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Synthesis of Fungitoxic Analogues of *N*-(2,2,2-Trichloro-1-methoxyethyl)formamide

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Abstract

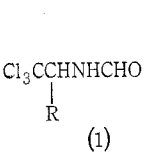
The synthesis of 40 fungitoxic analogues of the systemic fungicides *N*-(2,2,2-trichloro-1-methoxyethyl)formamide and triforine is described. The compounds comprise *N*-(2,2,2-trichloro-1-alkoxyethyl)formamides and related alkylaminoethyl, alkylthioethyl and arylthioethyl derivatives.

Systemic fungicidal activity against powdery mildew of wheat, *Erysiphe graminis*, has recently been demonstrated[1] for *N*-(2,2,2-trichloro-1-methoxyethyl)formamide (1; R = OMe), a compound related to the systemic fungicide triforine (2), *N*,*N*′-bis-(1-formamido-2,2,2-trichloroethyl)piperazine, which is active against several plant diseases.[2,3] In order to investigate the effect on biological activity of replacing the methoxyl group of (1; R = OMe) a number of compounds of the types (1; R = O–alkyl), (1; R = NH–alkyl) and (1; R = S–alkyl) have been prepared. Several *N*-(2,2,2-trichloro-1-arylthioethyl)formamides (3; X = S) have also been synthesized to compare their fungitoxicity with the antifungal properties of *N*-(2,2,2-trichloro-1-aryloxyethyl)formamides (3; X = O)[1,4] and *N*-(2,2,2-trichloro-1-arylaminoethyl)-formamides (3; X = NH).[1,5,6]

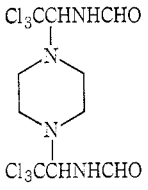
The original method used by Feist[7] for the preparation of (1; R = OMe) consisted of treating the ether (4) with sodium methoxide. Reaction of (1; R = OH)

[1] Carter, G. A., Summers, L. A., and Wain, R. L., *Ann. Appl. Biol.*, 1972, **70**, 233.
[2] Ost, W., Thomas, K., Jerchel, D., and Appel, K. R., Ger. Pat. 1901421 (1969) (*Chem. Abstr.*, 1970, **72**, 3053s).
[3] E.g. Schicke, P., and Veen, K. H., Proc. 5th Brit. Insect. Fungic. Conf., Brighton, 1969, p. 569; Fuchs, A., Doma, S., and Voros, J., *Neth. J. Plant Pathol.*, 1971, **77**, 42; Ost, W., von Bruchhausen, V., and Drandarevski, C., *Pestic. Sci.*, 1971, **2**, 219; Smith, P. M., and Spencer, D. M., *Pestic. Sci.*, 1971, **2**, 201; Ebenebe, C., Fehrmann, H., and Grossmann, F., *Plant Dis. Rep.*, 1971, **55**, 691; Fuchs, A., Viets-Verweij, M., Voros, J., and de Vries, F. W., *Acta Phytopathol.*, 1971, **6**, 347; Schicke, P., Adlung, K. G., and Drandarevski, C. A., Proc. 6th Brit. Insect. Fungic. Conf., Brighton, 1971, p. 82; Adlung, K. G., and Drandarevski, C. A., Proc. 6th Brit. Insect. Fungic. Conf., Brighton, 1971, p. 577; Fuchs, A., Viets-Verweij, M., and de Vries, F. W., *Phytopathol. Z.*, 1972, **75**, 11; Gilpatrick, J. D., *Plant Dis. Rep.*, 1973, **57**, 457; Sherald, J. L., Ragsdale, N. N., and Sisler, H. D., *Pestic. Sci.*, 1973, **4**, 719.
[4] Summers, L. A., *Aust. J. Chem.*, 1972, **25**, 671.
[5] Malz, H., Grewe, F., Dorken, A., and Kaspers, H., Brit. Pat. 1123850 (1968) (*Chem. Abstr.*, 1969, **70**, 3506a).
[6] Vogeler, K., *Pflanzenschutz-Nachr.* '*Bayer*', 1969, **22**, 289.
[7] Feist, F., *Ber. Deut. Chem. Ges.*, 1912, **45**, 956.

with dimethyl sulphate also gave (1; R = OMe) but in low yield.[7] Since then there have been no reports of the preparation of compounds of type (1; R = O–alkyl) although analogous derivatives of acetamide, e.g. (5; R = OMe and OEt), have been obtained from (5; R = Cl) either by making the intermediate pyridine salt (6; R = Me) react with the appropriate alcohol[8] or by treating the intermediate (7; R = Me) with an alcohol.[9] The last method has recently been modified[10] for the preparation of compounds of type (8) from (1; R = Cl) and dihydric alcohols.



(1)



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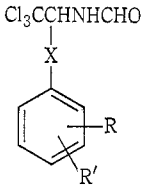

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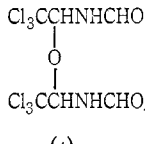
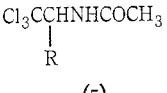


(4)



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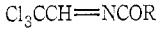

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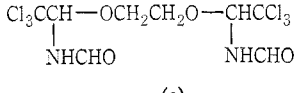

(8)

Table 1. ***N*-(2,2,2-Trichloro-1-alkoxyethyl)formamides (1)**

Solvent of recrystallization was light petroleum except where indicated otherwise

R	M.p. (°C)	B.p. (°C/mm)	Molecular formula	Found (%) C	H	N	Requires (%) C	H	N
OC_2H_5	—	110/1	$C_5H_8Cl_3NO_2$	27·5	3·6	6·0	27·2	3·6	6·3
$O(CH_2)_2CH_3$	—	106/0·4	$C_6H_{10}Cl_3NO_2$	30·8	4·1	6·0	30·7	4·2	5·9
$OCH(CH_3)_2$	53	—	$C_6H_{10}Cl_3NO_2$	30·5	4·2	6·0	30·7	4·2	5·9
$O(CH_2)_3CH_3$	—	109/0·2	$C_7H_{12}Cl_3NO_2$	34·1	5·0	5·7	33·8	4·8	5·6
$OCH_2CH(CH_3)_2$	62	—	$C_7H_{12}Cl_3NO_2$	34·1	4·6	5·5	33·8	4·8	5·6
$OCH(CH_3)CH_2CH_3$	—	130/2	$C_7H_{12}Cl_3NO_2$	34·1	4·7	5·7	33·8	4·8	5·6
$OC(CH_3)_3$	97[A]	—	$C_7H_{12}Cl_3NO_2$	34·0	4·7	5·5	33·8	4·8	5·6
$O(CH_2)_4CH_3$	—	141/1	$C_8H_{14}Cl_3NO_2$	36·9	5·3	5·5	36·6	5·3	5·3
$OCH_2CH{=}CH_2$	—	117/0·7	$C_6H_8Cl_3NO_2$	31·3	3·3	6·0	31·0	3·4	6·0

[A] Recrystallized from light petroleum–benzene.

We prepared (1; R = OMe) by treating (1; R = Cl) with sodium methoxide but higher members of the series (1; R = O–alkyl) were not readily prepared from the corresponding sodium alkoxides due to their decomposition in the strongly alkaline conditions. The *N*-(2,2,2-trichloro-1-alkoxyethyl)formamides, listed in Table 1, were

[8] Dovlatyan, V. V., and Kostanyan, D. A., *Arm. Khim. Zh.*, 1966, **19**, 612 (*Chem. Abstr.*, 1967, **66**, 75781b).

[9] Drach, B. S., Sinitsa, A. D., and Kirsanov, A. V., *Zh. Obshch. Khim.*, 1969, **39**, 2192 (*Chem. Abstr.*, 1970, **72**, 42706b).

[10] Ost, W., Thomas, K., and Jerchel, D., Ger. Pat. 2030464 (1971) (*Chem. Abstr.*, 1971, **74**, 141007x).

much more easily prepared from (1; R = Cl), and in good yield, by making the pre-formed pyridine salt (6; R = H)[11] react with the appropriate alcohol (cf.[8]).

There are several possible routes to *N*-(2,2,2-trichloro-1-alkylaminoethyl)-formamides (1; R = NH–alkyl) based on modifications of methods adopted for the preparation of related arylamino compounds (cf.[4]). The chlorine atom of (1; R = Cl) may be replaced by reaction with amines while treatment of (7; R = H) with amines provides another route to these derivatives. A third method utilizes

Table 2. *N*-(2,2,2-Trichloro-1-alkylaminoethyl)formamides (1)
Solvent of recrystallization is benzene–light petroleum

R	M.p. (°C)	Molecular formula	Found (%) C	H	N	Requires (%) C	H	N
$NH(CH_2)_2CH_3$	[A]	$C_6H_{11}Cl_3N_2O$	31·3	4·9	11·8	30·8	4·7	12·0
$NHCH(CH_3)_2$	72	$C_6H_{11}Cl_3N_2O$	30·8	5·0	11·8	30·8	4·7	12·0
$NH(CH_2)_3CH_3$	[A]	$C_7H_{13}Cl_3N_2O$	34·2	5·4	11·0	33·9	5·2	11·3
$NHCH_2CH(CH_3)_2$	82	$C_7H_{13}Cl_3N_2O$	34·2	5·5	11·6	33·9	5·2	11·3
$NHCH(CH_3)CH_2CH_3$	57	$C_7H_{13}Cl_3N_2O$	34·3	5·5	11·6	33·9	5·2	11·3
$NHC(CH_3)_3$	121	$C_7H_{13}Cl_3N_2O$	34·1	5·5	11·7	33·9	5·2	11·3
$NH(CH_2)_4CH_3$	[A]	$C_8H_{15}Cl_3N_2O$	37·1	5·7	10·4	36·7	5·7	10·7
$NHCH_2CH{=}CH_2$	65	$C_6H_9Cl_3N_2O$	31·0	4·1	11·8	31·1	3·9	12·1

[A] Oil which decomposed on attempted distillation at 1 mm.

Table 3. *N*-(2,2,2-Trichloro-1-alkylthioethyl)formamides (1)
Solvent of recrystallization is benzene–light petroleum unless indicated otherwise

R	M.p. (°C)	Molecular formula	Found (%) C	H	N	Requires (%) C	H	N
SCH_3	126[A]	$C_4H_6Cl_3NOS$	21·8	2·4	6·4	21·5	2·7	6·3
SC_2H_5	96[B]	$C_5H_8Cl_3NOS$	25·6	3·3	5·9	25·3	3·4	5·9
$S(CH_2)_2CH_3$	90	$C_6H_{10}Cl_3NOS$	28·7	3·9	5·6	28·7	4·0	5·6
$SCH(CH_3)_2$	92	$C_6H_{10}Cl_3NOS$	28·9	3·8	5·6	28·7	4·0	5·6
$S(CH_2)_3CH_3$	32	$C_7H_{12}Cl_3NOS$	31·3	4·4	5·4	31·7	4·5	5·3
$SCH_2CH(CH_3)_2$	[C]	$C_7H_{12}Cl_3NOS$	31·4	4·3	5·4	31·7	4·5	5·3
$SCH(CH_3)CH_2CH_3$	59	$C_7H_{12}Cl_3NOS$	31·9	4·4	5·2	31·7	4·5	5·3
$SC(CH_3)_3$	118	$C_7H_{12}Cl_3NOS$	31·5	4·6	5·5	31·7	4·5	5·3
$SCH_2CH{=}CH_2$	81	$C_6H_8Cl_3NOS$	28·8	3·0	5·7	29·0	3·2	5·6

[A] Lit.[2] 122–123°. [B] Recrystallized from benzene. [C] Oil which decomposed on attempted distillation at 1 mm.

the reaction of alkyl isocyanates with (1; R = OH) whereby *N*-(2,2,2-trichloro-1-alkylaminoethyl)formamides are formed with accompanying evolution of carbon dioxide. This last method has been used to prepare *N*-(2,2,2-trichloro-1-methyl-aminoethyl)formamide (1; R = NHMe)[5] and we prepared the corresponding ethylamino derivative (1; R = NHEt) in a similar way. The higher members of the *N*-(2,2,2-trichloro-1-alkylaminoethyl)formamide series (Table 2) were obtained by reaction of (1; R = Cl) with equivalent amounts of the appropriate amine in the presence of triethylamine (cf.[9,12]).

[11] Boehme, H., Eiden, F., and Schunemann, D., *Arch. Pharm.* (Weinheim), 1961, **294**, 307.
[12] Ulrich, H., Tucker, B., and Sayigh, A. A. R., *J. Org. Chem.*, 1968, **33**, 2887.

N-(2,2,2-Trichloro-1-alkylthioethyl)formamides (Table 3) and *N*-(2,2,2-trichloro-1-arylthioethyl)formamides (Table 4) were prepared similarly by treating *N*-(1,2,2,2-tetrachloroethyl)formamide (1; R = Cl) with the appropriate thiol in aqueous alkali (cf.[4,10,13,14]).

The results of biological tests for fungicidal activity on these series of compounds are reported elsewhere.[15]

Table 4. *N*-(2,2,2-Trichloro-1-arylthioethyl)formamides (3; X = S)

Solvent of recrystallization is benzene–light petroleum

R	R′	M.p. (°C)	Molecular formula	Found (%) C	H	N	Requires (%) C	H	N
H	H	94[A]	$C_9H_8Cl_3NOS$	37·8	3·0	5·0	37·8	3·0	4·9
H	2-Me	130	$C_{10}H_{10}Cl_3NOS$	40·4	3·5	4·9	40·1	3·6	4·6
H	3-Me	108	$C_{10}H_{10}Cl_3NOS$	40·2	3·7	4·7	40·1	3·6	4·6
H	4-Me	144	$C_{10}H_{10}Cl_3NOS$	40·0	3·6	4·7	40·1	3·6	4·6
H	2-Cl	134	$C_9H_7Cl_4NOS$	33·8	2·4	4·5	33·8	2·3	4·4
H	3-Cl	139	$C_9H_7Cl_4NOS$	33·7	2·4	4·5	33·8	2·3	4·4
H	4-Cl	178	$C_9H_7Cl_4NOS$	34·0	2·4	4·4	33·8	2·3	4·4
H	4-NO_2	167	$C_9H_7Cl_3N_2O_3S$	32·8	2·3	8·3	32·7	2·3	8·5
2-Cl	4-Cl	133	$C_9H_6Cl_5NOS$	30·6	1·7	3·9	30·6	1·7	4·0
3-Cl	4-Cl	143	$C_9H_6Cl_5NOS$	30·4	1·6	3·9	30·6	1·7	4·0

[A] Lit. 82° (Boehme, H., and Mueller, A., *Arch. Pharm.* (Weinheim), 1963, **296**, 54).

Experimental

Microanalyses were performed by Dr F. B. Strauss, Microanalytical Laboratories, Oxford. The n.m.r. spectrum (60 MHz) was determined for a 10% w/v solution in deuterochloroform with tetramethylsilane as internal standard. Petrol as solvent refers to light petroleum of b.p. 60–80°.

N-(*2,2,2-Trichloro-1-methoxyethyl*)*formamide* (*1*; *R* = *OMe*)

N-(1,2,2,2-Tetrachloroethyl)formamide[16,17] (1; R = Cl) (3 g) in methanol (15 ml) was treated at 20° with sodium methoxide dissolved in methanol [from sodium (0·4 g) and methanol (15 ml)]. An immediate reaction occurred. The mixture was cooled and filtered, and the solvent partly removed under vacuum. The residue was diluted with water. The precipitate (1·5 g) of the product was collected. It crystallized from benzene–petrol as colourless crystals, m.p. 140° (lit.[7] 139°) (Found: C, 23·4; H, 2·6; N, 6·7. Calc. for $C_4H_6Cl_3NO_2$: C, 23·2; H, 2·9; N, 6·7%). It showed an i.r. absorption (Nujol mull) at 1680 cm^{-1} (CO). The n.m.r. spectrum showed a singlet at δ 3·61 (OCH_3), a doublet at 5·60–5·78 (CCl_3CH), a broad signal centred at 6·45 (NH) and a singlet at 8·50 (CHO).

N-(*2,2,2-Trichloro-1-alkoxyethyl*)*formamides*

These compounds (Table 1) were prepared as follows: 1-(2,2,2-trichloro-1-formamidoethyl)-pyridinium chloride[11] (6; R = H) (0·05 mol) was suspended in excess of the appropriate alcohol (0·25 mol) and the mixture heated on a steam bath for 20 min. The resultant mixture was poured onto crushed ice. An oil formed which sometimes solidified on standing at 2–48 h at 0°. The solid was washed with water, dried and crystallized. If the oil did not solidify it was extracted into ether.

[13] Boehme, H., and Mueller, A., *Arch. Pharm.* (Weinheim), 1963, **296**, 54.
[14] Weygand, F., Steglich, W., Lengyel, I., Fraunberger, F., Maierhofer, A., and Oettmeier, W., *Chem. Ber.*, 1966, **99**, 1944.
[15] Carter, G. A., Chamberlain, K., and Wain, R. L., *Ann. Appl. Biol.*, 1973, **75**, 49.
[16] Pianka, M., Edwards, J. D., and Smith, C. B. F., *J. Sci. Food Agr.*, 1966, **17**, 407.
[17] Pianka, M., and Edwards, J. D., Brit. Pat. 993051 (1965) (*Chem. Abstr.*, 1965, **63**, 9822).

The solution was then dried and the solvent evaporated. The residual oil was distilled under reduced pressure. Yields were 40–70%. All the products showed i.r. absorptions at about 1670–1690 cm^{-1} (CO).

N-(*2,2,2-Trichloro-1-methylaminoethyl)formamide* (*1*; *R* = *NHMe*)

Methyl isocyanate (6 g) in benzene (100 ml) was slowly added to a mixture of *N*-(2,2,2-trichloro-1-hydroxyethyl)formamide (1; R = OH) (19·3 g) and benzene (150 ml). Triethylamine (2 drops) was added and an exothermic reaction took place with the evolution of carbon dioxide. The reaction mixture was agitated at 35–40° until gas evolution ceased and was then cooled. The solid product was collected and dried. It crystallized from benzene and had m.p. 128° (lit.[5] 90°) (Found: C, 23·2; H, 3·4; N, 13·4. Calc. for $C_4H_7Cl_3N_2O$: C, 23·3; H, 3·4; N, 13·6%). Yield 40%.

N-(*2,2,2-Trichloro-1-ethylaminoethyl)formamide* (*1*; *R* = *NHEt*)

This *compound* was prepared similarly from ethyl isocyanate and *N*-(2,2,2-trichloro-1-hydroxyethyl)formamide. It crystallized from petrol–benzene and had m.p. 59° (Found: C, 27·0; H, 4·1; N, 12·4. $C_5H_9Cl_3N_2O$ requires C, 27·3; H, 4·1; N, 12·7%).

N-(*2,2,2-Trichloro-1-alkylaminoethyl)formamides*

These compounds (Table 2) were prepared as follows: *N*-(1,2,2,2-tetrachloroethyl)formamide[16,17] (1; R = Cl) (0·02 mol) was dissolved in tetrahydrofuran (25 ml) and a mixture of the appropriate alkylamine (0·02 mol) and triethylamine (0·02 mol) in tetrahydrofuran (25 ml) was slowly added with stirring, which was continued for 2 h at 20°. The mixture was then filtered and the solvent evaporated from the filtrate under reduced pressure. The residual oil (yields 50–75%) sometimes crystallized on standing. The solid was then recrystallized from benzene–petrol. In some cases the oils did not solidify and attempts to distil them at 1 mm pressure resulted in their decomposition. All the products showed i.r. absorptions at about 1660–1690 cm^{-1} (CO).

N-(*2,2,2-Trichloro-1-alkylthioethyl)formamides*

These compounds (Table 3) were prepared as follows: the appropriate alkylthiol (0·02 mol) was dissolved in a solution of sodium hydroxide (0·02 mol) in water (30 ml). This solution was added to *N*-(1,2,2,2-tetrachloroethyl)formamide (0·02 mol) in acetone (20 ml). A solid usually precipitated immediately, but in some cases an oil was formed which solidified on standing. In one case the oil did not solidify. The solids were washed with water and crystallized from benzene–petrol. Yields were 60–85%. All the products showed i.r. absorptions at about 1670–1690 cm^{-1} (CO).

N-(*2,2,2-Trichloro-1-arylthioethyl)formamides*

These compounds (Table 4) were prepared as follows: *N*-(1,2,2,2-tetrachloroethyl)formamide (0·02 mol) and the appropriate arylthiol (0·02 mol) were dissolved in acetone (20 ml). A solution of sodium hydroxide (0·02 mol) in water (30 ml) was then added rapidly with stirring. The product which precipitated was crystallized from benzene–petrol. Yields were 60–85%. All the products showed i.r. absorptions at about 1670–1690 cm^{-1} (CO).

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