604. *Trichloromethylthio-derivatives of Biological Interest.**

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A number of new *S*-alkoxy- and *S*-amino-derivatives from trichloromethanesulphenyl chloride, and several tetrachlorotetrahydrodithiadiazines have been prepared. Most of them showed biological activity against selected fungi.

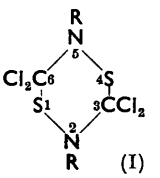
ATTENTION has been drawn recently to the fungicidal activity of compounds containing a trichloromethylthio-radical attached to a nitrogen atom [1] (*e.g.*, tetrahydro-*N*-trichloromethylthiophthalimide, " Orthocide "). The present work was designed to produce further compounds of this type and to determine whether the activity was affected by the replacement of the nitrogen–sulphur by an oxygen–sulphur linkage or by the elimination of one of the chlorine atoms.

At first, difficulty was experienced in condensing compounds containing an active hydrogen atom with trichloromethanesulphenyl chloride. Alcohols gave orthocarbonic esters, and amines formed highly coloured materials; to preserve the trichloromethylthio-radical intact, careful control of temperature was required. A number of condensing agents were used for the synthesis of *S*-alkoxytrichloromethanethiols. Trichloro-*S*-methoxymethanethiol was prepared by using sodium methoxide,[2] or, better, magnesium methoxide; potassium hydroxide in methanol gave the same product and was used with other simple alcohols.

When an excess of the alcohol was undesirable or the other reagents gave poor results, pyridine in an inert solvent was useful; *e.g.*, trichloro-*S*-(tetrahydrofurfuryloxy)methanethiol was obtained only by the use of pyridine, since potassium hydroxide caused degradation.

Pyrrolidine, piperidine, ethylenediamine, and piperazine were selected as amines for study because many biologically active derivatives of them are known. Connolly and Dyson [2] used aqueous sodium carbonate to condense trichloromethanesulphenyl chloride with organic bases and this technique was used in several instances. Since presence of water led to the partial decomposition of some of the products, and use of pyridine in an inert solvent gave poor yields of impure products, it was found better to use an excess of the amine taking part in the reaction.

Connolly and Dyson [3] cyclised trichloro-*S*-*p*-toluidinomethanethiol by alcoholic potassium hydroxide to form the tetrachlorotetrahydrodi-*p*-tolyl-1 : 4-dithia-2 : 5-diazine (I; R = *p*-tolyl). This was repeated and the analogous reactions were carried out with *o*- and *m*-toluidine but without isolation of the intermediate stages.



(I)

The biological tests are tabulated. The dithiadiazines were inactive. The results indicate that the nitrogen–sulphur linkage is not an essential feature of the activity of compounds related to " Orthocide," but there are other effects that cannot be explained at present.

* Patents pending.

[1] Kittleson, U.S.P. 2,553,770.
[2] Cf. Connolly and Dyson, *J.*, 1937, 827.
[3] Connolly and Dyson, *J.*, 1934, 822.

Experimental

Microanalyses were carried out by Dr. W. Zimmerman of the C.S.I.R.O., Melbourne.

Preparation of Mono- and Bis-trichloromethylthio-derivatives.—The compounds prepared are tabulated : only the methods giving the best yields are shown. Examples are detailed below. The reaction mixtures were diluted with water after the additions were completed, and the products extracted with ether and fractionally distilled or, for solids, recrystallized from methylene chloride and ether.

(*A*) To propan-1-ol (60 ml.), pyridine (20 ml.), and ether (20 ml.) at 0° was added a solution of trichloromethanesulphenyl chloride (21 ml.) in ether (100 ml.).

(*B*) A solution of trichloromethanesulphenyl chloride (10·8 ml.) in ether (50 ml.) was added slowly to a mixture of pyrrolidine (7·1 g.), sodium carbonate (10·5 g.), water (100 ml.), and ether (50 ml.), at 0°—5°.

(*C*) Trichloromethanesulphenyl chloride (10·8 ml.) in ether (50 ml.) was added to piperidine (15 g.) in ether (100 ml.) at 0° with stirring.

Trichloromethylthio-derivatives $CCl_3 \cdot SR$ *and* $(CCl_3 \cdot S)_2X$.

No.	R	Method of prepn.	Yield (%)	B. p./mm. (m. p.)	Biological activity *				
					F	*P*	*B*	*S*	*A*
1	OMe	*A*	69	63°/30	—	+	+	—	—
2	OPr^n	*A*	47	36—38°/1	+	+	+	—	+
3	OPr^i	*A*	53	67—68°/12	—	+	+	—	—
4	OBu^n	*A*	40	90—92°/11	—	—	—	—	—
5	OBu^i	*A*	55	63—64°/5	—	+	+	—	—
6	Allyloxy	*A*	58	106—108°/9	—	+	—	+	+
7	Pent-4-enyloxy	*A*	58	72°/1	—	+	—	—	—
8	Tetrahydrofurfuryloxy	*A*	88	116°/2	—	+	+	—	+
9	Pyrrolidino	*B*	39	68—70°/1	—	+	+	—	—
10	Piperidino	*C*	55	(29—30°)	—	+	+	—	—
11	*p*-Toluidino	*F*	64	(74—75°)	+	+	+	—	—
12	$X = -NH \cdot CH_2 \cdot CH_2 \cdot NH-$	*D*	53	(42—43°)	+	+	+	—	+
13	1 : 4-Bis(trichloromethylthio)-piperazine	*E*	89	(164—165°)	—	—	—	—	—

* *F*, *Fusarium graminaerum*. *P*, *Pythium ultimum*. *B*, *Botrytis allii*. *S*, *Saccharomyces cerevisiae*. *A*, *Aspergillus niger*. + = Inhibition of growth at 400 μg./ml. None of the compounds was active at 80 μg./ml.

No.	Found (%) : C	H	S	Cl	O or N	Formula	Required (%) : C	H	S	Cl	O or N
1	—	—	17·6	58·7	—	$C_2H_3OSCl_3$	—	—	17·3	58·3	—
2	23·2	3·8	15·7	—	8·2	$C_4H_7OSCl_3$	22·8	3·3	15·3	—	7·7
3	22·7	3·5	15·2	51·1	—	,,	22·8	3·3	15·3	51·2	—
4	27·6	4·4	14·5	47·5	—	$C_5H_9OSCl_3$	26·8	4·0	14·2	47·8	—
5	—	—	14·3	47·3	—	,,	—	—	14·2	47·8	—
6	23·3	2·7	15·9	51·0	—	$C_4H_5OSCl_3$	23·2	2·4	15·4	51·3	—
7	31·0	4·1	13·6	—	7·3	$C_6H_9OSCl_3$	30·6	3·8	13·6	—	6·8
8	28·6	3·6	13·1	—	12·9	$C_6H_9O_2SCl_3$	28·6	4·0	12·8	—	12·8
9	27·1	3·7	14·1	—	—	$C_5H_8NSCl_3$	27·2	3·6	14·6	—	—
10	—	—	13·7	45·0	5·6	$C_6H_{10}NSCl_3$	—	—	13·6	45·0	6·0
12	13·5	1·9	18·2	—	7·8	$C_4H_6N_2S_2Cl_6$	13·3	1·7	17·8	—	7·8
13	—	—	18·8	—	7·5	$C_6H_8N_2S_3Cl_6$	—	—	18·8	—	7·3

(*D*) To ethylenediamine (6 g.) and sodium carbonate (5 g.) in water (100 ml.) at 0° trichloromethanesulphenyl chloride (3 g.) in ether (50 ml.) was added with stirring.

(*E*) Trichloromethanesulphenyl chloride (10 ml.) was added dropwise to a mixture of piperazine hexahydrate (8 g.), 2N-sodium hydroxide (100 ml.), and ether (100 ml.) at <15°.

(*F*) To *p*-toluidine (10·8 g.) and pyridine (10 ml.) in ether (100 ml.) at 0—5° was added with stirring trichloromethanesulphenyl chloride (11 ml.) in ether (50 ml.).

3 : 3 : 6 : 6-*Tetrachloro*-2 : 3 : 5 : 6-*tetrahydro*-2 : 5-*di*-p-*tolyl*-1 : 4-*dithia*-2 : 5-*diazine*.—Crude trichloro-*S*-*p*-toluidinomethanethiol (12·8 g.) was dissolved in ether (300 ml.), and potassium hydroxide (8 g.) in dry ethanol (75 ml.) was added during 4 hr. with cooling and stirring. Water (150 ml.) was then added and the solid product collected. Evaporation of the ethereal layer of the filtrate gave more of the same material. Recrystallization from ethanol–methylene chloride gave a product (9 g.), m. p. 142° (decomp.) (cf. Connolly and Dyson [3]).

3 : 3 : 6 : 6-*Tetrachloro*-2 : 3 : 5 : 6-*tetrahydro*-2 : 5-*di*-m-*tolyl*-1 : 4-*dithia*-2 : 5-*diazine*.—*m*-Toluidine (12 g.), sodium carbonate (8 g.), trichloromethanesulphenyl chloride (10·8 ml.), and ether (200 ml.) were refluxed for 1 hr. The product was precipitated as an oil and its solution in ether was used, without further treatment, as described in the preceding paragraph. Recrystallization from ethanol or methylene chloride gave the *product*, m. p. 106° (Found : C, 44·1; H, 3·4; N, 6·2; S, 14·7; Cl, 32·3. $C_{16}H_{14}N_2S_2Cl_4$ requires C, 43·8; H, 3·2; N, 6·4; S, 14·6; Cl, 32·3%).

The *o-tolyl* isomer, similarly prepared, had m. p. 111—112° (Found : S, 14·4; Cl, 32·6%).

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