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THE STABILITY OF CHLORMERODRIN [3-(CHLOROMERCURIO)-2-METHOXYPROPYL UREA]: FACTORS AFFECTING ITS DECOMPOSITION IN AQUEOUS SOLUTION AND NATURE OF THE DECOMPOSITION PRODUCT

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SUMMARY

Chlormerodrin [3-(chloromercurio)-2-methoxypropyl urea] and its decomposition product formed in aqueous solution have been examined by PMR spectroscopy, and the decomposition product shown to be 3-(chloromercurio)-2-hydroxypropyl urea. Factors influencing the decomposition of chlormerodrin solutions have been examined and chloride ions shown to reduce the rate of decomposition. The decomposition route has been examined using tracer techniques.

INTRODUCTION

The organo-mercurial 3-(chloromercurio)-2-methoxypropyl urea, ("Chlormerodrin", tradename "Neohydrin") $H_2NCONHCH_2CH(OCH_3)CH_2HgCl$(I), has a place in pharmacology as a diuretic and in nuclear medicine as a kidney and brain scanning agent when labelled with ^{203}Hg or ^{197}Hg. In aqueous solutions of the labelled compound a radioactive impurity is frequently present in small amount and its identity and method of formation has been the subject of several investigations. Anghileri[1], working with the acetoxymercurio compound rather than chlormerodrin itself, considered that in alkaline solution the impurity was an anhydro derivative (II) derived from the hydroxymercurio form (III) although he presented no evidence to support this hypothesis.

$HN{=}CNHCH_2CH(OCH_3)CH_2Hg$ (II)

$H_2NCONHCH_2CH(OCH_3)CH_2HgOH$ (III)

It was claimed that, in rabbits, the impurity and "acetoxymerodrin" showed similar uptakes, distribution and retention in the kidneys. Another view, held by Cifka *et al.*[2,3] and other groups[4], is that the decomposition product is (3-chloromercurio)-2-hydroxypropyl urea (IV).

$H_2NCONHCH_2CH(OH)CH_2HgCl$ (IV)

Cifka has suggested that this product arises by a demethoxymercuration/hydroxymercuration sequence in aqueous solution. The nature of the impurity has been adduced from chromatographic data and by analogy between the methoxymercuration and hydroxymercuration reactions of olefines. In addition, a paper on the labelling of chlormerodrin by exchange with labelled mercuric chloride has shown that use of ethanol or water as solvent in place of methanol gave what were presumed to be the 2-ethoxy and 2-hydroxy compounds respectively as the only labelled compounds[5]. A later report on the labelling of chlormerodrin by exchange in water could not be substantiated[6] (ref. 7 and this work), and it would appear that the chromatographic system used for analyses failed to resolve the individual organo-mercurials. This problem in the analysis of these organo-mercurials has been investigated by Heinrich *et al.*[8]

Herzmann investigated the duration of kidney retention of chlormerodrin and its 2-hydroxy analogue[9]. The hydroxy compound was retained longer than chlormerodrin, thus its presence as an impurity in radioactive chlormerodrin preparations could be of considerable importance with respect to radiation dose to a patient. Despite this interest in its biological behaviour, the structure of the decomposition product does not appear to have been rigorously established and this paper reports the results of proton magnetic resonance studies on chlormerodrin and the decomposition product, and of the conditions under which the derivative is formed. On the basis of the results obtained we consider that Cifka's structure (IV) is the most probable one.

EXPERIMENTAL

PMR spectra were obtained on a Varian 100 MHz instrument (PCMU, U.K.A.E.A., Harwell, Berks). Dimethyl sulphoxide-d_6 was used as solvent, with tetramethylsilane as reference standard.

The chlormerodrin was prepared in our own laboratories and was labelled with either ^{197}Hg or ^{203}Hg. It usually contained 0.5–1.0% of the total activity as an unidentified inorganic form, and from 2–4% of the decomposition product.

Chloride ion determinations were made with a "Radelkis" chloride ion specific electrode (Pungor type) in conjunction with a mercuric sulphate reference electrode. Potential in mV was plotted against log (Cl^-), for chloride ion concentrations from 10^{-1} to 10^{-5} *M*. For the linear portion of the plot, 10^{-1} to 10^{-4} *M*, a change of 50.2 mV occurred for a 10-fold change in chloride concentration. Allyl urea did not interfere with determinations, even when in 100 to 500-fold excess.

The autoclave used was a small bench-top type. For each cycle, samples were placed in the autoclave, pre-heated to 100°, which was then brought up to operating pressure (25 psi) which was maintained for 20 min. Pressure was then rapidly reduced and samples allowed to cool in air.

Paper chromatography was carried out with Whatman No. 1 paper, using the following solvent systems: (*a*) 1-butanol/methanol/concd. ammonia soln./water 5/7/3/1; (*b*) 1-butanol/pyridine/water 10/3/3. The systems used by Cifka were tested and gave satisfactory results in agreement with published data[3]. The system of Anghileri[1] was not satisfactory however, no consistent results being obtained. Diphenyl carbazone solution (1% in ethanol) was used as a spray to detect mercury

containing compounds, and *p*-(dimethylamino)benzaldehyde solution (1% in 1 *N* HCl) for urea functions.

Attempts to prepare 3-(chloromercurio)-2-hydroxypropyl urea by synthesis from allyl urea and mercuric chloride in water gave an impure gum, the components of which could be separated if necessary by chromatography but which were never obtained crystalline nor rigorously pure.

RESULTS AND DISCUSSION

3-(*Chloromercurio*)-2-*methoxypropyl urea* (*I*)

The 100 MHz proton magnetic resonance spectrum is shown in Fig. 1. The resonance at τ 7.50 ppm can be ascribed to the solvent. The resonance at τ 6.75 ppm resolved into a large and a small peak when the spectrum was re-recorded, suggesting the presence of the DOH signal and another in close proximity. Naturally occurring

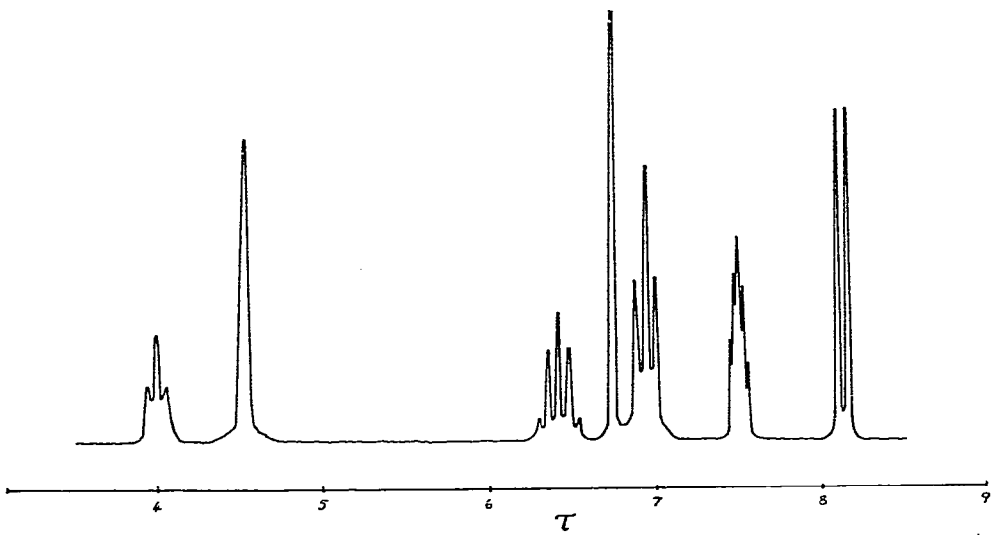
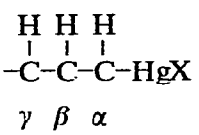


Fig. 1. 100 MHz PMR spectrum of 3-(chloromercurio)-2-methoxypropyl urea.

mercury contains the isotope ^{199}Hg (abundance 16.8%, spin $\frac{1}{2}$) which can couple with protons. This phenomenon has been investigated by several groups of workers, one interesting early use being to prove that mercury(II) addition complexes of olefines were correctly formulated as σ-bonded compounds[10,11]. The work most relevant to the present study is that of Brownstein[12], who studied a variety of methoxymercuration products of olefines. For the system:



values of $J(\mathrm{Hg{-}H_\alpha}) = 215 \pm 10$ Hz, were obtained whatever the nature of substituent X (excepting X = I) or the structure of the alkyl chain. $J(\mathrm{Hg{-}H_\beta})$ varied more widely,

no trend being apparent, values varying from 250 to 340 Hz for X=Br or Cl. For iodomercury compounds, no $^{199}Hg-^{1}H$ coupling was observed. This was ascribed to rapid iodomercury–alkyl exchange, a similar phenomenon being noted in other work[13]. In compounds of the type CH_3HgX and CH_3CH_2HgX iodomercury compounds did give $^{199}Hg-^{1}H$ satellites, although these were significantly broadened, this being ascribed to exchange[14]. The rapid exchange hypothesis in untenable in some of these examples however, as the rate of exchange is known from other studies (see ref. 15, p. 108 and discussion therein). Brownstein also noted that $^{199}Hg-^{1}H_2$ coupling did not occur, except in cases where sec-butyl compounds were invoived.

$^{199}Hg-^{1}H$ satellites should accordingly be observed for the protons on C(3) and the proton on C(2). No satellites were observed however, this being ascribed to the use of dilute solutions, possible coincidence of the satellites and other peaks, or to relaxation effects. The position of such satellite bands cannot be predicted, as previous values for $J(^{199}Hg-^{1}H)$ were obtained in different solvents. Evidence for $^{199}Hg-^{1}H$ coupling was obtained from measurement of integrals however. The spectrum between τ 6.0 and 9.0 ppm was examined at 250 Hz sweep width, and the areas of the doublet, triplet and quintet measured by planimetry. The observed ratio of the resonances ascribed to the protons on C(1), C(2) and C(3) respectively, 2.00/0.84/1.49, is in good agreement with the ratio of 2.00/0.83/1.66 predicted, assuming that the C(2) and C(3) protons are coupled with ^{199}Hg. Integrals, τ values and assignments are given in Table 1.

The coupling constants $J(H^1-H^2)$, $J(H^2-H^3)$, $J(H^3-NH)$ are all equal, being 5.5 Hz. No *geminal* coupling of the protons on C(3) was observed (compare ref. 12).

TABLE 1

PMR SPECTRUM OF 3-(CHLOROMERCURIO)-2-METHOXYPROPYL UREA

Description	τ value	Integral[a]	Assignment
Doublet	8.14	1.6 (1.49)	Protons on C(3)
Quintet	7.50	n.d.	Solvent
Triplet	6.96	2.2 (2.00)	Protons on C(1)
Singlet	6.75	3.5	Methoxyl protons + DOH protons
Quintet	6.41	0.9 (0.84)	Proton on C(2)
Singlet	4.52	2.0	$-NH_2$ protons
Triplet	3.98	1.0	$-NH-$ proton

[a] Using spectrometer integrator; values in brackets obtained from 250 Hz scan by planimetry; units are arbitrary; n.d.: not determined.

The decomposition product of chlormerodrin

An aqueous solution of chlormerodrin containing 4 parts of mercuric chloride to 100 parts of chlormerodrin was heated on a boiling water bath until no further decomposition of chlormerodrin took place (approx. 1 h). The main product had the chromatographic mobility reported for the supposed 3-(chloromercurio)-2-hydroxypropyl urea. The proportion of chlormerodrin remaining was estimated visually after paper chromatography and spraying to be 5%.

The 100 MHz proton magnetic resonance spectrum of the decomposition product is shown in Fig. 2a. When recorded at 60°, the resonances originally at τ 5.17,

4.35 and 3.99 ppm moved to τ 5.31, 4.68 and 4.08 ppm, respectively. The resonance at τ 6.75 ppm was resolved into a minor component at τ 6.75 and a broad peak at τ 6.93 ppm. Other resonances were unaffected, save that at τ 8.17 ppm which appeared as a doublet with broadened peaks at ambient temperature but as a clear quartet at

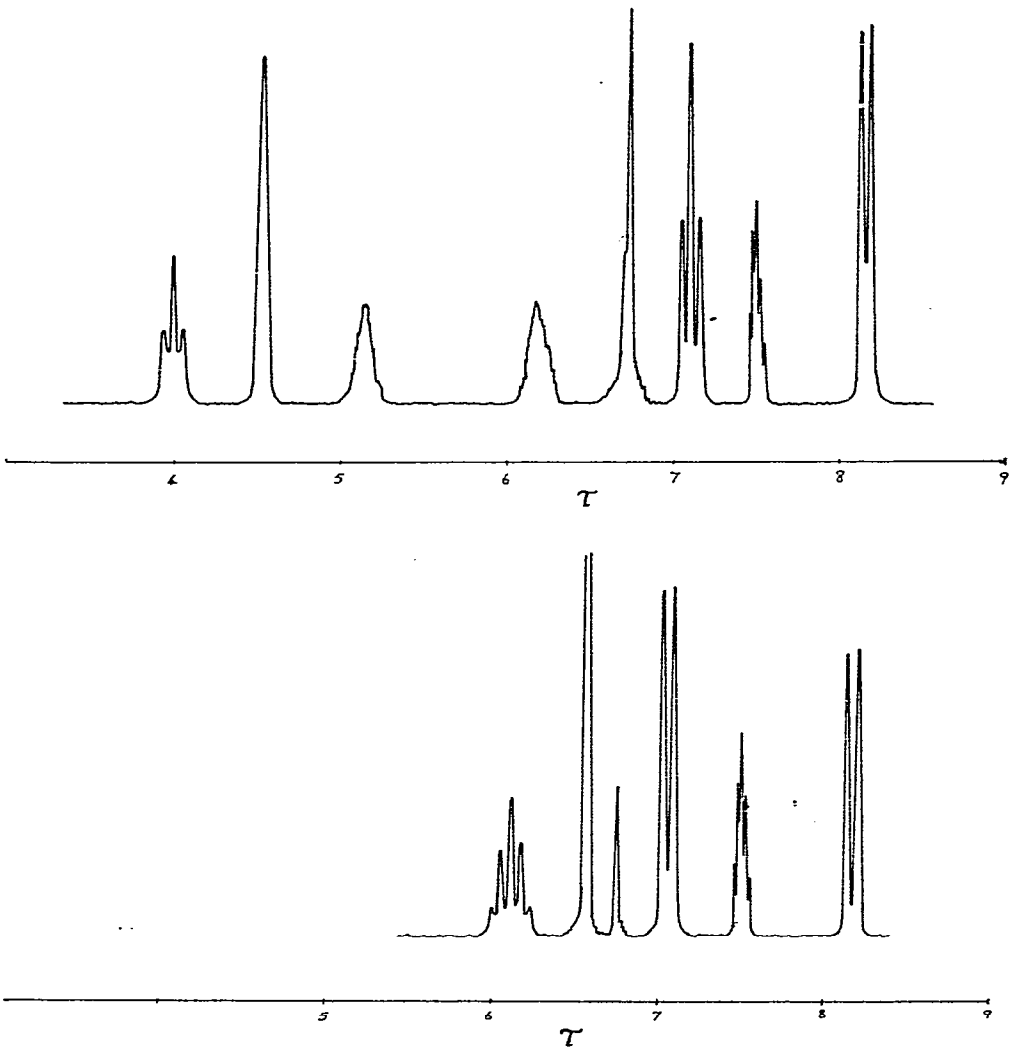


Fig. 2. 100 MHz PMR spectrum of the decomposition product of 3-(chloromercurio)-2-methoxypropyl urea; (a) after 1 h; (b) after 14 days, treatment with D_2O.

60°. The sample was treated with a drop of D_2O, and the spectrum re-recorded at ambient temperature. The resonances at τ 4.53 and 5.17 ppm were immediately eliminated: after 14 days the spectrum had been further simplified to give that shown in Fig. 2b. The simplified spectrum was also examined at 250 Hz sweep width. Integrals, τ values and assignments are given in Table 2.

TABLE 2

PMR SPECTRUM OF THE DECOMPOSITION PRODUCT OF CHLORMERODRIN

Description[a]	τ value	Integral[b]	Assignment
Quartet (quartet)	8.17	1.72	Protons on C(3)
Quintet (quintet)	7.51	n.d.	Solvent
Triplet (doublet)	7.08	2.00	Protons on C(1)
Singlet (singlet)	6.75	n.d.	DOH + methoxyl protons of residual chlormerodrin
Multiplet (quintet)	6.12	0.86	Proton on C(2)
Multiplet	5.17	1.20	Hydroxyl proton
Singlet	4.53	2.00	$-NH_2$ protons
Triplet	3.99	1.03	$-NH-$ proton

[a] Entries in brackets refer to the spectrum after D_2O exchange. [b] See footnote Table 1.

As with chlormerodrin, no ^{199}Hg–^{1}H satellites could be observed. Integrals indicated that ^{199}Hg–^{1}H coupling did occur however, Assignments have been made with regard to this evidence, the observed multiplicity of resonances assuming a first order spectrum, the known sensitivity of NH and OH proton resonances to temperature changes and to the ready exchange of such protons with D_2O. The $J(H^1–H^2)$, $J(H^2–H^3)$ and $J(H^3–NH)$ coupling constants were measured from 250 Hz sweeps, and were all equal, being 5.5 Hz. An unexplained feature is the small (1 Hz) coupling observed in the resonance at τ 8.17 ppm, assigned to the C(3) protons. This cannot be ascribed to long range H^3–H^1 coupling, as the triplet (or doublet) at τ 7.08 ppm shows no further splitting, or to OH–H^3 coupling as this would be eliminated on treatment with D_2O. The splitting could be due to the non-equivalence of the C(3) protons, *geminal* coupling of similar protons being reported by Brownstein (coupling constants of around 12 Hz), though none was observed for chlormerodrin. Non-equivalence of the C(3) protons implies further splitting in the quintet at τ 6.12 ppm. This is not observed, but the small coupling involved (1 Hz) may not be large enough to cause visible splitting of the quintet. The splitting could be due to a mercury isotope other than ^{199}Hg coupling with the C(3) protons. The small proportion of chlormerodrin present is insufficient to cause the splitting observed.

The foregoing evidence rules out the anhydro compound (II) postulated by Anghileri, as observed PMR spectral features cannot be reconciled to such a structure. The results obtained are completely consistent with the decomposition product being 3-(chloromercurio)-2-hydroxypropyl urea, as already postulated.

The stability of chlormerodrin in solution

Three solutions of chlormerodrin-^{203}Hg (specific activity 1.66 mCi/mM, concn. 4 mg/ml) were prepared in water, 0.1 *M* phosphate buffer at pH 7 and 0.9% sodium chloride solution respectively. The solutions were autoclaved for four autoclave cycles, samples being taken after each cycle and analysed by paper chromatography. Results are given in Table 3. An important feature of these results is the levelling off in the decomposition rate of the aqueous chlormerodrin solution after the initial rapid decomposition during the first autoclave cycle. This is not due to the establishment of an equilibrium between chlormerodrin and 3-(chlormercurio)-2-hydroxypropyl

TABLE 3

DECOMPOSITION OF CHLORMERODRIN SOLUTIONS ON AUTOCLAVING

Solution	Number of autoclave cycles	Chlormerodrin (%)	Hydrolysis product (%)	Mercuric ion (%)
Original stock	0	92.2	3.6	4.2
Aqueous	1	44.8	46.5	8.6
	2	44.2	52.0	3.9
	3	41.3	52.5	6.2
	4	40.3	51.4	8.3
0.1 *M* phosphate buffer, pH 7	1	92.0	3.3	4.6
	2	88.2	4.8	7.0
	3	87.7	4.5	7.7
	4	87.2	5.3	7.6
0.9% sodium chloride	1	91.0	4.7	4.2
	2	91.0	4.6	4.5
	3	89.0	8.0	3.0
	4	85.2	9.8	5.0

urea as addition of methanol to the solution of partially decomposed chlormerodrin and further autoclave treatment failed to reverse the reaction.

A series of ^{197}Hg-chlormerodrin solutions, concn. 4 mg/ml, were made up in aqueous saline solutions of various concentrations. The solutions were autoclaved for three cycles, samples being taken after each cycle, analysed by paper chromatography and scanned for radioactivity. The results are given in Table 4.

To ascertain whether slight variations in pH caused the differences in the extent of decomposition observed for the various chlormerodrin solutions, ten solutions of ^{197}Hg-chlormerodrin (4 mg/ml) in a series of phosphate buffers, all 0.1 *M*, varying in pH from 8.7 to 4.3, were prepared. These solutions were autoclaved for two successive cycles, being sampled between cycles and analysed as before. The pH values were essentially invariant throughout the experiment. For pH values between 8.7 and 6.0 decomposition could not be related to pH, being essentially the same in all cases at around 5%. Solutions at a pH of 5.5 or less showed a greater decomposition, between 10 and 20%. The most acidic solution tested (pH 4.3) was 40% decomposed. These results demonstrate that slight variations in pH are unlikely to be the cause of the difference observed in the behaviour of chlormerodrin in water and saline. A similar result has been reported by Kreevoy[16], who obtained identical rates for a deacetoxymercuration reaction at pH 4 and pH 6.

Mercuric chloride is known to promote the decomposition of organomercurials[17]. Although no correlation was detected between inorganic mercury content and extent of decomposition in the experiments reported in Tables 3 and 4, this possibility was investigated by adding mercuric chloride to chlormerodrin solutions. Addition of up to 12.5% by weight of mercuric chloride to saline solutions of chlormerodrin did not cause extensive decomposition on autoclaving. Under the reaction conditions employed, mercuric chloride catalysed decomposition is not an important factor.

TABLE 4

DECOMPOSITION OF CHLORMERODRIN IN SALINE SOLUTIONS

Solution	Number of autoclave cycles	Chlormerodrin (%)	Hydrolysis product (%)	Mercuric ion (%)
Original stock	0	95.8	2.8	1.5
In 0.9% NaCl	1	95.2	2.7	2.0
	2	95.2	2.2	2.7
	3	93.9	1.9	4.2
In 0.36% NaCl	1	95.6	2.8	1.6
	2	94.7	3.3	2.0
	3	95.6	2.6	1.7
In 0.18% NaCl	1	94.7	3.1	2.2
	2	93.8	3.4	2.8
	3	92.8	4.8	2.4
In 0.09% NaCl	1	93.9	4.0	2.1
	2	93.7	3.5	2.8
	3	93.0	5.3	1.7
In 0.045% NaCl	1	88.2	6.4	5.4
	2	90.3	7.8	1.9
	3	86.6	11.1	2.3
In 0.018% NaCl	1	84.3	12.7	3.0
	2	80.3	17.1	2.6
	3	79.0	18.7	2.3
Aqueous	1	55.8	42.0	2.2
	2	48.5	47.0	4.1
	3	43.5	51.6	4.9

The chloride ion concentration in chlormerodrin solutions

Attempts to measure the ionisation of chlormerodrin in pure water with a chloride ion specific electrode (see Experimental) could not be carried out over a range of concentrations due to the low solubility of chlormerodrin. The average of five determinations showed that 0.8×10^{-2} *M* solutions of chlormerodrin ionised to the extent of 0.76%. Using pure chlormerodrin, twice recrystallised from water and labelled with ^{191}Hg, the chloride ion concentration in solutions before and after autoclaving was measured. The average change in potential on autoclaving for four solutions (0.79×10^{-2} *M*) was 31 mV, representing a 6-fold increase in chloride ion concentration. The average extent of decomposition of these solutions was 70%. As the only change in the solutions was the decomposition of 70% of the chlormerodrin to 3-(chloromercurio)-2-hydroxypropyl urea, the increase in free chloride ions must be due to this product. The hydroxy compound must therefore ionise to a greater extent than chlormerodrin, thus on autoclaving, production of the hydroxy compound is accompanied by an increase in chloride ion concentration. The chloride ion concentration increases until it is high enough to have the same effect as sodium chloride, reducing the rate of decomposition. The result is to produce an extensive decomposition during the first autoclave treatment of an aqueous chlormerodrin solution, with relatively little decomposition on further heating.

The decomposition of chlormerodrin

0.291 g of pure inactive chlormerodrin and 6.3 mg of $^{203}HgCl_2$ (0.12 mCi/m*M*) were dissolved in 5.2 ml water, and heated in a 10 ml flask fitted with a reflux condenser on a boiling water bath. Samples were taken at intervals and analysed by paper chromatography. The chromatograms were examined by radioactivity scanning and by spraying with a mercury detecting reagent. Two radioactive components were detected in all samples (except that at zero time of reaction), corresponding to mercuric ion and 3-(chloromercurio)-2-hydroxypropyl urea. The spray reagent showed the chlormerodrin content of the reaction mixture to decrease throughout the experiment. No uptake of radioactivity by chlormerodrin was detected. Results are given in Table 5.

TABLE 5

DECOMPOSITION OF INACTIVE CHLORMERODRIN IN THE PRESENCE OF $^{203}HgCl_2$

Time of reaction (min)	% Activity in $HgCl_2$	% Activity in the hydroxy compound
0	100	
10	32.9	67.1
20	33.7	66.3
30	32.7	67.3
45	27.0	73.0
65	30.0	70.0
85	29.8	70.2
115	29.0	71.0
145	28.5	71.5

The absence of radioactive chlormerodrin confirms the results of Cifka, and provides further evidence that the reported preparation of chlormerodrin-^{203}Hg by exchange in aqueous solution[6] is in error.

0.046 g of pure chlormerodrin and 0.004 g of mercuric chloride in 5 ml water were autoclaved until no further decomposition occurred (30 min). The solution was cooled and examined by paper chromatography. It still contained a trace of chlormerodrin, but this did not alter during the subsequent experiment (visual estimation). 0.2 ml of $^{203}HgCl_2$ solution (1.28 mg, 0.77 mCi) was added to the solution, which was heated on a boiling water bath and sampled at intervals. Samples were examined by paper chromatography, the chromatograms being scanned for radioactivity and visualized with both mercury and urea sensitive sprays. Initially, only the mercuric chloride spot was radioactive, the 3-(chloromercurio)-2-hydroxypropyl urea becoming radioactive as the experiment proceeded. The chlormerodrin did not become radioactive, but later in the experiment an unknown radioactive component was detected which was not sensitive to the mercury or urea-detecting sprays. Results are given in Table 6.

The incorporation of ^{203}Hg into the decomposition product by decomposing inactive chlormerodrin in the presence of $^{203}HgCl_2$ supports the suggestion of Cifka, made on the basis of the known behaviour of methoxymercuration products (see ref. 17 for discussion), that chlormerodrin breaks down to allyl urea, methanol and inorganic mercury. The allyl urea and inorganic mercury then recombine, incorporating water, to give the hydroxy analogue. The results in Table 5 do not establish this route however, as the results given in Table 6 show that when the inactive hydroxy com-

TABLE 6

EXCHANGE BETWEEN $^{203}HgCl_2$ AND 3-(CHLOROMERCURIO)-2-HYDROXYPROPYLUREA

Time of reaction (min)	% Activity in $HgCl_2$	% Activity in hydroxy compound	% Activity in unknown
0	100		
10	86.5	13.5	
20	74.3	25.7	
30	65.7	32.6	1.7
45	56.1	41.4	2.5
65	47.6	49.0	3.4
85	43.9	52.8	3.3
115	41.4	54.9	3.7
145	35.3	58.8	5.9

pound is heated with $^{203}HgCl_2$ it incorporates radioactivity. Thus chlormerodrin could decompose to the hydroxy compound without loss of mercury, then the hydroxy compound could exchange with $^{203}HgCl_2$.

The decomposition of chlormerodrin in the presence of allyl urea (urea-^{14}C)

0.5 mCi of potassium cynate-^{14}C (24 mCi/m*M*) was transferred to a 50 ml Erlenmeyer flask with 20 ml of methyl cyanide. The flask was equipped with a magnetic stirrer and a reflux condenser. 0.5 ml of redistilled allyl bromide was added, and the mixture heated under gentle reflux. Samples were taken at 1,2 and 4 h, being added to an equal volume of concentrated ammonia solution. Samples were placed on chromatography paper and scanned for radioactivity before being developed, to check on the possible loss of cyanate from the paper by hydrolysis to ammonia and carbon dioxide. Scans after development showed no such losses occurred, the main product corresponding to allyl urea. Reaction was stopped at $5\frac{1}{2}$ h by adding 20 ml concd. ammonia solution, the mixture evaporated under reduced pressure to a syrup, and applied to thick paper and chromatographed in solvent a. Autoradiography and radioactivity scanning showed the following components: Fast moving material (3%) R_f 0.94, allyl urea (97%) R_f 0.84, traces, R_f 0.67 and 0.25. The allyl urea was eluted from the paper with methanol, the extracts filtered, concentrated, then made up to 10 ml. (Allyl urea, urea-^{14}C, 1.8 mg/g of soln., 430 μCi/m*M*). The route[18,19] potassium cyanate, allyl cyanate, allyl isocyanate, plus ammonia thus gives a good route to allyl urea (urea-^{14}C).

3 ml of the allyl urea (urea-^{14}C) methanolic solution was evaporated to dryness under reduced pressure, then evaporated to dryness twice with water. 5.0 mg of inactive allyl urea and 34.1 mg of inactive chlormerodrin were added and dissolved in 6 ml of water. The solution was stirred on a boiling water bath, sampled at intervals, and the samples examined by paper chromatography followed by radioactivity scanning, autoradiography, and spraying with mercury and urea detecting reagents. The build-up of the spot due to 3-(chloromercurio)-2-hydroxypropyl urea observed visually parallelled the build up of radioactivity in the same place on the chromatogram. See Table 7.

The incorporation of labelled allyl urea into 3-(chloromercurio)-2-hydroxy-

TABLE 7

DECOMPOSITION OF CHLORMERODRIN IN THE PRESENCE OF ALLYL UREA (UREA-^{14}C)

Time of reaction (min)	% Activity in allyl urea	% Activity in hydroxy compound
0	100	
10	91.7	8.3
30	83.1	16.9
60	74.4	25.6
90	67.2	32.8
150	67.7	32.3
210	63.5	36.5
270	61.0	39.0
360	60.1	39.9
450	60.5	39.5

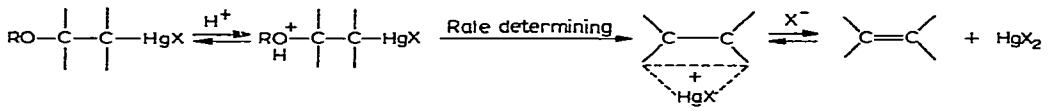
propyl urea when inactive chlormerodrin decomposes, and the results obtained from decomposition studies using $^{203}HgCl_2$ provide strong evidence that chlormerodrin decomposes to give allyl urea, methanol and inorganic mercury, the allyl urea and mercury then recombining in aqueous solution to give the 2-hydroxy compound. Any alternative explanation requires chlormerodrin and its 2-hydroxy analogue to decompose by intrinsically different mechanisms, which is unlikely for such closely related compounds. While this mechanism accords with published work on other organomercurials, the effect of chloride ions does not. In a series of investigations, Kreevoy *et al.*[20–22] have shown that acid catalysed and solvolytic demethoxymercurations of iodomercury compounds are catalysed by iodide ions. The rate was given by:

$$\text{rate} = [k_2 + k_3 \cdot (I^-) + k_4 \cdot (I^-)^2] \cdot (H^+) \cdot (S)$$

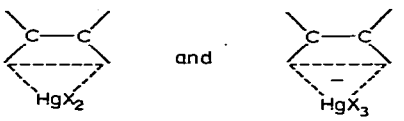
where (S) = substrate concentration.

Ichikawa *et al.*[23] found a similar equation to hold for chloromercury compounds, although the most important term in the rate equation in such cases involved first order dependence on chloride ion concentration.

Kreevoy presented a mechanism for the breakdown, involving an initial rapid, reversible protonation of the substrate[21]. This was followed by the rate determining step, the loss of the alkoxyl group and formation of a mercury–olefin complex which subsequently gave the olefine and mercuric halide.



The catalytic effect of halide was ascribed to the ability of halide ions to complex with the mercury of the organomercurial, giving complexes of the type



as well as that shown here.

The differing ability of chloride and iodide to complex with mercury was related to the differing importance of the first and second order rate equation terms with respect to halide when chloro and iodomercurials were compared.

The effect of chloride and phosphate ions on chlormerodrin decomposition cannot be a simple matter of ionic strength, as Cifka found that theophylline promoted decomposition[2]. A zero order rate with respect to chloride ions was found in previous work, thus if chlormerodrin behaves in a manner at all similar, there should be similar decomposition rates in water and saline even if chloride ions have no catalytic effect whatsoever. As chloride ions prevent decomposition, the pathway suggested by Kreevoy cannot apply to chlormerodrin, although the final effect—breakdown to an olefin, an alcohol and inorganic mercury—is the same. A different rate determing step appears necessary to account for these results. Elucidation of this point will require a detailed study of the kinetics of decomposition of chlormerodrin and of analogous compounds.

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