C}_{10}\text{H}_{15}\text{Cl}_3\text{N}_2\text{O}_2\text{S}_4$ requires Cl, 24.8%).

Condensations with disodium ethylenebisdithiocarbamate (Table VI)

The condensations were carried out by one of two methods. Method I involved the addition of disodium ethylenebisdithiocarbamate (0.025 mole; one equivalent), in dimethylformamide (50 ml), to the chloro-compound (0.05 mole; two equivalents), in acetone (50 ml), cooled to –60°, allowing the reaction mixture to warm up to room temperature, filtering, concentrating the filtrate, pouring it into water (200 ml), allowing the gum that precipitated to solidify, triturating it with water, filtering off the solid and drying it in air.

Method II involved the addition of disodium ethylenebisdithiocarbamate (0.0125 mole; one equivalent) in dimethylformamide (50 ml), to the chloro-compound (0.025 mole; two equivalents) in dimethylformamide (30 ml), at room temperature, filtering the reaction mixture after 4 h, pouring the filtrate into water (250 ml), allowing the precipitate to crystallise, filtering off the solid, triturating it with propan-2-ol (80 ml) and drying it in air.

The compounds could not be recrystallised, as decomposition occurred.

Condensations of ethyl N-(1,2,2,2-tetrachloroethyl) carbamate with various nucleophiles (Table VII)

The chloro-compound (1 equivalent) and the nucleophile (1.1 equivalents) were heated under reflux in acetone for 3 h. The reaction mixture was filtered and the filtrate poured into excess water. The compound was filtered off and recrystallised from a suitable solvent.

n-Butyl N-(1-methyldithiocarbamoyl-2,2,2-trichloroethyl)carbamate (Compound No. 62)

This compound was prepared similarly to Compound No.

TABLE VI
Ethylenebis-(S-alkanamidoalkyl)dithiocarbamates, $(R^1 \cdot CO \cdot NH \cdot CHR \cdot S \cdot CS \cdot NH \cdot CH_2)_2$
prepared from the appropriate chloro-alkylamide and disodium ethylenebisdithiocarbamate

No. of compound	Method	Derivative obtained	R	R ¹	M.p., °C	Yield, %	Appearance	Formula	Nitrogen, % Found Required	
50	I	Ethylenebis-[S-1-(N-formamido-2,2,2-trichloroethyl)dithiocarbamate	CCl ₃	H	90*	44	Amorphous greyish solid	C ₁₀ H ₁₂ Cl ₆ N ₄ O ₂ S ₄	10.2	10.0
51	II	Ethylenebis-[S-1-(N-acetamido-2,2,2-trichloroethyl)dithiocarbamate	CCl ₃	Me	195–197(d.)	20	Amorphous white solid	C ₁₂ H ₁₄ Cl ₆ N ₄ O ₂ S ₄	9.5	9.4
52		Ethylenebis-[S-(N-fluoroacetamido)-methyl] dithiocarbamate ²³	H	CH ₂ F						
53		Ethylenebis-[S-1-(N-fluoroacetamido-2,2,2-trichloroethyl)dithiocarbamate ²³	CCl ₃	CH ₂ F						
54	I**	Ethylenebis-[S-(N-chloroacetamido)-methyl]dithiocarbamate	H	CH ₂ Cl	129(d.)	60	White plates	C ₁₀ H ₁₂ Cl ₂ N ₄ O ₂ S ₄	13.3	13.2
55	II	Ethylenebis-[S-1-(N-chloroacetamido-2,2,2-trichloroethyl)dithiocarbamate	CCl ₃	CH ₂ Cl	175–177(d.)	35	Amorphous white solid	C ₁₂ H ₁₄ Cl ₂ N ₄ O ₂ S ₄	8.7	8.5

* Softens at 50°

** Triturated with water, then with ethanol

TABLE VII
Miscellaneous compounds, CCl₃·CHR·NHR¹ prepared from nucleophilic reagent named and ethyl N-(1,2,2,2-tetrachloroethyl)carbamate

No. of compound	Reagent	Derivative obtained	R	R ¹	M.p., °C	Yield, %	Appearance	Formula	Analysis, % Found Required	
57	Sodium thiophenate	Ethyl N-(1-thiophenyl-2,2,2-trichloroethyl)carbamate ^a	SPh	CO ₂ Et	94–95	73	White crystals	C ₁₁ H ₁₂ Cl ₃ NO ₂ S	Cl, 32.1	Cl, 32.6
58	Potassium phthalimide	Ethyl N-(1-phthalimido-2,2,2-trichloroethyl) carbamate ^b	N·CO·C ₆ H ₄ ·CO	CO ₂ Et	162–163	38	White crystals	C ₁₃ H ₁₁ Cl ₃ N ₂ O ₄	N, 7.6	N, 7.6
59	Potassium cyanide	Ethyl N-(1-cyano-2,2,2-trichloroethyl)carbamate ^a	CN	CO ₂ Et	103.5–104	30	White crystals	C ₆ H ₇ Cl ₃ N ₂ O ₂	Cl, 43.1	Cl, 43.4
60	Ethyl potassium xanthate	Ethyl N-(1-ethoxydithioformyl-2,2,2-trichloroethyl)-carbamate ^{a,c}	S·CS·OEt	CO ₂ Et	78–78.5	38	Short thick needles	C ₈ H ₁₂ Cl ₃ NO ₂ S ₃	{ Cl, 31.2 N, 4.0 }	{ Cl, 31.3 N, 4.1 }
61	Sodium methylthio-carbamate	Ethyl N-(1-methylthio-carbamoyl-2,2,2-trichloroethyl)carbamate ^{d,e,f}	S·CS·NHMe	CO ₂ Et	142–143.5	47	White rhombs	C ₇ H ₁₁ Cl ₃ N ₂ O ₂ S ₂	N, 8.8	N, 8.6
63	Sodium diethylthio-carbamate**	Ethyl N-(1-diethylthio-carbamoyl-2,2,2-trichloroethyl)carbamate ^c	S·CS·NEt ₂	CO ₂ Et	94–95	43	White rhombs	C ₁₀ H ₁₇ Cl ₃ N ₂ O ₂ S ₂	Cl, 28.9	Cl, 28.9

* Reaction mixture was poured into water and extracted with ether; the ether extract was dried; on removal of the ether a solid remained that was crystallised from benzene-petroleum

** Sodium diethylthiocarbamate, in water, was added to the chloro-compound, in acetone, with stirring at –60°; stirring was maintained then for 2 h, the reaction mixture diluted with water and the solid filtered off and recrystallised

Solvents for crystallisation: ^a petroleum; ^b acetone; ^c benzene–petroleum; ^d benzene; ^e toluene; ^f propan-2-ol–ligroin

61 but using n-butyl N-(1,2,2,2-tetrachloroethyl)carbamate. The compound (XI; R = S·CS·NHMe, R¹ = CO₂Buⁿ) was obtained (28%) as fine white needles (from benzene–petroleum, then ligroin–toluene, then aqueous propan-2-ol), m.p. 140–140.5° (Found: Cl, 29.6. C₉H₁₅Cl₃N₂O₂S₂ requires Cl, 30.1%).

N-[1-(8-Oxyquinoline)-2,2,2-trichloroethyl]formamide (Compound No. 64)

To 8-hydroxyquinoline (77.7 g) and N-(1,2,2,2-tetrachloroethyl)formamide (113 g), in acetone (400 ml), was added rapidly an aqueous solution of 23 g of sodium hydroxide. The mixture was stirred vigorously for 2 h and the precipitated solid was filtered off, washed well with water and dried *in vacuo* (77.5 g). The compound (XI; R = 8-oxyquinolyl, R¹ = CHO) was obtained as buff prisms, m.p. 168° (decomp.) (Found: Cl, 33.7. C₁₂H₉Cl₃N₂O₂ requires Cl, 33.4%).

Experimental and results

Detection of dimethyldithiocarbamate and ethylenebisdithiocarbamate ions

The compound (~0.01 g) was dissolved in boiling 95% aqueous ethanol (5 ml). To the solution cooled to ~40° was added a solution of copper acetate in 95% aqueous ethanol (~1 ml). A change in colour to brown indicated the presence

of the dimethyldithiocarbamate or ethylenebisdithiocarbamate ion (designated in Tables 'at ~40°'). Where no brown colour appeared at ~40°, the test solution was brought to boil and kept at boiling point for 6 sec (designated in Tables 'boiling'). Absence of a brown colour is recorded by a – sign, presence by a + sign.

Detection of dimethyldithiocarbamate ion in the presence of acid

None of the dimethyldithiocarbamoylmethyl esters (VII) that were available for the copper acetate test gave a positive test by the above techniques. It was thought that the acid that would be expected to result from the hydrolysis of such an ester may suppress the formation of the brown copper dimethyldithiocarbamate. Therefore the following tests were carried out: cinnamic acid, expected to result from the hydrolysis of dimethyldithiocarbamoylmethyl cinnamate (Compound No. 44) was added (a) in excess, (b) in an equivalent proportion, to sodium dimethyldithiocarbamate, in 95% aqueous ethanol, and then copper acetate, in 95% aqueous ethanol, was added. Where cinnamic acid was (a) in excess, no brown colour was obtained; (b) in an equivalent proportion, a brown colour was obtained.

Fungitoxicity tests

All the tests were carried out by the Montgomery–Moore²⁶ slide germination technique, and the values of LD₉₅ were

determined against *Venturia inaequalis* (Cooke) Wint.; *Botrytis cinerea* Pers.; *Fusarium bulbigenum*, Cooke & Massee, var. *lycopersici* (Brushii) Wollenw. and *Cercospora melonis* Cooke as described in Part I.²⁷ Instead of methanol solutions acetone solutions of the test compounds were used. Tables VIII–XV show the results of fungitoxicity tests with 59 dithiocarbamate derivatives and with five compounds of related interest.

Discussion

The activity of the compounds depended on the presence in the molecule of a fungitoxiphore (dithiocarbamate, 8-hydroxyquinolyl). The compounds were generally more active against *Venturia* and activity against *Botrytis*, *Fusarium* and *Cercospora* was always linked with activity against *Venturia*.

Van der Kerk and his collaborators²⁹ found that the growth-active compound dimethyldithiocarbamoylacetic acid was non-fungicidal *in vitro* and fungicidal *in vivo*. They assumed that the compound was metabolised in plants to dimethyldithiocarbamate ions which were responsible for the activity; the carboxymethyl group was considered to act as a carrier for the dimethyldithiocarbamate ions. The formation of conjugates of dialkyldithiocarbamic acid *in vivo* was shown by Dekhuijzen³⁰ and others: 1-(dimethyldithiocarbamoyl)- β -glucoside³¹ and β -(dimethyldithiocarbamoyl)alanine³² were isolated from plants, γ -(dimethyldithiocarbamoyl)- α -aminobutyric acid³³ from micro-organisms treated with sodium dimethyldithiocarbamate and 1-(1-diethyldithiocarbamoyl)- β -D-glucopyranosiduronic acid³⁴ from the urine of man treated with 'Antabuse' (tetraethylthiuram disulphide).

The dimethyldithiocarbamoylcarboxamides (Compounds Nos. 1–7), amides of dimethyldithiocarbamoylacetic acid found inactive *in vitro* by van der Kerk,²⁹ were fungicidally inactive or had low fungicidal activity *in vitro*, and did not yield dimethyldithiocarbamate ions in the presence of copper acetate. Compounds Nos. 8 and 9 behaved similarly, as would be expected from the similar attachment of the dimethyldithiocarbamoyl group to the α -carbon atom. The *in vitro* activity against *Venturia* was found to depend on the ability of the compound to yield dimethyldithiocarbamate ions. Thus, *N*-(dimethyldithiocarbamoylmethyl)amides (Table IX) and *N*-(1-dimethyldithiocarbamoyl-2,2,2-trichloroethyl)amides (Table XI) were highly active against *Venturia* (some of them were also active against the other fungi). These compounds readily split off the dithiocarbamate ion in the presence of copper acetate and may undergo hydrolysis possibly by a mechanism similar to that discussed by Pianka & Polton²³ for the hydrolysis of *N*-methylenefluoroacetamides to fluoroacetamide (in which greater stability to hydrolysis was paralleled by lower insecticidal activity).

The electron influence of the phenyl ring in Compounds Nos. 15 and 16, having the effect of reducing the electron density on the sulphur atom of CHR^1S , may bring about resistance to hydrolysis to dimethyldithiocarbamate ions and a lowering in fungicidal activity.

Rossi & Corradini²⁴ observed the fungicidal activity of alkylthioformylmethyl acetates, methyl-, ethyl- and dimethyl- and diethyl-dithiocarbamoylmethyl acetates and benzoates. Of our dimethyldithiocarbamoylmethyl esters (Table XII), only those derived from aliphatic acids (Compounds Nos. 36–39, 42, 43, 45, 46) showed high activity. Dimethyl-dithiocarbamoylmethyl acetate (Compound No. 36), propionate (No. 37) and butyrate (No. 38) were highly active against *Venturia* and active against *Botrytis*. The acetate and the *n*-butyrate were also active against *Cercospora*, and the *n*-butyrate against *Fusarium*. The laurate (Compound No. 39) had lower activity against *Venturia*, probably because of its higher molecular weight. Unsaturation, as in the acrylate (Compound No. 42) and crotonate (No. 43), did not enhance activity, whereas substitution by a methyl- (Compound No. 45) or *m*-nitrophenyl-group (No. 46) gave bimodal dosage-response curves for *Venturia*. Dimethyldithiocarbamoylmethyl esters derived from aromatic acids (Compounds Nos. 40, 41, 44) showed low activity irrespective of the nature of the nuclear substituent. The failure to detect the dithiocarbamate ion in these esters may be due to either (a) interference of the acid radical, resulting from the hydrolysis of the ester, with the copper acetate test, or (b) the strength of the ester bond. The mechanism outlined for the amides would not be expected to operate to the same degree with the esters. Generally the chloromethyl esters show much higher thermal and hydrolytic stability than the *N*-chloromethyl-amides. Whereas dimethyldithiocarbamoylmethyl *p*-chlorobenzoate (Compound No. 40) gave a negative copper acetate test and was inactive, its amide analogue (Compound No. 13) gave a positive copper acetate test and was highly active against *Venturia*, as were the other benzamide derivatives (Compounds Nos. 12 and 26). If, then, it is assumed that failure to detect the dithiocarbamate ion in the esters is due to resistance to hydrolysis, and that the dithiocarbamate ion is responsible for the fungicidal activity, it would also be necessary to assume that the hydrolysis of the ester bond in the dimethyldithiocarbamoylmethyl derivatives of aliphatic acids is due to enzyme activity in the fungal spores. Enzyme activity does not extend, however, to the hydrolysis of the α -carbon-sulphur bond in the dimethyldithiocarbamoylmethyl derivatives of aromatic acids, the dimethyldithiocarbamoylcarboxamides and ester (II) (Table VIII), ethers (Compounds Nos. 47–49) and the dimethyldithiocarbamoylmethyl heterocycles (Compounds Nos. 9, 15, 16).

All the ethylenebisdithiocarbamate derivatives (Table XIV) liberated the ethylenebisdithiocarbamate ion. However, those without the CCl_3 -group had low activities (Compounds Nos. 52 and 54). Substitution with a CCl_3 -group rendered these compounds highly active (Nos. 53 and 55, also Nos. 50 and 51), possibly because of their greater lipid solubility and ability to penetrate through the cuticle of the spores.

Certain dimethyldithiocarbamate derivatives exhibited bimodal dosage-response curves against *Venturia* (Compounds Nos. 22, 26, 27, 29, 30, 33, 38, 42, 45, 46). These were first observed by Dimond *et al.* for tetramethylthiuram disulphide.³⁵ Contrary to observations of polymodal curves for nabam³⁶ and zineb³⁷ no such evidence was found in corresponding ethylenebisdithiocarbamate derivatives.

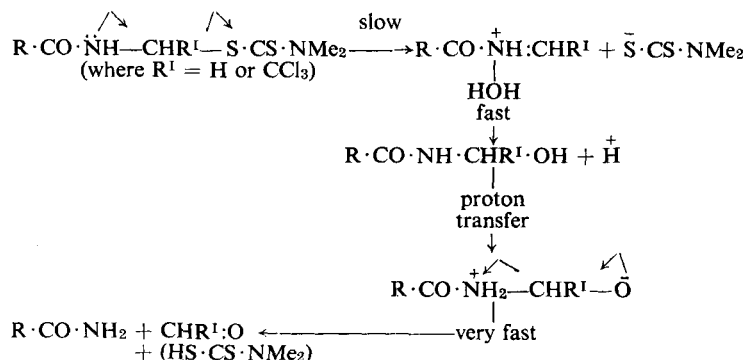


TABLE VIII
Results of copper acetate and fungitoxicity tests with
(dimethyldithiocarbamoyl)carboxamides (I) and esters (II) and (III)

No. of compound	Formula	R	R ^I	Test with copper acetate		Venturia	Botrytis	Fusarium	Cercospora
				at ~40°	boiling				
LD ₉₅ values, ppm									
1	I	H	H	—	—	> 100	> 1000	> 1000	> 1000
2	I	H	Me	—	—	> 100	> 1000	> 1000	> 1000
3	I	Me	Me	—	—	> 100	> 1000	> 1000	> 1000
4	I	H	Pr ^I	—	—	> 1000	> 1000	> 1000	> 1000
5	I	H	CH ₂ ·OH	—	—	> 1000	> 1000	> 1000	> 1000
6	I	H	CH ₂ ·OMe	—	—	> 100	> 1000	> 1000	> 1000
7	I	H	EtS·CH ₂	—	—	> 1000	> 1000	> 1000	> 1000
8	II			—	—	> 1000	> 1000	> 1000	> 1000
9	III			—	—	> 1000	> 1000	> 1000	> 1000

TABLE IX
Results of copper acetate and fungitoxicity tests with *N*-(dimethyldithiocarbamoylmethyl) carboxamides (IV)

No. of compound	R	Test with copper acetate at ~40°	Venturia	Botrytis	Fusarium	Cercospora
			LD ₉₅ values, ppm			
10	Fluoromethyl	+	2	> 1000	> 1000	> 100
11	Chloromethyl	+	2	> 100	> 1000	> 100
12	Phenyl	+	8	> 100	> 1000	> 100
13	<i>p</i> -Chlorophenyl	+	15	> 1000	> 1000	> 1000
14	Dimethyldithiocarbamoylmethyl	+	3	> 1000	> 1000	> 1000

TABLE X
Results of copper acetate and fungitoxicity tests with various
N-(dimethyldithiocarbamoylmethyl)-heterocycles (V)

No. of compound	R	Test with copper acetate		Venturia	Botrytis	Fusarium	Cercospora
		at ~40°	boiling				
15	Phthalimido*	—	—	> 100	> 1000	> 1000	> 1000
16	3-(Benzoxazol-2-onyl)	—	—	> 1000	> 1000	> 1000	> 1000

* This compound was prepared by the method of Chien-Pen Lo²⁸

TABLE XI
Results of copper acetate and fungitoxicity tests
with *N*-(1-dimethyldithiocarbamoyl-2,2,2-trichloroethyl)amides (VI)

No. of compound	R	Test with copper acetate at ~40°	Venturia	Botrytis	Fusarium	Cercospora
			LD ₉₅ values, ppm			
17	H	+	2	> 100	> 1000	> 100
18	Methyl	+	3	> 100	> 100	> 100
19	Ethyl	+	19	> 1000	> 1000	> 1000
20	Isopropyl	+	10	> 1000	> 1000	> 1000
21	Fluoromethyl	+	3	> 1000	> 1000	110
22	Chloromethyl	+	3,10,22	~ 100	~ 100	56
23	Thiocyanatomethyl	+	6	> 100	> 100	> 100
24	Vinyl	+	3	> 1000	> 1000	> 1000
25	Prop-1-enyl	+	3	> 1000	> 1000	> 1000
26	Phenyl	+	9,19,30	> 100	> 100	> 100
27	2-Furyl	+	2,13,30	> 100	> 100	> 100
28	Methoxy	+	6	> 100	> 100	> 100
29	Ethoxy	+	4,9,20	120	43	—
30	n-Butoxy	+	< 2,6,16	46	> 100	56
31	n-Hexyloxy	+	22	> 100	> 100	> 100
32	n-Dodecyloxy	+	3	> 1000	> 1000	> 1000
33	2-Chloroethoxy	+	5,10	> 100	> 100	> 100
34	Dimethyldithiocarbamoylmethyl	+	7	~ 100	> 30	~ 100
35	Ethoxydithioformylmethyl	+	1.5	95	> 100	85

TABLE XII
Results of copper acetate and fungitoxicity tests with
(dimethyldithiocarbamoyl)methyl esters (VII)

No. of compound	R	R ^I	Test with copper acetate at ~40° boiling	Venturia	Botrytis	Fusarium	Cercospora
				LD ₉₅ values, ppm			
36	H	Methyl	Not done*	6	> 50	> 100	> 50
37	H	Ethyl	Not done*	5	~ 100	> 100	> 100
38	H	n-Propyl	Not done*	4,10,45	75	75	55
39	H	n-Undecyl	—	30	> 1000	> 1000	> 1000
40	H	p-Chlorophenyl	—	> 1000	> 1000	> 1000	> 1000
41	H	p-Nitrophenyl	Not done*	> 100	> 100	> 1000	> 1000
42	H	Vinyl	—	7,70,80	> 100	> 100	> 100
43	H	Prop-1-enyl	Not done*	9	~ 100	50	> 100
44	H	Phenylvinyl	—	> 100	> 1000	> 1000	> 1000
45	Methyl	Methyl	Not done*	10,15,100	65	27	> 100
46	m-Nitrophenyl	Methyl	—	10,90, > 100	< 100	> 1000	30-50

* compound not available for this test

TABLE XIII
Results of copper acetate and fungitoxicity tests with
dimethyldithiocarbamoylmethyl ethers (VIII)

No. of compound	Formula	X	Test with copper acetate at ~40° boiling	Venturia	Botrytis	Fusarium	Cercospora
				LD ₉₅ values, ppm			
47	VIII	O	—	> 100	> 100	> 100	> 100
48	VIII	S	Not done*	> 100	> 1000	> 1000	> 1000
49	IX		—	> 100	> 1000	> 1000	> 1000

* compound not available for this test

TABLE XIV
Results of copper acetate and fungitoxicity tests with
ethylenebis-(S-alkanamidoalkyl) dithiocarbamates (X)

No. of compound	R	R ^I	Test with copper acetate at ~40°	Venturia	Botrytis	Fusarium	Cercospora
				LD ₉₅ values, ppm			
50	CCl ₃	H	+	7	55	25	15
51	CCl ₃	Me	+	10	55	45	22
52	H	CH ₂ F	+	> 100	> 1000	> 1000	> 1000
53	CCl ₃	CH ₂ F	+	12	50	25	10
54	H	CH ₂ Cl	+	> 100	> 1000	> 1000	> 100
55	CCl ₃	CH ₂ Cl	+	17	> 100	55	23

TABLE XV
Results of fungitoxicity tests with miscellaneous derivatives (XI)

No. of compound	R	R ^I	Venturia	Botrytis	Fusarium	Cercospora
			LD ₉₅ values, ppm			
56	Hydroxy	CO ₂ Et	> 1000	> 1000	> 1000	—
57	Thiophenyl	CO ₂ Et	> 1000	> 1000	> 1000	> 1000
58	Phthalimido	CO ₂ Et	> 1000	> 1000	> 1000	> 1000
59	Cyano	CO ₂ Et	> 1000	> 1000	> 1000	> 1000
60	Ethoxydithioformyl	CO ₂ Et	> 100	> 1000	> 100	> 1000
61	Methyldithiocarbamoyl	CO ₂ Et	42	> 100	> 100	—
62	Methyldithiocarbamoyl	CO ₂ Bu ⁿ	> 100	> 1000	> 100	> 100
29	Dimethyldithiocarbamoyl	CO ₂ Et	4,9,20	120	43	—
63	Diethyldithiocarbamoyl	CO ₂ Et	> 100	> 100	> 1000	> 1000
64	8-Hydroxyquinolyl	CHO	4	> 1000	9	1.5

A typical bimodal dosage-response curve against *Venturia* is shown for ethyl *N*-(1-dimethyldithiocarbamoyl-2,2,2-trichloroethyl)carbamate (Fig. 1).

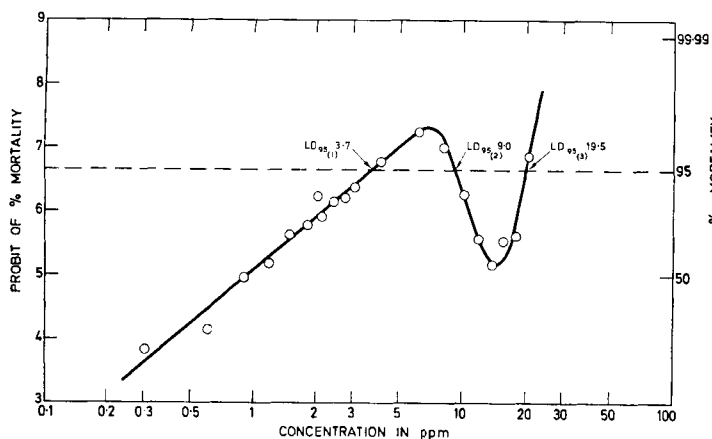


FIG. 1. Dosage-response curve against *Venturia* for ethyl *N*-(1-dimethyldithiocarbamoyl-2,2,2-trichloro-ethyl)carbamate (VI: R=OEt; compound No. 29)

Ethyl *N*-(1-thiophenyl)- (Compound No. 57), (1-phthalimido)- (No. 58), (1-cyano)- (No. 59), (1-diethyldithiocarbamoyl)- (No. 63) and (1-ethoxydithioformyl)- (No. 60) 2,2,2-trichloroethylcarbamates were inactive or had low activity, although substitution in Compound No. 18 of an ethoxydithioformyl group enhanced its activity (Compound No. 35) against *Venturia*, *Botrytis* and *Cercospora*. Of the two derivatives of *N*-methyldithiocarbamic acid (Compounds Nos. 61 and 62), one was much more active than the other, whereas the derivative of 8-hydroxyquinoline (No. 64) had high activity against *Venturia*, *Fusarium* and *Cercospora*.

Conclusions

On the relationship between fungitoxicity and chemical structure of dithiocarbamate derivatives certain conclusions may be drawn.

- The *in vitro* activity [except for the esters mentioned under (e)] depends on the ease with which the dimethyldithiocarbamate group is split off from the rest of the molecule.
- In the ethylenebisdithiocarbamate derivatives, substitution with a lipid-soluble group enhances activity.
- Certain dimethyldithiocarbamate derivatives exhibit bimodal dosage-response curves, but their ethylenebisdithiocarbamate analogues do not.
- Whereas dimethyldithiocarbamate derivatives are generally more active against *Venturia*, the ethylenebisdithiocarbamates have more general antifungal activity.

- Dimethyldithiocarbamoylmethyl aryl esters have low activity, whereas dimethyldithiocarbamoylmethyl lower aliphatic esters show high activity.

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