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Chloromercuric Salts of 5-Alkyl-5-nitrotetrahydro-1,3-oxazines

by

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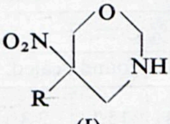
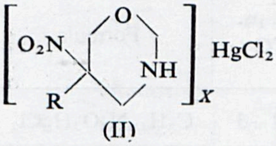
Organomercuric compounds received relatively recently considerable attention owing to their practical use as biologically active agents (e.g. fungicides [1] or some known drugs) and also thanks to their possible use as starting substances in the synthesis of nucleosides [2, 3].

In continuing our experiments on formation of analogues of nucleosides containing a 5-alkyl-5-nitrotetrahydro-1,3-oxazine ring [4] we examine now the products obtained by the action of mercuric chloride on the above 1,3-oxazine derivatives.

5-Alkyl-5-nitrotetrahydro-1,3-oxazines (I) were obtained from primary nitroparaffins with the normal chain (from C_2 to C_6), formaldehyde and ammonia, in principle according to the known methods either directly from the nitroparaffin of the diols produced by addition of two moles of formaldehyde to the respective nitroparaffins [5—10]. However, we improved the yields of (I) by using a *c.* 8% excess of formaldehyde in the reaction of cyclization and a prolonged reaction time. This created conditions unfavourable to the formation of *N*-substituted products which can readily be produced from nitroethane [6] and 1-nitropropane [5].



(I)



(II)

a — $R{=}CH_3$
b — $R{=}C_2H_5$ for a, c, d and e, $x = 1$
c — $R{=}n\text{-}C_3H_7$ for b, $x = 2$
d — $R{=}n\text{-}C_4H_9$
e — $R{=}n\text{-}C_5H_{11}$

The results of the reaction of formation of (I) are tabulated in Table I. All bases (I) were purified by distillation under reduced pressure.

Note. Paper LXXXVII on "Chemistry of Nitroalkanes".

The compounds (I) were reacted with stoichiometric quantity of mercuric chloride in methanol or ethanol to yield white, fine-crystalline precipitates of (II) which are insoluble in water.

TABLE I

Compounds I	Time of heating, hrs.	Yield, %	m. ps. of hydrochlorides °C*	b. ps. °C/mm Hg	n_D^{20}
a	5	10	164—165	70— 2/0.20	1.4766 **
b	10	25	196—198	78—81/0.15	1.4795
c	5.5	25	186—188	81— 2/0.20	1.4775
d	6	30	174—176	90— 1/0.10	1.4722
e	5	36	185—187	92— 4/0.25	1.4722 **

* m. ps. detd. here. ** n_D^{20} at 18.5°.

It should be pointed out that x is different from 1 when R is C_2H_5.

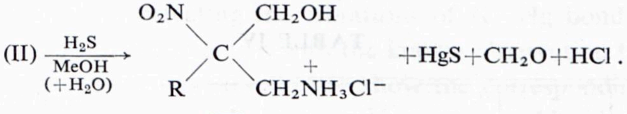
The results of these reactions are tabulated in Table II. Salts (II) are stable at room temperature, but when heated, the organic part decomposes at their m.p. and mercuric chloride partly sublimes. Also a prolonged boiling in alcohol produces a decomposition manifested by the formation of an insoluble precipitate. They did not react with aqueous sodium carbonate, but aqueous sodium hydroxide decomposes them to yield yellow precipitates which contain HgO. The ethereal extract contained unchanged 1,3-oxazine derivatives (I).

TABLE II

Compounds II	Yield, %	m. ps. °C	Formula	Analyses					
				% C		% H		% N	
				calcd.	found	calcd.	found	calcd.	found
a	50	121—3	$C_5H_{10}N_2O_3HgCl_2$	14.4	15.1	2.3	2.9	6.7	6.7
b	90	124—5	$C_{12}H_{24}N_4O_6HgCl_2$	24.3	24.4	4.1	4.6	9.4	9.2
c	82	131—2	$C_7H_{14}N_2O_3HgCl_2$	18.9	19.2	3.1	3.5	6.2	5.8
d	76	136—8	$C_8H_{16}N_2O_3HgCl_2$	20.9	21.6	3.5	4.3	6.1	6.1
e	60	137—8	$C_9H_{18}N_2O_3HgCl_2$	22.9	22.8	3.8	4.3	5.9	5.9

Demercuration of (II) by passing hydrogen sulphide through their ethereal suspensions led to precipitation of HgS and hydrochloride of oxazine derivatives (I). When demercuration was carried out in methanol (or ethanol), the reaction was accompanied by the ring opening to yield hydrochlorides of 2-alkyl-2-nitro-3-aminopropanols (III):

(1)



(III)

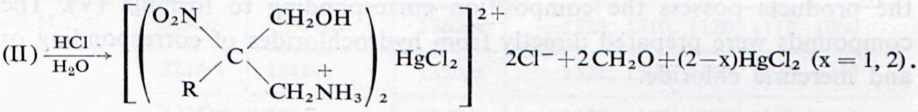
a − R=CH_3 c − R=n-C_3H_7 e − R=n-C_5H_{11}
b − R=C_2H_5 d − R=n-C_4H_9

Obviously hydrochloric acid was liberated from mercuric chloride through the action of hydrogen sulphide and the ring opening occurred in the usual way [5−10], as the water necessary for the reaction is present in methanol and is also formed from methanol and HCl.

We also examined the ring opening of salts (II). The reaction was carried out by the method worked out for 5-alkyl-5-nitroterahydro-1,3-oxazines [10]. It consists in refluxing the compound in conc. hydrochloric acid diluted with ethanol. Formaldehyde was evolved.

The products, white crystalline substances, readily soluble unlike (II), proved to be double salts (IV) of (III) with mercuric chloride.

(2)



(IV)

a − R=CH_3 c − R=n-C_2H_7 e − R=n-C_5H_{11}
b − R=C_2H_5 d − R=n-C_5H_{11}

Demercuration of (IV) in dilute hydrochloric acid with hydrogen sulphide furnished hydrochlorides (III) identical with those previously prepared.

The properties of (IV) are tabulated in Table III.

TABLE III

Compounds IV	Yield, %	m. ps.	Formula	Analyses % C calcd.	% C found	% H calcd.	% H found	% N calcd.	% N found	% Cl calcd.	% Cl found*
b	85	116−118.5	$C_{10}H_{26}N_4O_6HgCl_4$	18.75	18.95	4.1	4.5	8.75	8.5	22.2	11.7
c	80	134−135	$C_{12}H_{30}N_4O_6HgCl_4$	21.6	22.0	4.5	4.9	8.4	8.3	21.3	10.3
d	75	158−159	$C_{14}H_{34}N_4O_6HgCl_4$	24.2	24.2	4.9	5.4	8.0	7.55	20.4	11.0
e	73	112−114	$C_{16}H_{38}N_4O_6HgCl_4$	—	—	—	—	7.7	7.5	19.6	9.4

* by potentiometric titration.

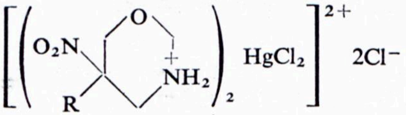
The titration gave only a half of the chlorine content present in the molecule. This is in agreement with formula (IV).

TABLE IV

Compounds V	Yield, %	m. ps.	Formula	Analyses					
				% C		% H		% N	
				calcd.	found	calcd.	found	calcd.	found
b	45	159–160	$C_{12}H_{26}N_4O_6HgCl_4$	22.75	22.95	3.93	3.80	8.45	9.34
c	60	131–132	$C_{14}H_{30}N_4O_6HgCl_4$	25.0	25.1	4.46	4.2	8.35	8.65

To verify the structure of compounds (IV) we prepared double salts by reacting (III) with mercuric chloride. The products were identical with (IV). It means that the composition of the double salts (IV) does not depend on the method of preparation, and the ratio is constant: double salts of two moles of (III) and one mole of mercuric chloride.

We also examined the reaction of compounds (IV) with formaldehyde to see if 1,3-oxazine derivatives could be formed. According to the analytical results, the products possess the composition corresponding to formula (V). The same compounds were prepared directly from hydrochlorides of corresponding oxazines and mercuric chloride.



(V)

b – $R=C_2H_5$
c – $R=n\text{-}C_3H_7$

This was found for two compounds (when R was C_2H_5 and $n\text{-}C_3H_7$). The properties of the compounds are given in Table IV.

Infrared spectra

Infrared spectra were examined for 5-nitro-5-alkyltetrahydro-1,3-oxazines (I) and their salts with mercuric chloride (II). The main bands of the IR spectra are tabulated in Table V.

Here are the main features of the spectra of both groups of compounds.

The bands of (II) were of higher intensities, and some bands were shifted to lower fraquencies. For instance, the intensity of NH bands in the salts was nearly doubled and they were shifted by 150–180 cm^{-1}. This is typical of complex organic salts indicating the formation of covalent bond NH–Hg [12]. Mercury is not bound with oxygen atoms forming part of heterocyclic rings (which is obvious considering a higher affinity of Hg to nitrogen than to oxygen). This is also manifested by unchanged frequencies of hemiacetal bands (C—O—C—N) of the 1,3-oxazine rings [13]. The bands below 1300 cm^{-1} show a microstructure.

We did not succeed in detecting the vibrations of N—Hg bond in the region of 800—400 cm^{-1}. This is in agreement with the known observation that complexes of heterocyclic systems with mercury do not show the corresponding bands [14], contrary to the spectra of non-cyclic bases with mercuric chloride [15, 16].

TABLE V

Substances R	NH	as NO_2	s NO_2	C–O–C–N
Ia$^+$ CH_3	3350m	1560vs	1355s	1310, 1160, 1125, 1060
Ib$^+$ C_2H_5	3350m	1560vs	1350s	1334, 1165, 1122, 1075
Ic$^+$ n-C_3H_7	3340m	1558vs	1340m	1310, 1160, 1120, 1060
Id$^+$ n-C_4H_9	3350m	1550vs	1378m	1320, 1160, 1120, 1060
Ie$^+$ n-C_5H_{11}	3340w	1545—38vs	1350m	1310, 1216, 1150—1115, 1020
IIa^{++} CH_3	3200s	1560vs	1350s	1310, 1170, 1130, 1005
IIb^{++} C_2H_5	3280s	1545vs	1350m	1330, 1150, 1110, 1075, 1025
IIc^{++} n-C_3H_7	3230m	1550vs	1360m	1338, 1310, 1120, 1118, 1060
IId^{++} n-C_4H_9	3236m	1545vs	1350m	1322, 1300, 1160, 1120, 1060
IIe^{++} n-C_5H_{11}	3236m	1545vs	1340m	1300, 1180, 1120, 1075, 1035

+ Examined as films. ++ Examined as mulles in nujol.

Comparison of the spectra of (III) and (IV) shows a similarity between the spectra of ligands and the complexes. In all spectra the following bands are present: OH (~ 3500—3390 cm^{-1}), $\overset{+}{N}H_3$ (~ 3180—3000 and 1595—1580 cm^{-1}), NO_2 (1550 and 1345—1330 cm^{-1}). Higher intensity and a micro-structure of bands of complexes is noticeable below 1300 cm^{-1}.

The conductivity of solutions of some complex salts (II) in nitrobenzene and acetonitryle gave an evidence that the compounds are non-electrolytes.

As far as (IV) and (V) are concerned, they are electrolytes in agreement with the suggested formulae. Similar properties of mercuric chloride complexes have been reported for complexes with pyridine or with alkylammonium salts [11, 17].

NMR examination of complexes (II) in deuterated dimethylsulphoxide shows that the spectra of the complexes are much the same as those of 5-alkyl-5-nitro-tetrahydro-1,3-oxazines with three quartets corresponding to three different methylene groups [18].

No differences between the spectra of (II a) and (II b) were found either, although their stoichiometric composition is different. The only difference between the spectra of (I) and (II) consists in the absence of signals of *N*-protons in complexes. This may be due to a strong shielding of the N—H group by mercuric chloride.

Experimental

5-Alkyl-5-nitrotetrahydro-1,3-oxazines (I)

To a mixture of primary nitroparaffin (1 mol) and 30% aqueous formaldehyde (3 mol), aqueous (25% 1 M) ammonia solution was added dropwise under stirring, and heated on a water bath. After one hour an excess of 30% aqueous formaldehyde (0.5 M) was added and warming to ~ 95° was continued for several hours. The resulting liquor was cooled to make a heavy oil separate which subsequently was collected. The aqueous layer was extracted twice with Et_2O, the extract added to the oil, dried over Na_2SO_4 and Et_2O evaporated. The residual oil was cooled and dissolved in alc. HCl. After 1—2 days white crystalline oxazine hydrochloride precipitated. The precipitate was filtered, washed with alcohol and ether, and finally purified by crystallization from EtOH. Free base (I) was obtained by adding chloroformic solution of ammonia to the suspension of the hydrochloride (10 g) in dry $CHCl_3$ (100 ml) [19]. After separating NH_4Cl the chloroform was distilled off. The residual, colourless or straw-yellow oil, was distilled under reduced pressure at $< 100°$.

The analytical data are collected in Table I. The hydrochloride of (Ia) was hitherto undescribed. For $C_5H_{10}N_2O_3 \cdot HCl$, calcd.: C, 33.0; H, 6.05; N, 15.4%; found: C, 33.1; H, 6.1; N, 15.3%.

2-Alkyl-2-nitro-3-aminopropanol hydrochlorides (III)

The products were prepared according to the known methods [5—9] from 1,3-oxazines derivatives (I) by heating with hydrochloric acid diluted with alcohol. To speed up the removal of water, benzene was added at the end of hydrolysis and the solution was evaporated to the moment when crystalline hydrochloride appeared.

Chloromercuric salts of 5-alkyl-5-nitrotetrahydro-1,3-oxazine (II)

5-Alkyl-5-nitrotetrahydro-1,3-oxazines (I) (0.01 mol) was dissolved in EtOH (40 ml) and mercuric chloride (0.01 mol) solution in ethanol was added under vigorous stirring. The solution was warmed to 50° and cooled. Product (II) precipitated. A second crop was obtained by evaporation of the filtrate. The yield was 60—90%.

Salts (II) are white crystalline precipitates, readily soluble in hot EtOH, Me_2CO, MeCN; sparingly soluble in Et_2O, benzene, $CHCl_3$; insoluble in water.

Reaction of (II) with sodium hydroxide

To chloromercuric salts (II) (0.005 mol) in Et_2O or CCl_4 aq. 5% NaOH (0.02 mol) was added. The whole was shaken for 1/2 hour. The precipitate (HgO and NaCl) was removed and the solvent was evaporated from the filtrate. The residual oil was dissolved in alc. HCl. The precipitated hydrochlorides proved to be identical with hydrochlorides of (I).

Reaction of hydrogen sulphide with (II)

Chloromercuric salts (II) (0.005 mol) was suspended in anhyd. Et_2O (15—20 ml) and dry H_2S was introduced into the suspension. After one hour the precipitate of mercuric sulphide was removed, washed with ether and hot alcohol. The filtrate was evaporated under reduced pressure to dryness. The oily residue was treated with alc. HCl and crystallized from alcohol.

The products proved to be identical with hydrochlorides of (I).

Hydrolysis of chloromercuric salts (II) with dilute hydrochloric acid

Chloromercuric salts (II) (0.002 mol) were dissolved in EtOH (50 ml) to which conc. HCl (1 ml) and water (5 ml) were added. The distillate of the mixture obtained showed the presence of formaldehyde, detected as dinitrophenyl-hydrazone. The dry residue was extracted with hot EtOH. On cooling white precipitate of (IV) was collected. It was recrystallized from EtOH—benzene or EtOH—Et_2O.

Reaction of (III) with mercuric chloride

2-Alkyl-2-nitro-3-aminopropanol (III) hydrochloride (0.001 mol) was dissolved in EtOH (5 ml), mercuric chloride (0.001 mol) added and the reaction mixture was warmed for 1/2 hour. On evaporation the white crystalline product (IV) was formed in EtOH$-$Et$_2$O mixture. The compd. proved to be identical with (IV) prepared as above.

Demercuration of (IV)

The reaction was carried out in the same way as the reaction of (II) with hydrogen sulphide.

Reaction of (IV) with formaldehyde

The reaction was carried out in the usual way as described for the reaction of 2-nitro-3-aminopropanol derivatives to yield 5-nitro-tetrahydro-1,3-oxazines. The reaction of (IV) with formaldehyde yielded product (V).

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