A METHOD FOR ROUTINE PREPARATION OF VERY PURE CHLORMERODRIN LABELLED WITH ^{197}Hg OR ^{203}Hg WITH HIGH SPECIFIC ACTIVITY.

Iwona Lisewska, Jan Potocki and Antoni Pasternak.

Institute of Nuclear Research
Radioisotopes Production and Distribution Centre
Swierk, Poland.

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SUMMARY

A method for routine production of 3-chloromercuri-2-methoxy-propylurea-^{197}Hg or ^{203}Hg with a high specific activity and high radiochemical purity, has been elaborated. Important for the method are: good and standardized $HgCl_2$, the maintenance of molar ratios $HgCl_2$ to sodium acetate and allylurea 1:1 and 1:5 respectively, and the time of heating of the reaction mixture in the autoclave with overpressure 0.2 - 0.3 At, not less than 6 hrs. The use of anhydrous ethyl ether for washing the precipitate removes both organic and inorganic radiochemical impurities. The method enables one to work with quantities of $HgCl_2$ lower than 1 mg.

3-Chloromercuri-2-metoxypropyl-urea (Chlormerodrin, neohydrine) labelled with ^{197}Hg or ^{203}Hg is used in medical diagnosis for localisation of brain tumors (1, 2), investigation of blood circulation in the central nervous system (3) and renal scintigraphy (4-6).

The methods used for the preparation of this compound are isotopic exchange (6) and synthesis (7 - 12) . More important is the synthesis and in accordance with Towland (8), the course of reaction is following:

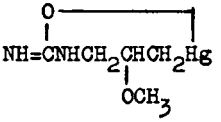
1. $Hg(OCOCH_3)_2 + NH_2CONHCH_2CH{=}CH_2 \xrightarrow[68^\circ]{CH_3OH} NH_2CONHCH_2\overset{OCH_3}{\underset{|}{C}}HCH_2HgOCOCH_3 + CH_3COOH$

2. $NH_2CONHCH_2CH(OCH_3)CH_2HgOCOCH_3 + NaX \rightarrow NH_2CONHCH_2CH(OCH_3)CH_2HgX + NaOCOCH_3$

X = Cl, Br

In this reaction three other compounds (I - III) are formed (8):

I. $NH_2CONHCH_2\underset{\underset{OH}{|}}{C}HCH_2HgCl$

II. 

III. $NH_2-\overset{\overset{O}{\|}}{C}-NHCH_2\underset{\underset{OCH_3}{|}}{C}HCH_2HgOH$

The best method for the analytical control of the radiochemical purity is paper chromatography with use of the mixture pyridine : butanol : water (3: 10: 3) as a solvent. In this system the main product (neohydrine) has Rf = 0.6, organic impurities mainly Rf's 0.2 and 0.4, inorganic mercury Rf = 0.9 (13).

In the present investigation this synthetic method was followed resulting in 40 - 50% of organic impurities. In this case the purification is absolutely necessary because in the medical diagnosis the impurities are useless and may have an innocuous effect. Some authors (10) recommended the crystallisation from anhydrous methanol as a purification process, but in this case the overall radiochemical yield is not higher than 20%.

During the elaboration of a method for the routine production of labelled chlormerodrin some parameters influencing the yield and purity of the product were investigated. Using as the substrates $^{203}HgCl_2$, sodium acetate and allylurea we found unexpectedly that a very important factor influencing the course of the reaction is the molar ratio

of sodium acetate to $^{203}HgCl_2$; the higher this ratio is, the more impurity with Rf = 0.13 (unidentified compound) is formed. Figure 1 shows the dependency between this ratio and the yield of the impurity with Rf = 0.13.

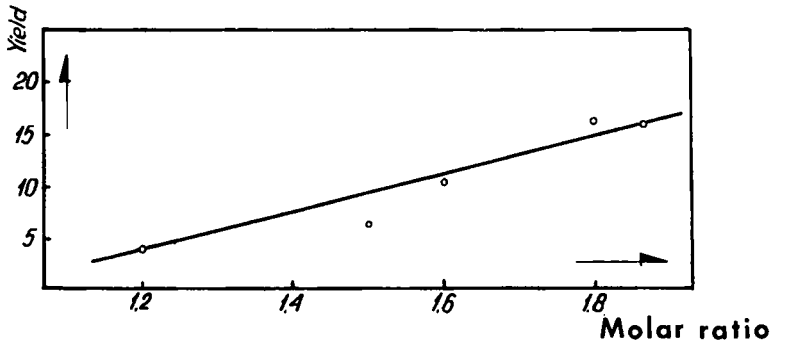


Fig. 1. Yield of the compound with Rf = 0.13 on the chromatogram as a function of molar ratio of sodium acetate to $HgCl_2$.

The influence of the ratio allylurea : $^{203}HgCl_2$ on the yield has been also investigated. It was expected that the excess of allylurea will increase the yield. But, as is shown in figure 2, the optimal ratio is about 5 : 1. The further increase of allylurea in the reaction mixture caused only a little increase in the yield of the product.

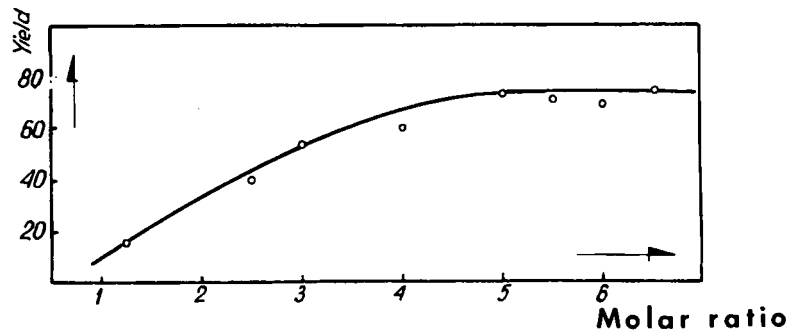


Fig. 2 ; Yield of 3-chloromercuri-2-methoxypropyl-urea in dependency on the molar ratio of allylurea to $HgCl_2$.

During the investigation of the reaction kinetics, we found that in the first moment an intermediate is formed, identified on the chromatograms as a spot with Rf = 0.56.

After some time (the reaction is carried out at elevated temperature) the compound with Rf = 0.56 is transformed into chlormerodrin (Rf = 0.6). The optimal yield is reached after about 6 hrs. Figure 3 illustrates the kinetics of the reaction.

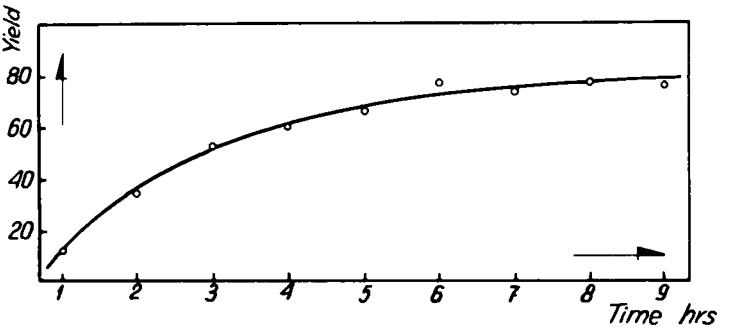


Fig. 3. Yield of 3-chloromercuri-2-methoxypropylurea in dependency on the time of heating.

The further problem is to minimize the losses of the obtained product in the purification process. Washing with dry ethyl ether was found to be the best method for this purpose. After six washings all impurities (organic and inorganic) were removed including the most insoluble compound identified on the chromatograms as a spot with Rf = 0.4. The last washings should be clear.

Very important for the process is also the quality of ^{203}Hg or ^{197}Hg. Since this compound is obtained from irradiated ^{203}HgO or ^{197}HgO, a special method was elaborated to obtain the standardized preparation. The ^{203}HgO (or ^{197}HgO) irradiated in reactor was dissolved directly in the quarz ampula in which it was irradiated in hot 17% acetic acid. Then a stoichiometric quantity of HCl was added. The obtained solution was then freeze-dried.

All these investigations were the basis for the choice of the following most favourable conditions in which the pure 3-chloromercuri-2-methoxypropyl-urea could be routinely obtained with high specific activity.

To the solution of ^{203}Hg (or ^{197}Hg)-acetate, the stoichiometric quantity of hydrochloric acid is added. Then the solution is freeze-dried. The dried compound is dissolved in anhydrous methyl alcohol. To the

solution, the allylurea and sodium acetate in anhydrous methyl alcohol are added. The reaction mixture in a penicillin bottle tightly stoppered with a capsule is heated in the autoclave at a temperature of 102 ÷ 105°C (overpressure of 0.2 - 0.3 atm) for 6 - 8 hrs. The coarse crystals seen at the start of reaction disappear after this time and the solution becomes clear. The cold solution is transferred to a distillation flask and the methyl alcohol is distilled off on the water bath.

The residue is washed out 6 times with dry ethyl ether and dissolved in a warm (45°C) 0.9% NaCl solution. The radiochemical yield of the precess is 60 - 70%, the radiochemical purity of the product 97 - 98%. Chlormerodrin was synthetized from 0.5 mCi to 100 mCi ^{203}Hg. The specific activity of $^{203}HgCl_2$ used in the synthesis was equal to 1 mCi/mg. The specific activity of the obtained product was 550 μCi/mg chlormerodrin. The advantage of this method is that it enables to work with very small quantities of $HgCl_2$. The minimal amount used in the described experiments was 0.5 mg $HgCl_2$. For securing the work by remote control at the quantities mentioned above, the volume of the reaction mixture is regulated by addition of methyl alcohol which has no effect on the reaction.

CONCLUSIONS.

1. The routine production of 3-chloromercuri-2-methoxypropyl-urea requires standardized $HgCl_2$ (labelled with ^{197}Hg or ^{203}Hg) which is obtained by the method described above.
2. The molar ratio of sodium acetate and allylurea to the $HgCl_2$ should be 1 : 1 and 5 : 1 respectively. The heating time of reaction mixture should be not less than 6 hrs.
3. Washing with dry ether removes all impurities.
4. The method enables to work with very small quantities of $HgCl_2$, what is especially important in the work with expensive ^{197}Hg. The specific activity of the product obtained depends only on the specific activity ^{197}Hg or ^{203}Hg used.

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