439. *Trihalogenomethyl Compounds of Potential Therapeutic Interest. Part II.*[1] *The Synthesis of Some 2- and 5-Trichloromethyl-4-oxazolidones.*

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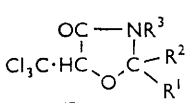
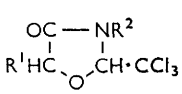
Series of 2- and 5-trichloromethyl-4-oxazolidones (I and II) have been prepared for biological testing.

In Part I [1] of this series we described the preparation of 2,5-bistrichloromethyl-4-oxazolidone (I; $R^1 = R^3 = H$, $R^2 = CCl_3$) and its degradation with alkali to the corresponding 5-dichloromethylene compound (III; $R^1 = R^3 = H$, $R^2 = CCl_3$). Neither compound showed appreciable pharmacological activity. The present paper deals with two series of compounds, (I) and (II), possessing only one trichloromethyl grouping. Both series were prepared by condensating the appropriate α-hydroxy-amides and carbonyl compounds in the presence of an acid catalyst with removal of water of reaction azeotropically; [2] for the lower aldehydes which were too volatile for this procedure, their acetals were used instead. In the first series (I), trichlorolactamide was condensed with a wide variety of aliphatic and aromatic aldehydes and ketones including some keto-esters, alkoxy-ketones, etc., and in general the yields were satisfactory. Where R^1 and R^2 were different, *cis*- and *trans*-isomers were formed concurrently and were, in many cases, separated by fractional crystallisation; we have designated these as α- and β-isomers corresponding to the higher- and lower-melting forms, respectively.


(I)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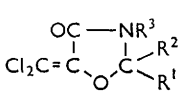
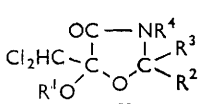

(III)


(IV)

N-Methylation was effected in a few cases by treatment at 0° with an equivalent of sodium hydroxide and dimethyl sulphate; under more drastic conditions with an excess of base, *N*-methylation took place with concomitant elimination of hydrogen chloride to give the corresponding 5-dichloromethylene-3-methyl derivatives (III; $R^3 = Me$). With

[1] Part I, Bowman, Campbell, and Tanner, *J.*, **1963**, 692.
[2] Cornforth and Cornforth, *J.*, **1949**, 1028.

sodium ethoxide and methoxide, however, the products were the corresponding 5-alkoxy-5-dichloromethyl-4-oxazolidones (IV; $R^4 = H$) since reductive dehalogenation followed by hydrolysis yielded pyruvic acid; with methyl iodide and two mol. of alkoxide the corresponding 3-methyl derivatives (IV; $R^4 = Me$) were produced. We presumed that these alkoxy-derivatives were formed by base-catalysed addition of alkanol to the 5-dichloromethylene compounds formed initially in the presence of base and, indeed, it was found that this provided an alternative method for their preparation. A number of the simpler 5-trichloromethyl-4-oxazolidones showed hypnotic activity in mice, the most active being the β-isomer of compound (I; $R^1 = Me$, $R^2 = Pr^n$, $R^3 = H$) which was active at 16 mg./kg.

In the second main series, *viz.*, the 2-trichloromethyl-4-oxazolidones (II), fewer compounds were prepared since pharmacological activity was restricted to the lower homologues; attempts to use tertiary α-hydroxy-amides were not successful, probably owing to their ready dehydration under the reaction conditions. 2-Trichloromethyl-4-oxazolidones are more stable to alkali than the corresponding 5-derivatives [1] and *N*-alkylation was effected readily. Thioglycollamide was condensed with chloral to give 2-trichloromethyl-4-thiazolidone from which the corresponding sulphoxide and sulphone were obtained by standard methods. The most active member of series (II) was 3-methyl-2-trichloromethyl-4-oxazolidone (II; $R^1 = H$, $R^2 = Me$) which antagonised metrazole convulsions in rodents at doses down to 32 mg./kg. without signs of obvious neurotoxicity.

Experimental

Preparation of 2- and 5-Trichloromethyl-4-oxazolidones.—A mixture of the appropriate α-hydroxy-amide (0·1 mole), carbonyl compound (0·12 mole), benzene or toluene (100 ml.), and toluene-*p*-sulphonic acid (0·01 mole) was refluxed through a Dean and Stark apparatus until no further water was evolved. The cooled mixture was washed with aqueous sodium hydrogen *carbonate*, then water, and the solvent was removed *in vacuo*. The residue was crystallised from the appropriate solvent; where two isomers were obtained, these were separated by repeated fractional crystallisation. *Compounds* prepared in this manner from trichlorolactamide or chloral are listed, respectively, in Tables 1 and 2.

In three cases where the aldehyde was too volatile for the above procedure, its acetal (0·2 mole) was used and the reaction carried out with trichlorolactamide (0·2 mole) in cyclohexane (300 ml.) in the presence of toluene-*p*-sulphonic acid (0·01 mole) with removal of ethanol of reaction as its azeotrope with cyclohexane (b. p. 65°). In this manner 5-*trichloromethyl*-4-*oxazolidone*, plates (from methanol), m. p. 229° (Found: C, 23·4; H, 2·2. $C_4H_4Cl_3NO_2$ requires C, 23·5; H, 2·0%), 2-*methyl*-, b. p. 116°/0·01 mm., n_D^{20} 1·5250 (Found: C, 27·6; H, 2·8. $C_5H_6Cl_3NO_2$ requires C, 27·5; H, 2·8%), and 2-*ethyl*-5-*trichloromethyl*-4-*oxazolidone*, b. p. 101°/0·005 mm., n_D^{20} 1·5258 (Found: C, 31·2; H, 3·5. $C_6H_8Cl_3NO_2$ requires C, 31·0; H, 3·5%), were obtained.

3-*Alkyl*-2-*trichloromethyl*-4-*oxazolidones* (II; R^2 = Alkyl).—These *compounds* are also listed in Table 2 and were obtained in substantially the same yield by either of the two following methods: (*a*) The parent oxazolidone (0·02 mole) in acetone (50 ml.) containing the alkyl halide (0·06 mole) and anhydrous potassium carbonate (0·06 mole) was heated on the steam-bath under reflux for 3 hr. and the mixture was then poured into water. The product was isolated with ether. (*b*) A solution of the oxazolidone (0·02 mole) in methanol containing sodium methoxide (0·025 mole) and the alkyl halide (0·025 mole) was refluxed for 2 hr. and worked up as above.

3-*Methyl*-5-*trichloromethyl*-4-*oxazolidones* (I; $R^3 = Me$).—Dimethyl sulphate (0·11 mole) was added to a solution of the oxazolidone (0·1 mole) in ethanol (100 mole) and N-sodium hydroxide (100 ml.) at 0°. After being stirred at this temperature for 24 hr., the mixture was neutralised with acetic acid and diluted with water; the product (20—35%) was then isolated with ether and crystallised from light petroleum (b. p. 40—60°). In this manner 2,2,3-*trimethyl*-, needles, m. p. 101—102° (Found: C, 34·1; H, 4·1. $C_7H_{10}Cl_3NO_2$ requires C, 34·2; H, 4·1%), 2,2-*diethyl*-3-*methyl*-, prisms, m. p. 66—67° (Found: C, 39·4; H, 5·1. $C_9H_{14}Cl_3NO_2$ requires C, 39·4; H, 5·1), and 2,3-*dimethyl*-2-*n*-*propyl*-5-*trichloromethyl*-4-*oxazolidone* (α-isomer)

TABLE 1.

5-Trichloromethyl-4-oxazolidones (I; $R^3 = H$).

R^1	R^2	Isomer	Yield (%)	M. p.	Form *	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
Me	Et	α	17	141—143°	Prisms	$C_7H_{10}Cl_3NO_2$	33·8	4·1	34·1	4·1
Me	Et	β	16	123—125	Prisms	$C_7H_{10}Cl_3NO_2$	34·0	3·9	34·1	4·1
Et	Et		70	119—120	Prisms	$C_8H_{12}Cl_3NO_2$	36·7	4·4	36·9	4·6
Me	Pr^n	α	22	148—149	Prisms	$C_8H_{12}Cl_3NO_2$	37·0	4·5	36·9	4·6
Me	Pr^n	β	2·5	134—135	Needles	$C_8H_{12}Cl_3NO_2$	37·1	4·8	36·9	4·6
Me	Pr^i	α	17·5	169—170	Needles	$C_8H_{12}Cl_3NO_2$	36·9	4·7	36·9	4·6
Me	Pr^i	β	3·5	139—140	Needles	$C_8H_{12}Cl_3NO_2$	36·8	4·4	36·9	4·6
Me	Bu^n	α	39	133—134	Prisms	$C_9H_{14}Cl_3NO_2$	39·4	5·0	39·4	5·1
Me	Bu^n	β	35	101—102	Needles	$C_9H_{14}Cl_3NO_2$	39·6	5·1	39·4	5·1
Me	Bu^i	α	56	132	Prisms	$C_9H_{14}Cl_3NO_2$	39·5	4·9	39·4	5·1
Me	Bu^i	β	5	116—117	Needles	$C_9H_{14}Cl_3NO_2$	39·6	5·0	39·4	5·1
Me	Bu^t	α	28	212—214	Needles	$C_9H_{14}Cl_3NO_2$	39·5	5·2	39·4	5·1
Me	Bu^t	β	1	166—170	Needles	$C_9H_{14}Cl_3NO_2$	39·1	4·9	39·4	5·1
Me	Allyl	α	14	152—153	Prisms	$C_9H_{12}Cl_3NO_2$	39·6	4·3	39·7	4·4
Me	Allyl	β	6·6	112—114	Needles (*a*)	$C_9H_{12}Cl_3NO_2$	39·8	4·4	39·7	4·4
Me	n-C_7H_{15}	α	13	138—139	Prisms	$C_{12}H_{20}Cl_3NO_2$	45·7	6·1	45·5	6·4
Me	n-C_7H_{15}	β	22	101—102	Needles	$C_{12}H_{20}Cl_3NO_2$	45·3	6·3	45·5	6·4
Me	CH_2·COMe	α	20	167—170	Prisms	$C_8H_{10}Cl_3NO_3$	35·2	3·5	35·0	3·7
Me	CH_2·COMe	β	15	143—146	Needles	$C_8H_{10}Cl_3NO_3$	35·2	3·6	35·0	3·7
Me	CH_2·CO_2Me	α	6	159—160	Needles	$C_8H_{10}Cl_3NO_4$	33·0	3·7	33·1	3·5
Me	CH_2·CO_2Me	β	5	157—159	Plates	$C_8H_{10}Cl_3NO_4$	33·0	3·5	33·1	3·5
Me	CH_2·CO_2Et	α	14	137	Plates	$C_9H_{12}Cl_3NO_4$	35·5	3·8	35·5	4·0
Me	CH_2·CO_2Et	β	5	95—98	Plates	$C_9H_{12}Cl_3NO_4$	35·7	4·0	35·5	4·0
Pr^n	Pr^n		26	101—103	Needles	$C_{10}H_{16}Cl_3NO_2$	41·5	5·4	41·6	5·6
Spirocyclopentane			54	178—179	Plates	$C_8H_{10}Cl_3NO_2$	37·4	3·9	37·2	3·9
Spirocyclohexane			93	200—201	Plates	$C_9H_{12}Cl_3NO_2$	39·8	4·4	39·7	4·4
Spirocycloheptane			54	169—170	Needles (*b*)	$C_{10}H_{14}Cl_3NO_2$	41·8	4·8	41·9	4·9
Me	Ph	α	35	188—189	Needles	$C_{11}H_{10}Cl_3NO_2$	44·8	3·5	44·9	3·4
Me	CH_2Ph	α	10	190—192	Prisms	$C_{12}H_{12}Cl_3NO_2$	47·0	3·7	46·7	3·9
Et	Ph	α	4·5	145—147	Prisms	$C_{12}H_{12}Cl_3NO_2$	47·0	3·9	46·7	3·9
Ph	Ph		5·6	156—158	Prisms	$C_{16}H_{12}Cl_3NO_2$	54·0	3·5	53·9	3·4
Me	CH_2·CH_2·CO_2H	α	39	184	Prisms	$C_8H_{10}Cl_3NO_4$	33·3	3·4	33·1	3·5
Me	CH_2·CH_2·CO_2H	β	19	129	Needles (*b*)	$C_8H_{10}Cl_3NO_4$	33·2	3·5	33·1	3·5
H	Ph	α	35	132—133	Prisms (*a*)	$C_{10}H_8Cl_3NO_2$	43·0	2·8	42·8	2·9
H	Ph	β	7	123—124	Prisms (*a*)	$C_{10}H_8Cl_3NO_2$	42·9	2·9	42·8	2·9

* Crystallised from methanol, except (*a*) benzene and (*b*) acetone.

TABLE 2.

2-Trichloromethyl-4-oxazolidones (II).

R^1	R^2	Yield (%)	M. p. or b. p./mm.	Form *	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
H	H	47	184°	Plates (*a*)	$C_4H_4Cl_3NO_2$	23·6	1·9	23·5	2·0
H	Me	77	100	Prisms (*a*)	$C_5H_6Cl_3NO_2$	27·5	2·9	27·5	2·8
H	Et	45	59—60	Needles (*b*)	$C_6H_8Cl_3NO_2$	30·8	3·4	31·0	3·5
H	Allyl	51	84°/0·5	n_D^{20} 1·5170	$C_7H_8Cl_3NO_2$	34·4	3·3	34·4	3·3
H	CH_2Ph	41	73—74	Needles (*b*)	$C_{11}H_{10}Cl_3NO_2$	44·6	3·2	44·8	3·4
Me	H	13·5	182—183	Prisms (*a*)	$C_5H_6Cl_3NO_2$	27·5	2·6	27·5	2·8
Me	H	4	156—157	Prisms (*a*)	$C_5H_6Cl_3NO_2$	27·7	2·7	27·5	2·8
Me	Me	84	80°/0·5	n_D^{20} 1·5049	$C_6H_8Cl_3NO_2$	31·0	3·4	31·0	3·5
Me	Et	72	96°/0·5	n_D^{20} 1·4981	$C_7H_{10}Cl_3NO_2$	34·2	4·1	34·1	4·1
Me	Allyl	41	100°/0·5	n_D^{20} 1·4892	$C_8H_{10}Cl_3NO_2$	37·3	4·0	37·2	3·9
Me	CH_2Bu^i	31	130°/0·5	n_D^{20} 1·4886	$C_{10}H_{16}Cl_3NO_2$	41·8	5·6	41·6	5·6
Me	n-C_6H_{13}	55	130°/0·5	n_D^{20} 1·4872	$C_{11}H_{18}Cl_3NO_2$	43·5	5·9	43·6	6·0
Me	CH_2Ph	51	56—57	Plates (*c*)	$C_{12}H_{12}Cl_3NO_2$	46·8	3·9	46·7	3·9
Me	CH_2·CH_2·NMe_2,HCl	48	203	Needles (*a*)	$C_9H_{16}Cl_4N_2O_2$	33·4	5·0	33·2	5·0
Me	CH_2·CH_2·NMe_3·I †	62	198	Prisms (*a*)	$C_{10}H_{18}Cl_3IN_2O_2$	27·9	4·1	27·8	4·2

* Crystallised from (*a*) acetone, (*b*) methanol, (*c*) light petroleum (b. p. 40—60°). † Free base treated with methyl iodide in large excess for 17 hr. at room temperature and excess of reagent removed *in vacuo*.

prisms, m. p. 63—65° (Found: C, 39·6; H, 5·1. $C_9H_{14}Cl_3NO_2$ requires C, 39·4; H, 5·1%), were obtained.

5-Dichloromethylene-4-oxazolidones (III).—A solution of 2,2-diethyl-5-trichloromethyl-4-oxazolidone (26 g., 0·1 mole) in ethanolic N-sodium hydroxide (200 ml.) was heated at 40° for 2 hr., then neutralised with acetic acid. Dilution with water yielded a gum which crystallised from aqueous methanol, yielding *5-dichloromethylene-2,2-diethyl-4-oxazolidone* (68%), plates, m. p. 116° (Found: C, 42·9; H, 5·0. $C_8H_{11}Cl_2NO_2$ requires C, 42·9; H, 5·0%); *5-dichloromethylene-2-methyl-2-n-propyl-4-oxazolidone* (α-isomer) was obtained similarly as needles, m. p. 109° (Found: C, 42·9; H, 5·0. $C_8H_{11}Cl_2NO_2$ requires C, 42·9; H, 5·0%).

By addition of dimethyl sulphate (0·12 mole) to the above initial reaction mixture and then working up as before after heating at 40° for 3 hr., *5-dichloromethylene-2,2,3-trimethyl-*, needles, m. p. 87—89° (Found: C, 40·4; H, 4·3. $C_7H_9Cl_2NO_2$ requires C, 40·0; H, 4·3%), *5-dichloromethylene-2,2-diethyl-3-methyl-*, prisms, m. p. 53° (Found: C, 45·4; H, 5·5. $C_9H_{13}Cl_2NO_2$ requires C, 45·4; H, 5·5%), and *5-dichloromethylene-2,3-dimethyl-2-n-propyl-4-oxazolidone* (α-isomer), b. p. 110°/0·4 mm., n_D^{20} 1·5179 (Found: C, 45·4; H, 5·5. $C_9H_{13}Cl_2NO_2$ requires C, 45·4; H, 5·5%), were obtained.

5-Alkoxy-5-dichloromethyl-4-oxazolidones (IV).—The appropriate 5-trichloromethyl- or 5-dichloromethylene-4-oxazolidone (0·02 mole) was added to a solution of sodium alkoxide (0·08 mole) in alkanol (25 ml.), and the solution was refluxed for 1 hr. The product (10—40%) was then isolated as in previous experiments and crystallised from aqueous methanol. *N*-Methylation was achieved by refluxing the product with methyl iodide (3 mol.) in acetone solution in the presence of anhydrous potassium carbonate (3 mol.) for 6 hr. and isolation as before. The *oxazolidones* (IV) thus prepared are listed in Table 3.

Reduction of 5-Dichloromethyl-5-methoxy-2,2-dimethyl-4-oxazolidone.—A solution of the methoxyoxazolidone (1·14 g.) in ethanol (50 ml.) was shaken in hydrogen in the presence of

TABLE 3.

5-Alkoxy-4-oxazolidones (IV).

							Found (%)		Required (%)	
R^1	R^2	R^3	R^4	Isomer	M. p.	Formula	C	H	C	H
Me	Me	Me	H		184—185° *	$C_7H_{11}Cl_2NO_3$	37·2	5·0	36·9	4·9
Me	Me	Me	Me		84 †	$C_8H_{13}Cl_2NO_3$	39·8	5·3	39·7	5·4
Et	Me	Me	H		186—187 *	$C_8H_{13}Cl_2NO_3$	39·6	5·2	39·7	5·4
Et	Me	Me	Me		96—97 *	$C_9H_{15}Cl_2NO_3$	42·6	5·9	42·2	5·9
Me	Et	Et	H		118—119 †	$C_9H_{15}Cl_2NO_3$	42·4	6·1	42·2	5·9
Me	Et	Et	Me		58—59 *	$C_{10}H_{17}Cl_2NO_3$	44·4	6·3	44·4	6·3
Me	Me	Pr^n	H	α	134—135 *	$C_9H_{15}Cl_2NO_3$	42·7	5·9	42·2	5·9
Me	Me	Pr^n	Me	α	83—84 ‡	$C_{10}H_{17}Cl_2NO_3$	44·6	6·3	44·4	6·3
Et	Me	Pr^n	H	α	130—131 †	$C_{10}H_{17}Cl_2NO_3$	44·0	6·0	44·4	6·3
Et	Me	Pr^n	H	β	123—124 *	$C_{10}H_{17}Cl_2NO_3$	44·2	6·2	44·4	6·3
Et	Me	Pr^n	Me	α	85—86 ‡	$C_{11}H_{19}Cl_2NO_3$	46·9	6·7	46·6	6·7

* Needles. † Prisms. ‡ Plates.

10% palladised charcoal (150 mg.) and anhydrous potassium carbonate (3 g.) till uptake of gas ceased. After removal of solids, the filtrate was concentrated *in vacuo* to a small volume and concentrated hydrochloric acid (3 drops) was added. The mixture was then boiled for 5 min., evaporated to dryness *in vacuo*, and treated with an excess of sodium hydrogen carbonate solution; the resulting mixture was filtered and acidified with hydrochloric acid, and aqueous 2,4-dinitrophenylhydrazine hydrochloride was added. The crude yellow hydrazone (650 mg.) which separated had m. p. 175—180°, raised on recrystallisation from glacial acetic acid to 214—217° alone or mixed with pyruvic acid 2,4-dinitrophenylhydrazone.

2-Trichloromethyl-4-thiazolidone.—Chloral (20 g.) was added to a suspension of thioglycollamide (12 g.) in benzene (50 ml.). The amide dissolved rapidly and the resulting solution was kept at room temperature for 4 days, whereupon the *product* separated. It crystallised from aqueous methanol as plates (6·5 g., 23%), m. p. 166° (Found: C, 22·0; H, 2·1. $C_4H_4Cl_3NOS$ requires C, 21·8; H, 1·8%).

2-Trichloromethyl-4-thiazolidone 1-Oxide.—A solution of the parent thiazolidone (4 g.) in glacial acetic acid (10 ml.) containing 30% aqueous hydrogen peroxide (2·5 ml.) was kept at room temperature for 2 days. Removal of solvent under reduced pressure gave the crude

oxide as an oil which crystallised from aqueous methanol as prisms (850 mg., 20%), m. p. 185° (decomp.) (Found: C, 20·5; H, 1·7. $C_4H_4Cl_3NO_2S$ requires C, 20·3; H, 1·7%).

2-*Trichloromethyl*-4-*thiazolidone* 1,1-*Dioxide*.—0·1N-Aqueous potassium permanganate was added dropwise to a solution of the preceding oxide (4 g.) in acetic acid (20 ml.) until a permanent pink colour persisted. After removal of the excess of permanganate with sulphur dioxide, the solution was evaporated to dryness *in vacuo* and the residue extracted with methanol. Dilution of the hot methanolic extract with water until crystallisation took place, yielded the *dioxide* (1·1 g., 25%) as prisms, m. p. 160—161° (Found: C, 19·2; H, 1·4. $C_4H_4Cl_3NO_3S$ requires C, 190; H, 1·6%).

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