110. *Trihalogenomethyl Compounds of Potential Therapeutic Interest. Part I. The Structure of Wallach's Compound* $C_7H_4Cl_9NO_3$.

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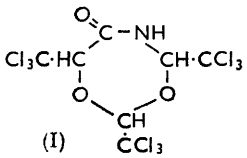
The crystalline compound, $C_7H_4Cl_9NO_3$, obtained from chloral and potassium cyanide is shown to be an oxazolidone (II).

Since 1955 a variety of trihalogenomethyl compounds, with biological activity ranging from hypnotic and anticonvulsant to amœbicidal and anthelmintic properties, have been synthesised in these laboratories. We began with the work reported here, and, although we found that Wallach's compound possessed little biological activity, it provided the incentive to explore the field more widely.

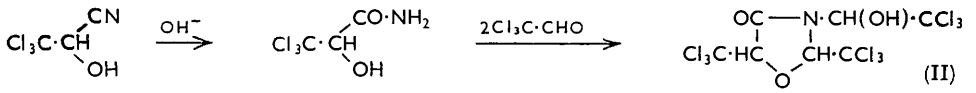
Chloral reacts with aqueous potassium cyanide to give chloral cyanohydrin and a crystalline solid first described by Wallach [1] in 1874 and subsequently [2,3] shown to be best represented by the formula $C_7H_4Cl_9NO_3$ resulting from reaction of three moles of chloral with one of cyanide. The unusual structure (I) was attributed to it by Crowther, McCombie, and Reade [3] who showed also that it could be obtained from chloral cyanohydrin and chloral in the presence of alkali, a method by which we have produced an

[1] Wallach, *Annalen*, 1874, **173**, 297.
[2] Cech, *Ber.*, 1876, **9**, 1020.
[3] Crowther, McCombie, and Reade, *J.*, 1914, **105**, 933.

analogous compound from acetone cyanohydrin. The main evidence for structure (I) was based upon studies of its benzoyl derivative, obtained by reaction with benzoyl chloride in the presence of pyridine, which was assumed to be *N*-benzoyl since it was unattacked by hot aqueous sodium carbonate. Its infrared spectrum, however, was not in accord with this structure since it had bands at 1746 (amide and ester), 1247 (ester C–O), and 1132 cm.$^{-1}$ (C–O–C). Consideration of the conditions of formation of Wallach's compound suggested it could be the oxazolidone (II) formed in the following manner:



(I)

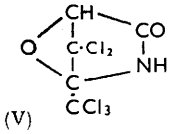


(II)

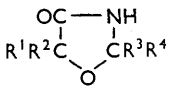
Its infrared spectrum agrees with this, having bands at 3300 (OH), 1746 (5-ring amide with trichloromethyl substituents), and 1150 cm.$^{-1}$ (C–O–C); this structure has been further confirmed by examination of some degradation products described by Crowther *et al.*[3] Acid hydrolysis of its benzoate furnished chloral and an amide-ester, $C_{12}H_9Cl_6NO_4$, previously formulated as (III) and for which we suggest structure (IV), the opening of the oxazolidone ring being confirmed by shift of the band due to the amide carbonyl group

$Cl_3C{\cdot}CH(OH){\cdot}O{\cdot}CH{\cdot}(CCl_3){\cdot}CO{\cdot}NH{\cdot}CO{\cdot}Ph$ (III)

$Cl_3C{\cdot}CH(OH){\cdot}CO{\cdot}NH{\cdot}CH(O{\cdot}CO{\cdot}Ph){\cdot}CCl_3$ (IV)



(V)

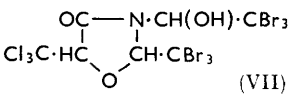


(VI)

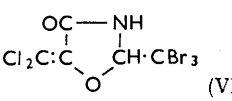
	a	b	c	d	e	f
R^1	Cl_2C:	CCl_3:	Me	CCl_3	Cl_2C:	CCl_3
R^2		H	H	H		H
R^3	CCl_3	Cl_2C:	CCl_3	Me	Me	CCl_3
R^4	H		H	Me	Me	H

to 1700 cm.$^{-1}$ with additional bands at 1747 and 1246 cm.$^{-1}$ (ester). Degradation of (IV) with alkali gave a neutral compound, $C_5H_2Cl_5NO_2$, previously ascribed structure (V), with removal of the elements of hydrogen chloride and benzoic acid, and in which the five-membered ring had been re-formed ($\nu_{max.}$ 1743 cm.$^{-1}$ in $CHCl_3$); bands were also present at 3110 (NH), 1649 (C=C), 1310 (C=C–O), and 1154 cm.$^{-1}$ (C–O–C), suggesting structure (VIa or b).

A decision in favour of structure (VIa) was obtained from a study of the behaviour of the related 2- and 5-trichloromethyl-oxazolidones (VIc and d) in alkaline media; only (VId) suffered dehydrochlorination to give a 5-dichloromethylene-4-oxazolidone (VIe). Final confirmation that the amide, $C_5H_2Cl_5NO_2$, was 5-dichloromethylene-2-trichloromethyl-4-oxazolidone (VIa) was secured from its synthesis by treatment of 2,5-bis-trichloromethyl-4-oxazolidone (VIf) with alkali.



(VII)



(VIII)

It is of interest that Crowther *et al.*[3] reported a similar condensation of chloral cyanohydrin with bromal to give a product, now formulated as (VII), whose benzoate on treatment with alkali gave a " cyclic " compound which, by analogy with the work described above, must be 5-dichloromethylene-2-tribromomethyl-4-oxazolidone (VIII); loss of the elements of hydrogen chloride rather than hydrogen bromide is in accord with the proposed mechanism of formation and reactions of this class of compound.

Experimental

Infrared spectra were determined for Nujol mulls unless otherwise stated.

3-(1-Hydroxy-2,2,2-trichloroethyl)-2,5-bistrichloromethyl-4-oxazolidone (II) *and its Degradation Products* (IV and VIa).—Prepared from chloral and either potassium cyanide or chloral cyanohydrin in the presence of potassium hydroxide,[3] the *oxazolidone* separated from benzene as prisms, m. p. 122—123° (decomp.) (Found: C, 17·9; H, 0·97; Cl, 68·2; N, 3·1. Calc. for $C_7H_4Cl_9NO_3$: C, 17·9; H, 0·86; Cl, 68·0; N, 3·0%). Its benzoyl derivative had m. p. 141—142° and was converted by acid hydrolysis into the amide (IV), m. p. 168—169°.

The oxazolidone (VIa) was obtained as prisms, m. p. 209° (from methanol) (Found: C, 21·3; H, 0·55; Cl, 61·9. Calc. for $C_5H_2Cl_5NO_2$: C, 21·1; H, 0·70; Cl, 62·2%).

3-(1-Hydroxy-2,2,2-trichloroethyl)-5,5-dimethyl-2-trichloromethyl-4-oxazolidone.—10N-Sodium hydroxide (3 ml.) was added to a mixture of chloral hydrate (10 g.) and acetone cyanohydrin (4 g.) in water (25 ml.). After standing overnight, the *oxazolidone* was filtered off and obtained as prisms, m. p. 134—135° (from methanol) (Found: C, 25·2; H, 2·4; Cl, 56·1. $C_8H_9Cl_6NO_3$ requires C, 25·3; H, 2·6; Cl, 56·1%).

5-Methyl-2-trichloromethyl-4-oxazolidone (VIc).—A suspension of lactamide (15 g.) in toluene (100 ml.) containing chloral (25 g.) and toluene-*p*-sulphonic acid (2 g.) was refluxed for 6 hr., water of reaction being removed in a Dean and Stark separator. After removal of solvent *in vacuo*, the residue gave the *oxazolidone* (10 g.) as platelets, m. p. 160—162° (from methanol) (Found: C, 27·6; H, 2·6. $C_5H_6Cl_3NO_2$ requires C, 27·5; H, 2·7%).

Treatment of this material (0·5 g.) in ethanol (5 ml.) and N-sodium hydroxide solution (5 ml.) on the steam bath for 0·5 hr., followed by removal of ethanol under reduced pressure and neutralisation with hydrochloric acid, furnished starting material, m. p. 159—161°.

2,2-Dimethyl-5-trichloromethyl-4-oxazolidone (VId).—A solution of trichlorolactamide (3 g.) in acetone (200 ml.) containing hydrogen chloride (2 g.) was refluxed for 6 hr. and evaporated to dryness. The residue yielded the *oxazolidone* as prisms, m. p. 177—178° (from acetone) (Found: C, 30·9; H, 3·3. $C_6H_8Cl_3NO_2$ requires C, 31·0; H, 3·4%).

Treatment with sodium hydroxide solution as in the previous example furnished *5-dichloromethylene-2,2-dimethyl-4-oxazolidone* (VIe) (68%) as needles, m. p. 174° (from aqueous methanol) (Found: C, 36·8; H, 3·6. $C_6H_7Cl_2NO_2$ requires C, 36·7; H, 3·6%).

2,5-Bistrichloromethyl-4-oxazolidone.—Chloral cyanohydrin (28 g.) was added in portions during 0·5 hr. to a solution of chloral hydrate (30 g.) in concentrated sulphuric acid (250 ml.), the temperature being maintained at 15—20° with external cooling. After 48 hr. at room temperature, the clear solution was poured on crushed ice and the product extracted with ether (2 × 100 ml.). The combined organic extracts were washed with sodium hydrogen carbonate solution until neutral, dried, and evaporated. Two crystallisations from aqueous methanol gave the *oxazolidone* (8 g., 12%) as needles, m. p. 204—205° (Found: C, 18·6; H, 0·8. $C_5H_3Cl_6NO_2$ requires C, 18·7; H, 0·9%).

Treatment with sodium hydroxide solution, as previously, furnished 5-dichloromethylene-2-trichloromethyl-4-oxazolidone (VIa) (32%), m. p. 209°, identical (mixed m. p. and infrared spectra) with previous material.

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