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Reaction of Dichlorvos, dichloroacetaldehyde and related compounds with nucleophiles and phenols

G. D. Khandelwal & B. L. Wedzicha

Procter Department of Food Science, University of Leeds, Leeds LS2 9JT, UK

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Model compounds are used to demonstrate functional group reactivity of dimethyl-2,2-dichlorovinyl phosphate (DDVP, Dichlorvos or Vapona) towards amino compounds, phenols and thiols. Methylation of thiols occurs as a result of a trans- methylation reaction by DDVP. In aqueous media, the dichlorovinyl portion of the DDVP molecule is converted predominantly to dichloroacetaldehyde (DCA), in the absence of added nucleophile. The reactions of DCA with thiols, amino acid, and phenols are reported and mechanisms are suggested. 1,1-Dichloroacetone and methyl dichloroacetate were also used as model compounds to provide a greater insight into the reactivity of the dichloro-moiety of DDVP and DCA. © 1998 Elsevier Science Ltd. All rights reserved

INTRODUCTION

The aim of this work has been the synthesis of the reaction products arising from the interaction of the pesticide Dichlorvos (dimethyl-2,2-dichlorovinyl phosphate, DDVP, Vapona) with food components, and the changes to these products when food is cooked. Dichlorvos was identified as an example of a particularly reactive post-harvest treatment agent; it is intended to establish the diversity of its reactivity with food components (thiols, amino compounds, phenols, etc.) and the mechanisms of the reactions involved.

Dichlorvos is known to be unstable towards hydrolysis with formation of the highly reactive dichloroacetaldehyde (DCA) and dimethyl hydrogen phosphate. The phosphorus atom is electron deficient and nucleophilic attack is the first step in the hydrolytic reaction (Pearson and Songstadt, 1967).

The methyl carbon atoms of DDVP carry a small positive charge and the ester is capable of acting as a weak methylating agent. Thus, DDVP is known to react with glutathione (Bedford and Robinson, 1972) and guanine (in DNA or RNA) (Löfroth, 1970; Lawley *et al.*, 1974) to give S-methylglutathione and N_7-methylguanine, respectively. The demethylation of DDVP causes the enol ester group to become unstable with subsequent hydrolysis to DCA and inorganic phosphate. Despite this well known formation of DCA in the reaction of DDVP with water, little information is available on the fate of DCA, or of the dichlorovinyl part of the DDVP molecule in biological systems or food. The dichlorovinyl moiety itself has been detected *in vivo* and *in vitro* (Casida *et al.*, 1962; Hodgson and Casida, 1962; Bull and Ridgeway, 1969) but it is converted rapidly to DCA.

In theory, DCA should be capable of reacting with components of living systems and food, e.g. primary amino groups in amino acids, peptides, proteins and nucleic acids, or thiol groups. This paper is concerned with the reactions of DDVP and DCA. It was decided to compare these reactions with those of 1,1-dichloroacetone which is expected to have lower carbonyl group reactivity. In addition, methyl dichloroacetate (MDCA) was included in this investigation as a related reactant with potentially the lowest reactivity.

MATERIALS AND METHODS

Outline of approach

Two distinct systems were used to synthesise reaction products in this work. Those reactions which were carried out in anhydrous ethanol, methanol or dichloromethane as a solvent, together with a catalyst, were used to obtain high yields of the products. On the other hand, aqueous systems containing 10% ethanol to aid dissolution of the reactants were used to verify that the same reactions took place in the environment of food.

Preparation of Dichlorvos

Dichlorvos was prepared using the method of Perkow (1954). Trimethylphosphite (20.7 g, 19.6 ml) was dissolved

in ether (60 ml), and chloral (24.5 g) in ether (70 ml) was added dropwise keeping the temperature below 20°C for 20 min. The mixture was stirred for a further 30 min at room temperature and evaporation of the solvent and distillation gave pure DDVP (yield 36 g, bp 100°C at 3 mm pressure). ^{1}H NMR: $\delta(CDCl_3)$ 6.96, (d, vinylic proton, J = 4.8 Hz), 3.76 (s, OMe), 3.96 (s, OMe).

Preparation of 1,1-dichloroacetaldehyde

To 1,1-dichloroacetaldehyde diethylacetal (3 ml) was added concentrated H_2SO_4 (1 ml) and the mixture distilled to give DCA (b.p. 86–88°C; Lit. 86–88°C (Perkow, 1954)) and the product was used immediately because it polymerises on standing, even at low temperature.

General procedure for the synthesis of reaction products

The reactants (DDVP, DCA and 1,1-dichloroacetone (40 mmol) and thiol (40–120 mmol) were dissolved separately in a solution of sodium ethoxide (NaOEt) or methoxide (NaOMe) (prepared from 0.92 g Na, 40 mmol in 50 ml dry ethanol or methanol), or in dichloromethane in the presence of triethylamine (Et_3N) as a catalyst. After stirring for a given time at room temperature, the mixture was diluted with water (50 ml), extracted with $CHCI_3$ (3×100 ml), and the combined organic layers were dried ($MgSO_4$). When Et_3N was used as a catalyst, the organic layer was washed with $NaHCO_3$ (10% w/v), with water and dried. The solvent was removed under reduced pressure (40°C) and the product isolated by bulb-to-bulb distillation (Büchi GKR-51 Kügelrohr distillation apparatus, Büchi, Switzerland) *in vacuo*. When MDCA was used as the reactant, equimolar amounts (40 mmol) of MDCA and nucleophile were dissolved in dry methanol (50 ml) and K_2CO_3 (40 mmol) was added as a catalyst. The reaction mixture was heated at 50°C for 5 h. The mixture was filtered, the filtrate poured into water and extracted with dichloromethane. After drying ($MgSO_4$), the solvent was evaporated under reduced pressure and the solid recrystallised.

The reactions of phenol and substituted phenols were carried out by mixing with DCA or 1,1-dichloroacetone as described above, and adding concentrated H_2SO_4 dropwise with vigorous stirring, keeping the temperature between 35 and 40°C. Water was added, the mixture extracted with ether and dried ($MgSO_4$). After evaporation of the solvent under reduced pressure, the residue was recrystallised.

The reactions in water (10% aq. alcohol) were carried out at 55°C and the adducts were isolated as described above.

IDENTIFICATION OF REACTION PRODUCTS

Reaction products isolated were subjected to microanalysis and identified by NMR, mass spectroscopy and infrared spectroscopy. NMR (^{1}H and ^{13}C) spectra were recorded from samples in $CDCl_3$ Data for each compound are as follows.

Reactions of Dichlorvos (DDVP) with thiols

Reaction with methyl 2-mercaptoacetate (Fig. 1, structure 1)
Reaction time, 48 h; yield: 55%; Et_3N as a catalyst; [DDVP]: [methyl 2-mercaptoacetate] = 1:1; colourless oil (b.p. 80°C/water pump pressure); IR (neat): 1735 cm^{-1}; MS: m/e 120,106, 74, 61; ^{1}H NMR: δ2.24 (s, SMe), 3.20 (s, CH_2), 3.72 (s, OMe). A residue (1.17 g) was also obtained.

Reaction with 2-mercaptoethanol (Fig. 1, structure 2)
Reaction time, 48 h; yield: 7%; Et_3N as a catalyst; [DDVP]:[2-mercaptoethanol] = 1:1; colourless oil (b.p. 80°C/water pump pressure); IR (neat): 3420 cm^{-1}; MS: m/e 92, 78, 61; HRMS calcd. for $C_3H_8O_5$: 92.02658; found: 92.02605; ^{1}H NMR: δ2.16 (s, SMe), 2.70 (t, 2H, J = 4.8 Hz), 3.20 (b, OH), 3.80 (m, 2H).

Reaction with cysteine ethyl ester (Fig. 1, structure 3)
Reaction time, 48 h; yield: 48%; Et_3N as a catalyst; [DDVP]:[cysteine ethyl ester] = 1:1; pale yellow oil (purified by column chromatography); this product was hydrolysed to the corresponding acid which was identical to an authentic sample of S-methylcysteine.

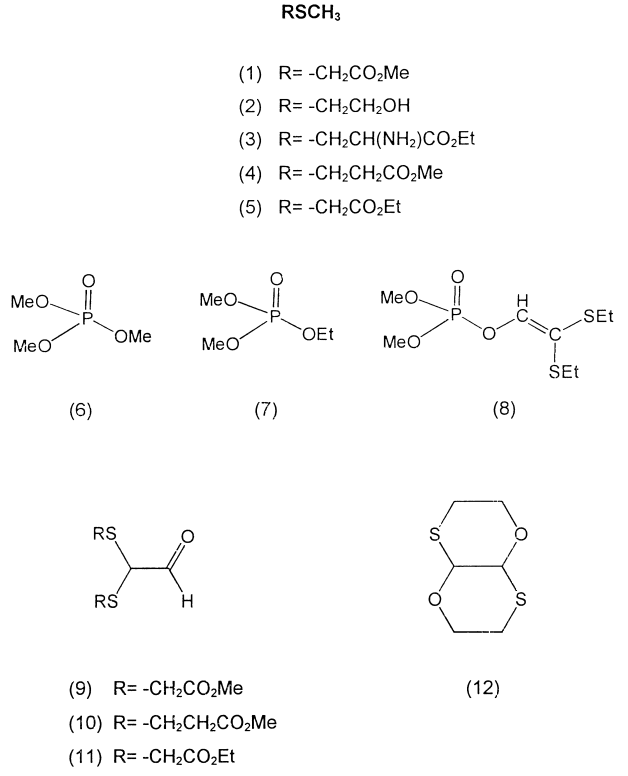


Fig. 1. Reactions of Dichlorvos and dichloroacetaldehyde with thiols.

Reaction with sodium methoxide (Fig. 1, structure 6)
Reaction time, 24 h; [DDVP]:[NaOMe] = 1:1; yield: 48%; colourless oil (b.p. 80°C/water pump pressure), identical to an authentic sample of trimethylphosphate; MS: m/e 140, 110, 95, 79, 69; HRMS calcd. for $C_3H_9PO_4$: 140.0237; found: 140.0238.

Reaction with methyl 2-mercaptoacetate (Fig. 1, structures 6 and 1)
NaOMe as a catalyst; [DDVP]:[2-mercaptoacetate] = 1:1; products 6 (55%) and 1 (27%) isolated.

Reaction with 2-mercaptoethanol (Fig. 1, structures 6 and 2)
NaOMe as a catalyst; [DDVP]:[2-mercaptoethanol] = 1:1; adducts 6 (26%) and 2 (49%) obtained.

Reaction with methyl 3-mercaptopropionate (Fig. 1, structures 4 and 6)
Reaction time, 24 h; NaOMe as a catalyst; [DDVP]:[methyl 3-mercaptopropionate] = 1:2; adducts 4 (55%) and 6 (26%) were obtained; MS of 4: m/e 134, 119, 84; HRMS calc. for $C_5H_{10}SO_2$: 134.0410; found: 134.0417; ^{1}H NMR: δ2.10 (s, 3H, SMe), 2.60-2.80 (m, 411), 3.70 (s, OMe); IR (neat): 1735 cm^{-1}.

Reaction with 2-mercaptoacetate (Fig. 1, structures 7 and 5)
Reaction time, 24 h; KOH in EtOH; [DDVP]:[2-mercaptoacetate] = 1:2; product 7, yield: 44%; colourless oil; MS: m/e 155, 141, 127; ^{1}H NMR: δ1.32 (t, 3H, J = 7 Hz), 3.60 (s, OMe), 3.80 (s, OMe), 4.32 (q, 2H, J = 7 Hz); product 5, yield: 51 %; colourless oil; MS: m/e 134, 120, 88, 61; HRMS calc. for $C_5H_{10}O_2S$: 134.0410; found: 134.0412; ^{1}H NMR: δ1.32 (t, 3H, J = 7 Hz), 2.24 (s, SMe), 3.20 (s, CH_2), 4.32 (q, 2H, J = 7 Hz).

Reaction with methyl 2-mercaptoacetate (Fig. 1, structures 1, 9 and 6)
Reaction time, 48 h; NaOMe as a catalyst; [DDVP]:[methyl 2-mercaptoacetate] = 1:3; from the ether extracts; adduct 1, yield: 27%; adduct 9, yield: 50%; colourless oil (b.p. 125°C/3 mm Hg); IR (neat): 3440 (b), 1735 (b) cm^{-1}; MS: m/e 252,223 (M-COH), 192, 179,147,119; ^{1}H NMR: δ9.44 (d, CHO), 5.0 (d, CH), 3.82 (s, OMe), 3.80 (s, OMe), 3.48–3.60 (m, 4H); Anal. calc. for $C_8H_{12}O_5S_2$: C, 38.09; H, 4.76; S, 25.39; found: C, 37.45; H, 4.80; S, 25.10. Product 6, yield: 16%, was also obtained from the $CHCl_3$ extraction of the aq. phase.

Reaction with methyl 3-mercaptopropionate (Fig. 1, structures 4, 10 and 6)
Reaction time, 20 h; NaOMe as a catalyst; [DDVP]:[methyl 3-mercaptopropionate] = 1:3; from the ether extracts were obtained, adduct 4, yield: 21%; adduct 10, yield: 61%; colourless oil (b.p. 150°C 3 mm Hg); IR (neat): 3440 (b), 1735 (b) cm^{-1}; MS: m/e 280,251 (M-COH), 161 (M-$SCH_2CH_2CO_2Me$); HRMS calc. for $C_{10}H_6O_5S_2$: 280.0439; found: 280.0435; ^{1}H NMR: δ9.24 (d, 1 H, J = 3.6 Hz), 4.44 (d, J = 3.6 Hz, 1 H), 3.72(s, 2×OMe), 3.00–2.60 (m, 8H); product 6, yield: 15% was obtained from the aq. layer by extraction with $CHCl_3$ When the reaction was carried out in 10% aq. EtOH, reaction time, 5 days; [DDVP]:[methyl 3-mercaptopropionate] = 1:2; only product 10 was obtained; yield: 82%.

Reaction with 2-mercaptoethanol (Fig. 1, structure 12)
Reaction time, 12–22 days; [DDVP]:[2-mercaptoethanol] = 1:2; in 10% aq. EtOH; yield: 72%; colourless solid from MeOH; m.p. 79–81°C; IR (KBr): 1445, 1410, 1370, 1295, 1245,1210, 1185, 1128, 1075,1050,1015, 1000, 960,925,895,865,838, 800, 780, 680, 660 cm^{-1}; MS: m/e 179 (M + 1), 150, 133, 119, 103,78; Anal. calc. for $C_6H_{10}O_2S_2$: C, 40.44; H, 5.61; S, 35.95; found: C, 40.00; H, 5.50; S, 36.00.

Reactions of 1,1-dichloroacetaldehyde (DCA)

Reaction with 2-mercaptoethanol (Fig. 1, structure 12)
Reaction time, 13 days; [DCA]:[2-mercaptoethanol] = 1:2; in 10% aq. EtOH; yield: 75%; colourless solid from MeOH; m.p. 79–81°C; identical to DDVP-mercaptoethanol reaction product.

Reaction with 2-mercaptoethanol (Fig. 1, structure 12)
Reaction time, 20 h; NaOMe as a catalyst; [DCA]:[2-mercaptoethanol] = 1:2; yield: 66%; colourless solid from MeOH; m.p. 79–81°C; identical to the above adduct.

Reaction with ethyl 2-mercaptoacetate (Fig. 1, structure 11)
Reaction time, 13 days; [DCA]:[ethyl 2-mercaptoacetate] = 1:2; in 10% aq. EtOH; yield: 36%; colourless oil; IR (neat): 1735 cm^{-1}; MS: m/e 281 (M + 1), 252 (M-CHO), 235,207, 165, 133.

Reaction with methyl 2-mercaptoacetate (Fig. 1, structure 9)
Reaction time, 20 h; NaOMe as a catalyst; [DCA]:[methyl 2-mercaptoacetate] = 1:2; yield: 52%; colourless oil; identical to DDVP-2-mercaptoacetate reaction product.

Reaction with methyl 3-mercaptopropionate (Fig. 1, structure 10)
Reaction time, 20 h; Et_3N as a catalyst; [DCA]:[methyl 3-mercaptopropionate] = 1:2; yield: 65%; identical to DDVP-methyl 3-mercaptopropionate reaction product.

Reaction with phenol (Fig. 2, structure 13)
Reaction time, 0.5 h; [DCA]:[phenol] = 1:2; yield: 84%; colourless fluffy solid from ethyl acetate/petroleum ether 40–60°C; m.p. 168–170°C; IR (KBr): 3100–3700 (b), 1600, 1612 cm^{-1}; MS: m/e 282, 247, 199 (M-$CHCl_2$);

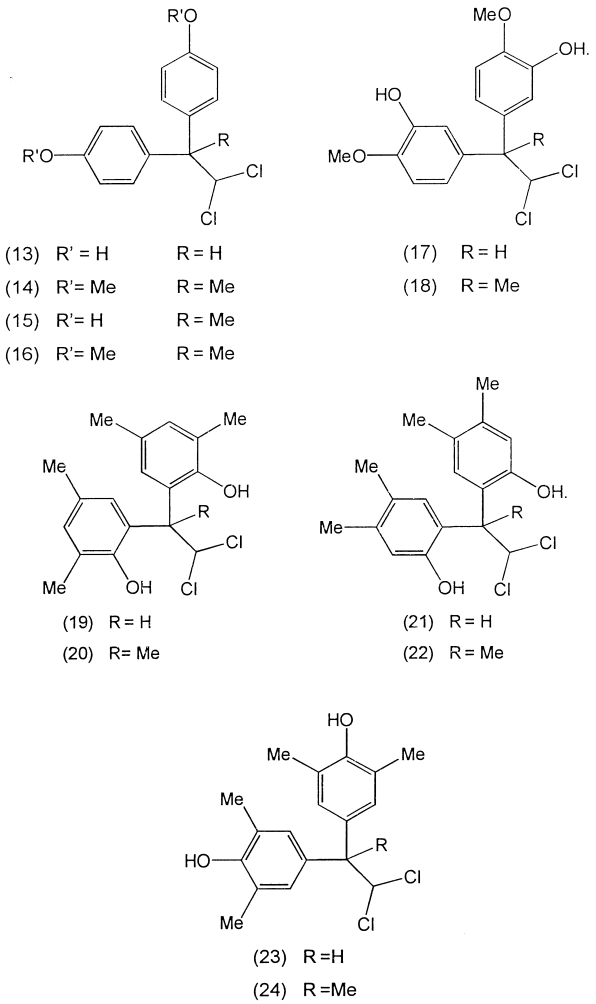


Fig. 2. Reactions of dichloroacetaldehyde and 1,1-dichloroacetone with phenol and substituted phenols.

HRMS calc. for $C_{14}H_{12}O_2Cl_2$: 282.0214; found: 282.0197; ^{1}H NMR: δ($CDCl_3$/DMSO-D_6) 7.24–7.08 (m, 4H), 6.92–6.68 (m, 4H), 6.56–6.40 (d, 2H, J = 7 Hz), 4.40–4.46 (b, 2H); ^{13}C NMR: δ($CDCl_3$/DMSO-D_6) 156.235, 131.121 , 129.187, 115.458 (aromatic C-atoms), 75.70, 61.128; Anal. calc. for $C_{14}H_{12}O_2Cl_2$: C, 59.36; H, 4.24; found: C, 59.15; H 4.40.

Reaction with anisole (Fig. 2, structure 14)
Reaction time; 0.5 h; [DCA]:[anisole] = 1:2; yield: 79%; colourless solid from EtOH; m.p. 108–110°C; IR (KBr): 1610, 1585 cm^{-1}; MS: m/e 311 (M + 1), 275, 241, 227 (M-$CHCl_2$), 203,169; ^{1}H NMR: δ($CDCl_3$/DMSO-D_6) 7.60–7.4 (m, 4H), 7.20–7.00 (m, 4H),6.52 (d, 2H, J = 9 Hz), 4.72 (d, 1 H, J = 9 Hz), 2.80 (s, 6H, OMe); ^{13}C NMR: δ($CDCl_3$/DMSO-D_6) 158.609, 132.223, 129.326, 113.887 (aromatic C-atoms), 75.32, 60.996; Anal. calc. for $C_{16}H_{16}O_2Cl_2.2H_2O$: C, 59.70; H, 4.45; found: C, 59.2; H, 4.7.

Reaction with o-*methoxyphenol (Fig. 2, structure 17)*
Reaction time, 0.5 h; [DCA]:[*o*-methoxyphenol] = 1:2; yield: 77%; colourless solid from aq. EtOH; m.p. 143–145°C; IR (KBr): 3100–3700 (b), 1610, 1595 cm^{-1}; MS: m/e 343 (M + 1), 307, 272, 259 (M-$CHCl_2$), 219; HRMS calc. for $C_{16}H_{16}O_4Cl_2$: 342.0425; found: 342.03769; ^{1}H NMR: δ($CDCl_3$/DMSO-D_6) 7.00–6.80 (m, 6H), 6.46 (d, 2H, J = 7 Hz), 4.40–4.46 (m, 2H), 3.80 (s, 6H); ^{13}C NMR: δ($CDCl_3$/DMSO-D_6) 147.341, 146.682, 146.187, 145.503, 133.293, 131.67, 120.537, 119.116, 115.265, 115.176, 111.904, 111.337 (aromatic C-atoms), 75.496, 61.732, 55.839 and 55.667 (2×OMe); Anal. calc. for $C_{16}H_{16}O_4Cl_2$: C, 55.98; H, 4.61; found: C, 56.05; H, 3.95.

Reaction with 2,4-dimethylphenol(Fig. 2, structure 19)
Reaction time, 0.5 h; [DCA]:[2,4-dimethylphenol] = 1:2; yield: 80%; colourless solid from ether/petroleum ether 40–60°C; m.p. 133–135°C; IR (KBr): 3400–3280 (b), 1600 cm^{-1}; MS: m/e 338, 255, 237 (M-$CHCl_2$), 135, 122, 91; ^{1}H NMR: δ($CDCl_3$/DMSO-D_6) 7.04–6.88 (m, 4H), 6.04 (d, 2H, J = 9.6 Hz), 5.2 (d, J = 9.6Hz), 4.60 (b, 2×OH), 2.20, 2.24 (singlets, 12H); Anal. calc. for $C_{18}H_{20}O_2Cl_2$: C, 63.90; H, 5.91; found: C, 64.15; H, 6.15.

Reaction with 3,4-dimethylphenol (Fig. 2, structure 21)
Reaction time, 0.5 h; [DCA]:[3,4-dimethylphenol] = 1:2; yield: 79%; colourless solid from aq. MeOH; m.p. 108–111°C (decomp.); IR (KBr): 3100–3700 (b), 1600 cm^{-1}; MS: m/e 338, 266, 255 (M-$CHCl_2$), 237; ^{1}H NMR: δ($CDCl_3$/DMSO-D_6) 7.12 (s, 2H), 7.0 (s, $CHCl_2$), 6.72 (s, 2H), 6.64–6.40 (b, 2×OH), 5.2 (d, 1 H, J = 9.6 Hz), singlets at 2.18 and 2.16 (12H); Anal. calc. for $C_{18}H_{20}O_2Cl_2$: C, 63.90; H, 5.91; found: C, 63.95; H, 6.00.

Reaction with 2,6-dimethylphenol (Fig. 2, structure 23)
Reaction time, 0.5 h; [DCA]:[2,6-dimethylphenol] = 1:2; yield: 85%; colourless solid from ether/petroleum ether 40–60°C; m.p. 150–152°C (decomp.); IR (KBr): 3300–3700 (b), 1600 cm^{-1}; MS: m/e 338,303, 268 (M-$CHCl_2$), 217; ^{1}H NMR: δ($CDCl_3$/DMSO-D_6) 7.0 (s, 4H), 6.34 (d, $CHCl_2$), 4.32 (d, 1H, J = 9 Hz), 4.12 (b, 2×OH), 2.20 (s, 12H); Anal. calc. for $C_{18}H_{20}O_2Cl_2$: C, 63.90; H, 5.91; found: C, 63.85; H, 6.20.

Reaction with ethanolamine (Fig. 4, structure 31)
Reaction time, 24 h; [DCA]:[ethanolamine] = 1:1; at room temperature in CH_2Cl_2; yield: 65%; colourless oil (b.p.100°C 3 mm Hg), MS: m/e 156 (M + 1), 120 (M-Cl), 90, 72; HRMS, calc. for $C_4H_7NOCl_2$: 155.05355; found 155.05460; ^{1}H NMR: δ($CDCl_3$) 5.60 (d, 1H, J = 7 Hz), 4.96 (d, 1H, J = 7 Hz), 3.6–4.12 (m, 2H), 3.16 (t, 2H), 2.68 (b, OH); Anal. calc. for $C_4H_7ONCl_2$: C, 30.76; H, 4.48; N, 8.97; found: C, 30.85; H, 4.50; N, 8.75.

Reaction with n-*butylamine (Fig. 4. structure 32)*
Reaction time, 20 h; at room temperature in MeOH; [DCA]:[*n*-butylamine] = 1:1; yield: 48%; colourless oil (b.p. 80°C/water pump pressure), decomposes very quickly.

Reactions of 1,1-dichloroacetone

Reaction with phenol (Fig. 2, structure 15)
Reaction time, 0.5 h; [dichloroacetone]:[phenol] = 1:2; yield: 81 %; colourless solid from ether/$CHCl_3$; m.p. 175–177°C; IR (KBr): 3700–3100 (b, OH), 1600,1612 cm^{-1}; MS: m/e 297, 261, 213 (M-$CHCl_2$); ^1H NMR: δ($CDCl_3$/DMSO-D_6) 7.24–7.08 (m, 4H, J = 9.6 Hz), 6.92–6.68 (m, 4H, J = 9.6 Hz), 6.50 (s, 1 H), 6.40–6.20 (b, 2H, OH), 1.92 (s, CMe); ^{13}C NMR: δ($CDCl_3$/DMSO-D_6) 155.431, 135.173, 128.845, 114.852 (aromatic C-atoms), 80.84,53.412, 23.181 (C.Me); Anal. calc. for $C_{15}H_{14}O_2Cl_2$: C, 60.00; H, 4.66; found: C, 60.15; H, 4.70.

Reaction with anisole (Fig. 2, structure 16)
Reaction time, 0.5 h; [dichloroacetone]:[anisole] = 1:2; yield: 76%; viscous oil; IR (neat): 1610, 1585 cm^{-1}; MS: m/e 325 (M + 1), 289, 255, 241 (M-$CHCl_2$), 217; ^1H NMR: δ($CDCl_3$/DMSO-D_6) 7.16–7.32 (d, 9Hz, 2H), 6.96–6.72 (d, 2H, J = 9 Hz), 6.56 (s, $CHCl_2$), 3.76 (s, 6H, 2×OMe), 1.96 (s, CMe); Anal calc. for $C_{17}H_{18}O_2Cl_2$: C, 62.76; H, 5.53; found: C, 62.95; H, 5.50.

Reaction with o-*methoxyphenol (Fig. 2, structure 18)*
Reaction time, 0.5 h; [dichloroacetone]:[*o*-methoxyphenol] = 1:2; yield: 74%; viscous oil; IR (neat): 3100–3700 (b), 1600 cm^{-1}; MS: m/e 356 (M + 1), 321, 287,273 (M-$CHCl_2$ + 1), 233, 205, 164, 125; HRMS calc. for $C_{17}H_{18}O_4Cl_2$: 356.04821; found: 356.04639; ^1H NMR: δ($CDCl_3$/DMSO-D_6) 7.00–6.80 (m, 6H), 6.44 (s, $CHCl_2$), 5.40 (b, 2H, OH), singlets at 3.80 and 3.84 (6H, OMe); Anal. calc. for $C_{17}H_{18}O_4Cl_2$: C, 50.87; H, 4.50; found: C, 51.00; H, 4.75.

Reaction with 2,4-dimethylphenol (Fig. 2, structure 20)
Reaction time, 0.5 h; [dichloroacetone]:[2,4-dimethylphenol] = 1:2; yield: 76%; colourless needles from ether/petroleum ether 40–60°C; m.p. 100–102°C; IR (KBr): 3700–3100 (b), 1600, 1612 cm^{-1}; MS: m/e 352, 281 (M-Cl_2), 269 (M-$CHCl_2$), 231; ^1H NMR: δ($CDCl_3$/DMSO-D_6) 7.44–7.40 (m, 2H), 7.14–7.12 (m, 2H), 6.92 (s, 1 H), 2.28 (s, 6H), singlets at 2.08 and 2.10 (9H); Anal. calc. for $C_{19}H_{22}O_2Cl_2$: C, 64.59; H, 6.18; Cl, 19.83; found: C, 64.80; H, 6.05; Cl, 19.65.

Reaction with 3,4-dimethylphenol (Fig. 2, structure 22)
Reaction time, 0.5 h; [dichloroacetone]:[3,4-dimethylphenol] = 1:2; yield: 80%; colourless solid from ether/petroleum ether 40–60°C; m.p. 143–144°C (decomp.); IR (KBr): 3480–3100 (b), 1600 cm^{-1}; MS: m/e 352, 281, 269 (M-$CHCl_2$), 251, 147; ^1H NMR: δ($CDCl_3$/DMSO-D_6) 7.44 (2H), 7.00 (s, 1 H), 6.64 (s, 2H), 4.80 (b,2×OH), singlets at 2.20 and 2.28 (12H), 2.04 (s, CMe); Anal. calc. for $C_{19}H_{22}O_2Cl_2$: C,64.59; H, 6.18; found: C,64.35; H, 6.25.

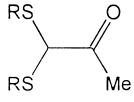
Reaction with 2.6-dimethylphenol (Fig. 2, structure 24)
Reaction time, 0.5 h; [dichloroacetone]:[2,6-dimethylphenol] = 1:2; yield: 81%; colourless solid from aq.MeOH; m.p.167–169°C (decomp.); IR (KBr): 3400–3200 (b), 1600 cm^{-1}; MS: m/e 352, 317, 282, 269 (M-$CHCl_2$), 231; ^1H NMR: δ($CDCl_3$/DMSO-D_6) 7.00 (s, 4H, aromatics), 6.62 (s, $CHCl_2$), 6.12 (b, 2×OH), 2.24 (s,12H), 1.96 (s, CMe); Anal. calc. for $C_{19}H_{22}O_2Cl_2$: C,64.59; H, 6.23; found: C,64.40; H, 6.40.

Reaction with methyl 2-mercaptoacetate (Fig. 3, structure 25)
Reaction time, 48 h; Et_3N as a catalyst; [dichloroacetone]:[methyl 2-mercaptoacetate] = 1:2; yield: 84%; colourless oil (b.p.165°C/3 mm Hg); IR (neat): 1735 cm^{-1} (b); MS: m/e 266, 235, 223 (M-COMe), 207, 161 (M-SCH_2COOMe); $C_9H_{14}O_5S_2$: requires 266.02874; found 266.02817; ^1H NMR: δ($CDCl_3$) 4.92 (s, 1H), 3.72 (s, 6H, OMe), 3.40 (d, 4H), 2.42 (s, COMe); Anal. calc. for $C_9H_{14}O_5S_2$: C,40.60; H, 5.26; S, 24.06; found: C,40.60; H, 5.46; S 23.80.

The identical product was isolated when NaOMe was used as a catalyst.

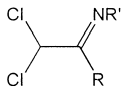
Reaction with ethyl 2-mercaptoacetate (Fig. 3, structure 26)
Reaction time, 48 h; Et_3N as a catalyst; [dichloroacetone]:[ethyl 2-mercaptoacetate] = 1:2; yield: 91%; colourless oil (b.p.170°C 3 mm Hg); IR (neat): 1730 (b) cm^{-1}; MS: m/e 294, 251 (M-COMe), 175 (M-SCH_2COOEt); ^1H NMR:δ ($CDCl_3$) 4.92 (s, 1H), 4.16 (q, 4H, J = 7Hz), 3.40 (d, 4H), 2.36 (s, 3H, COMe), 1.26 (t, 6H, J = 7 Hz); Anal. calc. for $C_{11}H_{18}O_5S_2$: C, 44.89; H, 6.12; S, 21.77; found: C, 44.65; H, 6.20; S 22.00.

Reaction with methyl 3-mercaptopropionate (Fig. 3, structure 27)
Reaction time, 48 h; Et_3N as a catalyst; [dichloroacetone]:[methyl 3-mercaptopropionate] = 1:2; yield: 91%; colourless oil (b.p. 160°C/3 mm Hg); IR (neat): 1708, 1735 cm^{-1}; MS: m/e 294, 251 (M-COMe), 207, 175 (M-CH_2CH_2COOMe), 143, 118 (M-2×SCH_2CH_2COOMe); ^1H NMR: δ($CDCl_3$) 4.6 (s, 1 H), 3.72 (s, 6H, OMe), 2.64–3.00 (m, 8H), 2.36 (s, 3H, COMe); Anal. calc. for $C_{11}H_{18}O_5S_2$: C, 44.80; H, 6.15; S, 21.90; found: C, 44.89; H, 6.12; S, 21.77.



(25) R = -CH_2CO_2Me
(26) R = -CH_2CO_2Et
(27) R = -$CH_2CH_2CO_2Me$
(28) R = -$CH_2CH_2CO_2Et$
(29) R = -CH_2CH_2OH
(30) R = -CH_2CO_2H

Fig. 3. Reactions of 1,1-dichloroacetone with thiols.



(31) R = H R' = -CH_2CH_2OH
(32) R = H R' = -$(CH_2)_3Me$
(33) R = Me R' = -$CH(CO_2Et)CH_2SH$
(34) R = Me R' = -$CH(CO_2Me)CH_2SMe$
(35) R = Me R' = -$CH(CO_2Me)CHMe_2$
(36) R = Me R' = -$CH(CO_2Me)Me$
(37) R = Me R' = -$CH(CO_2Me)CH_2CH_2SMe$
(38) R = Me R' = -$CH(CO_2Me)CH_2C_6H_4OH$-(p)
(39) R = Me R' = -CH_2CH_2SH
(40) R = Me R' = -CH_2CH_2OH
(41) R = Me R' = -$(CH_2)_3Me$
(42) R = Me R' = -$(CH_3)_3$

Fig. 4. Reactions of dichloroacetaldehyde and 1,1-dichloroacetone with amines.

Reaction with ethyl 3-mercaptopropionate (Fig. 3, structure 28)
Reaction time 48 h; Et_3N as a catalyst; [dichloroacetone]:[ethyl 3-mercaptopropionate] = 1:2; yield: 83%; colourless oil; IR (neat): 1730 cm^{-1}; MS: m/e 323 (M + 1), 279 (M-COMe), 221, 189 (M-SCH_2CH_2COOMe); HRMS calc. for $C_{13}H_{22}O_5S_2$: 322.09076; found: 322.0890; ^1H NMR: $\delta(CDCl_3)$ 4.56 (s, 1H), 4.16 (q, 4H, J = 7Hz), 2.60–3.00 (m, 8H), 2.36 (s, 3H, COMe), 1.26 (t, 6H, J = 7 Hz); Anal. calc. for $C_{13}H_{22}O_5S_2$: C, 48.44; H, 6.83; found: C, 47.20, H, 6.75.

Reaction with 2-mercaptoethanol (Fig. 3, structure 29)
Reaction time, 48 h; Et_3N as a catalyst; [dichloroacetone]:[2-mercaptoethanol] = 1:2; yield: 82%; colourless oil; IR (neat): 3420, 1715 cm^{-1}; MS: m/e 210, 167 (M-COMe), 133 (M-SCH_2CH_2OH); ^1H NMR: $\delta(CDCl_3)$ 4.76 (s, 1H), 3.68–4.00 (m, 4H), 3.36–3.48 (b, OH), 2.72–3.00 (m, 4H), 2.36 (s, 3H, COMe); Anal. calc. for $C_7H_{14}O_3S_2$: C, 40.00; H, 6.66; found: C, 40.90; H, 6.00.

Hydrolysis of 1,1-dichloroacetone-methyl 2-mercaptoacetate adduct (Fig. 3, structure 30)
Reaction time, 2 h; alcoholic NaOH; yield: 93%; colourless solid from acetone/petroleum ether; m.p. 170–172°C; IR (KBr): 1685, 1735 cm^{-1}; MS: m/e 239, 221 (M-H_2O), 183,165,149,131, 107, 93,75; ^1H NMR: $\delta(CDCl_3$/DMSO-$D_6)$ 5.6 (1 H), 3.40–3.60 (m, 4H), 2.40 (s, 3H, COMe); Anal. calc. for $C_7H_{10}O_5S_2$: C, 35.29; H, 4.20; found: C 34.70, H 3.95.

Reaction with cysteine ethyl ester (Fig. 4, structure 33)
Reaction time, 24 h; NaOMe or Et_3N as a catalyst; [dichloroacetone]:[cysteine ethyl ester] = 1:1; yield: 30%; pale yellow oil (decomposes on standing); IR (neat): 1735 cm^{-1}; MS: m/e 258 (M + 1), 222 (M + 1-HCl), 184 (M + 1-HCl), 184 (M + 1-CO_2Et), 174, 148, 133, 114, 100; ^1H NMR: $\delta(CDCl_3)$ 5.72 (s, 1H, $CHCl_2$), 4.44–4.00 (m, 3H), 3.60–3.00 (m, 3H), 1.88 (s, 3H, CMe), 1.44–1.20 (t, 3H, J = 7Hz, CH_2CH_3).

Reaction with S-methyl cysteine ethyl ester (Fig. 4, structure 34)
Reaction time, 24 h; NaOMe/MeOH as a catalyst; [dichloroacetone]:[S-methyl cysteine ethyl ester] = 1:1; yield: 35%; pale yellow viscous oil (decomposes quickly); IR (neat): 1745, 1665 cm^{-1}.

Reaction with L-valine methyl ester (Fig. 4, structure 35)
Reaction time, 2 h; NaOMe/MeOH as a catalyst; [dichloroacetone]:[L-valine methyl ester] = 1:1; yield: 37%; pale yellow oil; IR (neat):1745, 1665 cm^{-1}; MS: m/e 240 (M + 1), 196 (M-$CHMe_2$), 180 (M-COOMe), 156; HRMS calc. for $C_9H_{15}NO_2Cl$: 239.04798; found: 239.04779; ^1H NMR: $\delta(CDCl_3)$ 6.28 (s, 1 H, $CHCl_2$), 4.04 (d, J = 7Hz, 1H, CHCOOMe), 3.80 (s, 3H, OMe), 2.44 (q, J = 7 Hz, $CHMe_2$), 2.16, 1.0 (d, 3H, J = 3.6 Hz), 0.88 (d, 3H, J = 3.6 Hz).

Reaction with L-alanine methyl ester (Fig. 4, structure 36)
Reaction time, 2 h; NaOMe as a catalyst; [dichloroacetone]:[L-alanine methyl ester] = 1:1; yield: 44%; pale yellow oil; IR (neat):1745, 1665 cm^{-1}; MS: m/e 212 (M + 1), 178, 152 (M-CO_2Me), 128; HRMS calc. for $C_7H_{11}NO_2Cl_2$: 211.0194; found: 211.0170.; ^1H NMR: $\delta(CDCl_3)$ 6.20 (s, 1H, $CHCl_2$), 4.32 (q, 1H, J = 7 Hz), 3.80 (s, 3H, OMe), 2.16 (s, 3H, N = C.Me), 1.40 (d, 3H, J = 7 Hz, MeCHCOOMe).

Reaction with L-methionine methyl ester (Fig. 4, structure 37)
Reaction time, 3 h; NaOMe/MeOH as a catalyst; [dichloroacetone]:[L-methionine methyl ester] = 1:1; yield: 45%; pale yellow oil; IR(neat): 1745, 1665 cm^{-1}; MS: m/e 272 (M + 1), 238, 188, 162, 147, 127, 84; HRMS calc. for $C_9H_{15}NO_2Cl_2S$: 271.0210; found: 271.02005; ^1H NMR: $\delta(CDCl_3)$ 6.28 (s, 1H, $CHCl_2$), 4.40–4.60 (m, 1H, N.CH.CO_2Me) 3.80 (s, 3H, OMe), 2.20–2.76 (m, containing singlets at 2.20, 2.12, 10H); Anal. calc. for $C_9H_{15}NO_2Cl_2S$: C, 39.13; H, 5.45; N, 5.09; found: C, 38.35; H, 5.45; N, 4.5.

Reaction with L-tyrosine methyl ester (Fig. 4, structure 38)
Reaction time, 20 h; NaOMe/MeOH as a catalyst; [dichloroacetone]:[L-tyrosine methyl ester] = 1:1; yield: 39%; pale yellow viscous oil; IR (neat): 3420, 1665, 1745 cm^{-1}; ^1H NMR: $\delta(CDCl_3)$ 7.04–6.64 (m, 4H, aromatics), 6.16 (s, 1H, $CHCl_2$), 5.40–5.20 (b, 1H, OH), 4.40–4.12 (m, 1H, $CHCO_2Me$), 3.72 (s, 3H, OMe), 2.80–3.20 (m, 2H), 1.64 (s, 3H, CMe).

Reaction with cysteamine (Fig. 4, structure 39)
Reaction time, 4 h; refluxed in MeOH; [dichloroacetone]:[cysteamine] = 1:1; yield: 31%; colourless solid

from acetone/ether; m.p. 143–145°C (decomp.); MS: m/e 186 (M + 1), 169, 150, 130, 115, 102; HRMS calc. for $C_5H_9NSCl_2$: 185.98327; found: 185.99392; ^{1}H NMR: $\delta(CDCl_3)$ 6.28 (s, 1H), 4.2–3.00 (m, 5H), 2.06 (s, 3H, CMe).

Reaction with ethanolamine (Fig. 4, structure 40)
Reaction time, 20 h; refluxed in CH_2Cl_2; [dichloroacetone]:[ethanolamine] = 1:1; yield: 80%; colourless oil (b.p. 75°C/3 mm Hg); IR (neat): 3340 (b), 1665 cm^{-1}; MS: m/e 170 (M + 1), 134 (M + 1-HCl), 104, 86; HRMS calc. for $C_5H_9NOCl_2$: 171.00317; found: 170.99995; ^{1}H NMR: $\delta(CDCl_3)$ 5.64 (s, 1H, $CHCl_2$), 4.12–3.80 (m, 2H), 3.40–3.20 (m, 2H), 2.56–2.40 (b, 1 H), 1.60 (s, 3H, CMe); Anal. calc. for $C_5H_9NOCl_2$: C, 35.08; H, 5.06; N, 8.24; found: C,35.05; H, 5.30; N, 8.70.

Reaction with n-*butylamine (Fig. 4, structure 41)*
Reaction time, 0.5 h; refluxed in MeOH; [dichloroacetone]:[*n*-butylamine] = 1:1; yield: 36%; colourless oil (b.p. 100°C/water pump pressure); MS: m/e 182 (M + 1), 146, 116 (M-$(CH_2)_3$Me); HRMS calc. for $C_7H_{13}NCl_2$: 181.04250; found: 181.04240; ^{1}H NMR: $\delta(CDCl_3)$ 6.16 (s, 1H, $CHCl_2$), 3.40 (t, 2H, NCH_2), 2.04 (s, 3H, CMe), 1.80–1.20 (m, 4H), 1.00 (d, 3H, 7 Hz).

Reaction with t-*butylamine adduct (Fig. 4, structure 42)*
Reaction time, 0.5 h; in MeOH at room temperature; [dichloroacetone]:[*t*-butylamine] = 1:1; yield: 12%; colourless crystals from aq. MeOH; m.p. 123–125°C; IR (KBr): 3300,1650,1610 cm^{-1}; MS: m/e 254, 234, 198, 184, 170, 145, 128, 97; ^{1}H NMR:δ ($CDCl_3$) 6.12 (d, 1H, J = 4.8 Hz), 1.52 (s, CMe), 1.36 (s, 9H); Anal. calc. for $C_7H_3NCl_2$: C,46.40; H, 7.18; found: C,46.85; H, 6.90.

Reactions of methyl 1,1-dichloroacetate (MDCA)

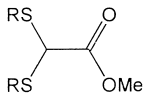
Reaction with methyl 2-mercaptoacetate (Fig. 5, structure 43)
Reaction time, 2 h; NaOMe/MeOH as a catalyst; [MDCA]:[methyl 2-mercaptoacetate] = 1:2; yield: 78%; colourless oil (b.p.180°C/3 mm Hg); IR (neat): 1745 (b) cm^{-1}; MS: m/e 283 (M + 1), 251, 223, 177, 149; HRMS calc. for $C_9H_{14}O_6S_2$: 282.02317; found: 282.02358; ^{1}H NMR: $\delta(CDCl_3)$ 4.88 (s, 1H, $CHCl_2$), 3.80 (s, OMe, 9H), 3.66 (d, 4H); Anal. calc. for $C_9H_{14}O_6S_2$: C, 38.30; H, 4.96; found: C, 38.05; H, 4.95.

Reaction with methyl 3-mercaptopropionate (Fig. 5, structure 44)
Reaction time, 3 h; NaOMe/MeOH as a catalyst; [MDCA]:[methyl 3-mercaptopropionate] = 1:2; yield: 82%; colourless oil (b.p.125°C/3 mm Hg); IR (neat): 1740 (b) cm^{-1}; MS: m/e 311 (M + 1), 247, 175, 143, 87; HRMS calc. for $C_{11}H_{11}O_6S_2$: 310.05447; found: 310.05735; ^{1}H NMR: $\delta(CDCl_3)$ 3.80 (s, 9H, OMe), 3.36 (s, 1H), 2.68–3.00 (m, 8H).

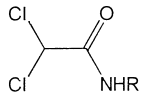
Reaction with glycine methyl ester (Fig. 5, structure 45)
Reaction time, 3 h; NaOMe/MeOH as a catalyst; [MDCA]:[glycine methyl ester] = 1:1; yield: 86%; colourless solid from aq. MeOH; m.p. 52–54°C; IR (KBr): 3250, 1725, 1640 cm^{-1}; MS: m/e 199, 168, 140, 111; ^{1}H NMR: $\delta(CDCl_3)$ 7.68 (b, 1H, NH), 6.20 (s, 1H, $CHCl_2$), 4.16 (d, 2H, J = 4.8 Hz), 3.83 (s, OMe); Anal. calc. for $C_3H_7O_3NCl_2$: C, 29.55; H, 3.45; N, 6.90; found: C, 29.55; H, 3.35; N, 7.00.

Reaction with ethanolamine (Fig. 5, structure 46)
Reaction time, 2 h; [MDCA]:[ethanolamine] = 1:1; yield: 76%; in MeOH at room temperature; colourless needles from aq. MeOH; m.p. 78–79°C; IR (KBr): 3280 (b), 1612 cm^{-1}; MS: m/e 172 (M + 1), 154 (M-OH), 138, 120, 106, 88; ^{1}H NMR: $\delta(CDCl_3)$ 8.24 (b, NH), 6.28 (s, 1 H), 3.80–3.40 (m, incldg. singlets, 9H); Anal. calc. for $C_4H_7NO_2Cl_2$: C, 28.07; H, 4.09; N, 8.18; found: C, 27.80; H, 3.90; N, 8.15.

Reaction with cysteamine (Fig. 5, structure 47)
Reaction time, 10 h; NaOMe/MeOH as a catalyst; [MDCA]:[cysteamine] = 1:1; yield: 87%; colourless crystals from $CHCl_3$/ether; m.p.155–15°C; IR (KBr): 3240, 1660 cm^{-1}; MS: m/e 188 (M + 1), 154, 128, 83; ^{1}H NMR: $\delta(CDCl_3)$ 8.60 (b, 1H, NH), 6.28 (s, 1H, $CHCl_2$), 3.68 (q, J = 6 Hz, 2H), 3.20 (s, with broadness, 4 + SH), 3.00 (t, J = 6 Hz, 2H); Anal. calc. for $C_4H_7ONC1_2$: C, 25.53; H, 3.72; N, 7.45; found: C, 25.40; H, 3.60; N, 7.50.



(43) R = -CH_2CO_2Me
(44) R = -$CH_2CH_2CO_2Me$



(45) R = -CH_2CO_2Me
(46) R = -CH_2CH_2OH
(47) R = -CH_2CH_2SH
(48) R = -$CH_2CH_2NHCH_2CH_2OH$
(49) R = -$(CH_2)_3Me$
(50) R = -$C(CH_3)_3$
(51) R = -$CH(CO_2Me)CHMe_2$
(52) R = -$CH(CO_2Me)CH_2OH$
(53) R = -$CH(CO_2Me)CH_2CH_2SMe$
(54) R = -$CH(CO_2Me)CH_2Ph$
(55) R = -$CH(CO_2Me)CH_2PhOH$ (*p*)

Fig. 5. Reactions of methyl dichloroacetate with thiols and with amines.

Reaction with 2-aminoethylaminoethanol (Fig. 5, structure 48).
Reaction time, 10 h; in MeOH at room temperature; [MDCA]:[2-aminoethylaminoethanol] = 1:1; yield: 93%; pale yellow oil; IR (neat): 3240, 1660 cm^{-1}; MS: m/e 215 (M + 1), 183, 143, 114, 99, 85, 69; Anal. calc. for $C_6H_{12}N_2O_2Cl_2$: C, 33.64; H, 5.60; N, 13.08; found: C, 33.60; H, 5.65; N, 13.15.

Reaction with n-*butylamine (Fig. 5, structure 49)*
Reaction time, 8 h; in MeOH at room temperature; [MDCA]:[*n*-butylamine] = 1:1; yield: 87%; colourless solid from aq. MeOH; m.p. 46–47°C; IR (KBr): 3240, 1660 cm^{-1}; MS: m/e 184 (M + 1), 150, 120, 106, 100; ^{1}H NMR: $\delta(CDCl_3)$ 6.80 (b, 1H, NH), 6.00 (s, 1H, $CHCl_2$), 3.20-3.52 (m, 2H), 1.20–1.80 (m, 4H), 0.96–1.08 (3H); Anal. calc. for $C_6H_{11}NOCl_2$: C, 39.34; H, 6.01; N, 7.65; found: C, 39.25; H, 6.15; N, 7.65.

Reaction with t-*butylamine (Fig. 5, structure 50)*
Reaction time, 8 h; in MeOH at room temperature; [MDCA]:[*t*-butylamine] = 1:1; yield: 75%; colourless solid from aq. MeOH; m.p. 176–178°C; IR (KBr): 1625, 1595 cm^{-1}; MS: m/e 184 (M + 1), 168, 150, 128, 100; ^{1}H NMR: $\delta(CDCl_3)$ 5.96 (s, 1H, $CHCl_2$), 3.60 (b, NH), 1.40 (s, 9H); Anal. calc. for $C_6H_{11}NOCl_2$: C, 39.34; H, 6.01; N, 7.65; found: C, 39.25; H, 6.30; N, 7.3.

Reaction with L-*valine methyl ester hydrochloride (Fig. 5, structure 51)*
Reaction time, 5 h; in MeOH at 50°C; K_2CO_3 as a catalyst; [MDCA]:[L-valine methyl ester hydrochloride]:[K_2CO_3] = 1:1:1; yield: 64%; viscous oil; IR (neat): 3315 (NH), 1745, 1675 (amide) cm^{-1}; MS: m/e 242 (M + 1), 210, 182, 167, 130, 114, 98; ^{1}H NMR: $\delta(CCl_4)$ 7.20–7.04 (d, 1 H, NH), 6.08 (s, 1 H, $CHCl_2$), 4.60–4.36 (dd, J = 4.8Hz, $C\underline{H}CO_2Me$), 3.80 (s, OMe), 2.60–2.08 (m, $CHMe_2$), 0.92 and 1.04 (doublets, $CHMe_2$); Anal. calc. for $C_8H_{13}NO_3Cl_2$: C, 39.66; H, 5.37; N, 5.78; found: C, 39.85; H, 5.00; N, 5.45.

Reaction with L-*serine methyl ester hydrochloride (Fig. 5, structure 52)*
Reaction time, 5 h; in MeOH at 50°C; K_2CO_3 as a catalyst; [MDCA]:[L-serine methyl ester hydrochloride]:[K_2CO_3] = 1:1:1; yield: 72%; colourless solid from EtOAc/petroleum ether 40–60°C m.p. 98–100°C; IR (KBr): 3515 (OH), 3280 (NH), 1725, 1665 (amide) cm^{-1}; MS: m/e 230 (M + 1), 212, 196, 178; ^{1}H NMR: $\delta(CDCl_3/DMSO\text{-}D_6)$ 8.24–8.12 (d, 1H, NH), 6.32 (s, $C\underline{H}Cl_2$), 4.68–4.44 (dd with broadness, OH and $C\underline{H}Cl_2$), 4.0 (t, 2H, CH_2OH), 3.78 (s, OMe); Anal. calc. for $C_6H_9NO_4Cl_2$: C, 31.44; H, 3.93; N, 6.11; found: C, 31.30; H, 3.92; N, 6.09.

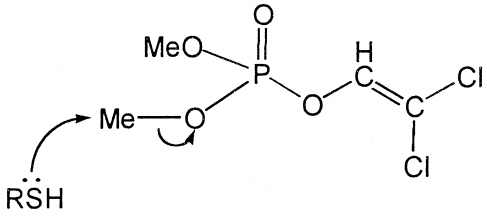
Reaction with L-*methionine methyl ester hydrochloride (Fig. 5, structure 53)*
Reaction time, 5 h; in MeOH at 50°C; K_2CO_3 as a catalyst; [MDCA]:[L-methionine methyl ester hydrochloride]:[K_2CO_3] = 1:1:1; yield: 69%; colourless solid from ether/petroleum ether 40–60°C; m.p. 54–55°C; IR (KBr): 3315 (NH), 1745, 1675 (amide) cm^{-1}; MS: m/e 274 (M + 1), 242, 226, 214, 199, 180, 167; ^{1}H NMR: $\delta(CCl_4/DMSO\text{-}D_6)$ 8.80–8.60 (d, 1 H, NH), 6.32 (s, $C\underline{H}Cl_2$), 4.68–4.32 (m, 1 H, $C\underline{H}CO_2Me$), 3.72 (s, OMe), 2.72–2.20 (m, 3H), 2.08 (s, SMe); Anal. calc. for $C_8H_{13}NO_3Cl_2S$: C, 35.03; H, 4.74; N, 5.10; found: C, 34.95; H, 4.80; N, 5.05.

Reaction with L-*phenylalanine methyl ester hydrochloride (Fig. 5, structure 54)*
Reaction time, 5 h; in MeOH at 50°C; K_2CO_3 as a catalyst; [MDCA]:[L-phenylalanine methyl ester hydrochloride]:[K_2CO_3] = 1:1:1; yield: 69%; colourless solid from EtOAc/petroleum ether 40–60°C; m.p. 81–83°C; IR (KBr): 3315 (NH), 1730, 1670 (amide) cm^{-1}; MS: m/e 290 (M + 1), 272, 258, 230, 196, 178, 162; ^{1}H NMR: $\delta(CCl_4/DMSO\text{-}D_6)$: 8.76–8.60 (d, 1 H, NH), 7.24 (s, aromatics, 5H), 6.38 (s, $C\underline{H}Cl_2$), 4.88–4.56 (m, $C\underline{H}CO_2Me$), 3.68 (s, OMe), 3.16–3.04 (m, 2H); Anal. calc. for $C_{12}H_{13}NO_3Cl_2$: C, 49.65; H, 4.48; N, 4.83; found: C, 49.75; H, 4.40; N, 4.90.

Reaction with L-*Tyrosine methyl ester hydrochloride (Fig. 5, structure 5)*
Reaction time, 5 h; in MeOH at 50°C; K_2CO_3 as a catalyst; [MDCA]:[L-tyrosine methyl ester hydrochloride]:[K_2CO_3] = 1:1:1; yield: 69%; colourless solid from acetone/ether; m.p. 136–138°C; IR (KBr): 3315, 3280, 1730, 1665 cm^{-1}; MS: m/e 306 (M + 1), 288, 274, 246, 230, 212, 178, 147, 107; ^{1}H NMR: $\delta(CCl_4/DMSO\text{-}D_6)$ 9.0 (bs, 1 H, OH), 8.80–8.64 (NH, d, 1H), 7.08–6.68 (m, 4H, aromatics), 6.44 (s, 1 H, $C\underline{H}Cl_2$). 4.60–4.40 (q, 1 H, $NHC\underline{H}CO_2Me$), 3.72 (s, 3H, OMe), 3.02–2.92 (d, 2H, CH_2Ph); Anal. calc. for $C_{12}H_{13}NO_4Cl_2$: C, 47.06; H, 4.25; N, 4.57; found: C, 46.65; H, 4.10; N, 4.6.

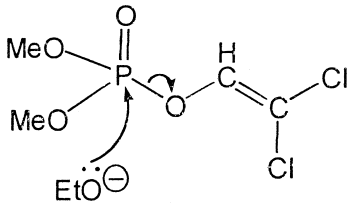
RESULTS AND DISCUSSION

The main reaction products which could be isolated when DDVP is allowed to react with 1 mole equivalent of a range of thiols (e.g. methyl mercaptoacetate, mercaptoethanol, cysteine ethyl ester, methyl mercaptopropionate, ethyl mercaptoacetate) were the S-methyl derivatives of these compounds (products 1–5), i.e. DDVP acted as a methylating agent for the thiol as follows:



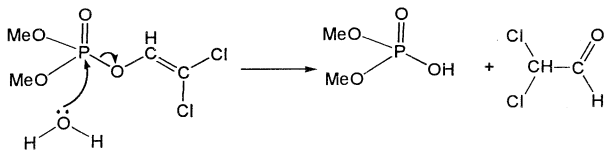
When the reaction of DDVP with thiols was carried out in methanol with sodium methoxide as a catalyst,

trimethyl phosphate (product 6) was obtained along with the S-methyl derivative. On the other hand, the trimethyl phosphate was the only product isolated in the absence of thiol under these conditions. In order to seek evidence for the type of mechanism involved, a reaction of DDVP with ethyl mercaptoacetate was carried out in ethanolic potassium hydroxide as a catalyst, giving rise to the S-methylmercaptoacetate (product 5) and ethyldimethylphosphate (product 7). It is suggested that two competing reactions are taking place; the methylation of the thiol compound, as shown above, and the base-catalysed cleavage of the phosphate-dichlorovinyl bond, as follows:

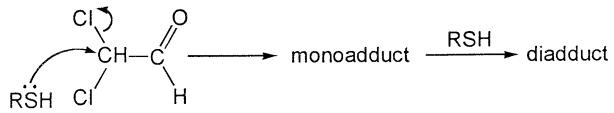


The dichlorovinyl moiety liberated is the enol form of DCA.

Nishizawa (1960) reports that DDVP reacts with ethanethiol to give product 8 in which both chlorine atoms of the DDVP molecule have been displaced by a nucleophilic reaction. In the present work, we have been unable to isolate any products with the dichlorovinyl ester moiety intact; instead, when the DDVP:thiol ratio is 1:3 (mol/mol), in methanol and in the presence of sodium methoxide as a catalyst, derivatives of acetaldehyde (products 9–11) are formed together with the S-methyl compound and trimethylphosphate. When the reactions are carried out in water, only products 9–11 are formed. We conclude that, in water, hydrolysis of the dichlorovinyl ester takes place spontaneously, i.e. without any participation from the thiol compound, e.g.



and that the derivative of acetaldehyde is formed as a result of a nucleophilic substitution of the two chlorine atoms of DCA, i.e.



Identical products were formed when DCA was allowed to react with the thiols under the same conditions, and the corresponding derivatives of 1,1-dichloroacetone (products 25–30) and MDCA (products 46, 47) could also be obtained, highlighting the reactivity of this dichloro-group.

Reaction of DDVP or DCA with mercaptoethanol gave rise to a substance which was identified tentatively as a bicyclic product (12). It is speculated that a bifunctional compound such as mercaptoethanol can react nucleophilically, as do the other thiols investigated, but the product cyclises by an, as yet, unknown mechanism. In contrast, reaction of 1,1-dichloroacetone with mercaptoethanol gives the usual diadduct (product 29). This could be reacting differently from DCA because its carbonyl group has a significantly lower reactivity, thereby preventing cyclisation.

Very different products are formed when phenols and substituted phenols react with the carbonyl group of DCA or 1,1-dichloroacetone to give products 13–24 where 2 mol of the phenolic compound react with 1 mol of the carbonyl compound. For the purposes of synthesis, this condensation reaction can be achieved most efficiently in the absence of solvent, using an excess of the phenol and H_2SO_4 as a catalyst at 35–40°C. Pure products can be obtained by simple recrystallisation. The reaction sequence leading to the products is suggested to involve nucleophilic attack by the phenol on the carbonyl group, followed by elimination of H_2O by the second molecule of phenol.

Glycine ethyl ester did not give the corresponding N-methyl derivative upon reaction with DDVP and, as expected, it is seen that the amino group is much less reactive as a nucleophile than the thiol group. The most important reactions investigated are those of a wide range of amines with DCA or 1,1-dichloroacetone, when Schiff bases 31–42 were isolated. These have not been obtained from aqueous solution, but it is anticipated that such products are formed reversibly, provided that the pH is not too low. It is particularly interesting to note that the Schiff base is formed preferentially when 1,1-dichloroacetone is allowed to react with amines which have also a thiol functional group (products 33 and 39). Furthermore, despite these products having an appropriate arrangement of atoms to allow cyclisation (through nucleophilic attack by $-SH$), they can be isolated in acyclic forms and appear to be stable. When the carbonyl group is replaced by a methyl ester, as in MDCA, reaction with a similar range of amines invariably gives the amides (products 45–55) with no evidence of attack at the $=CCl_2$ moiety.

CONCLUSION

In aqueous solution, DCA constitutes the reactive intermediate in the reactions of DDVP with nucleophiles. Thiols replace both chlorine atoms on this intermediate to give diadducts whereas amines react only with the carbonyl group. Phenol and substituted-phenols are expected to add to the carbonyl group.

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REFERENCES

Bedford, C. T. and Robinson, J. (1972) Alkylating properties of organophosphate. *Xenobiotica* **2**, 307–337.

Bull, D. L. and Ridgeway, R. L. (1969) Metabolism of trichlorfon in animals and plants. *Journal of Agricultural and Food Chemistry* **17**, 837–841.

Casida, J. E., McBribe, L and Niedermeir, R. P. (1962) Metabolism of 2,2-dichlorovinyl dimethyl phosphate in relation to residues in milk and mammalian tissues. *Journal of Agricultural and Food Chemistry* **10**, 370–377.

Hodgson, E. and Casida, J. E. (1962) Mammalian enzymes involved in the degradation of 2,2-dichlorovinyl dimethyl phosphate. *Journal of Agricultural and Food Chemistry* **10**, 208–214.

Lawley, P. D., Shah, S. A. and Orr, D. J. (1974) Methylation of nucleic acids by 2,2-dichlorovinyl dimethyl phosphate. *Chemico–Biological Interactions* **8**, 171–182.

Löfroth, G. (1970) Alkylation of DNA by dichlorvos. *Naturwissenschaften* **57**, 393–394.

Nishizawa, Y. (1960) Low-toxicity of organophosphorus insecticides. *Bulletin of the Agricultural Chemical Society of Japan* **24**, 261–264.

Pearson, R. G. and Songstadt, J. (1967) Application of the principle of hard and soft acids and bases to organic chemistry. *Journal of the American Chemical Society* **89**, 1827–1837.

Perkow, W. (1954) Reactions of alkyl phosphates I. Conversions with chloral and bromal. *Chemische Berichte* **87**, 755–758.