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Wickensfeld

Partial Translation of Letter From:

C. H. Boehringer Sohn
Ingelheim a. Rhein

EXHIBIT

July 29, 1957

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Nancy Bendish 2-18-73



Dear Dr. Frahl:

Dr. Kudsrus has been traveling quite a bit and did not get around to answering your letter of May 21, 1957. He asked me to answer your questions for him.

Van Sandeman, Berichte 90, 690, obtained, by the chlorination of dibenzodioxine in carbon tetrachloride, a tetrachloro derivative having a melting point of 284° to 290°C which is highly active in causing chloracne. This compound appears to be identical with the compound which is formed in producing tri-chlorophenol from symmetrical tetra chlorobenzene. The infra-red spectra are very similar, the melting points are identical, the mixed melting point shows no depression. Both have a strong tendency to sublime, both are volatile with water vapors, and both are soluble only in hot carbon-tetrachloride. The emerald green color of these compounds in concentrated sulfuric acid is characteristic. The dibenzodioxine free of chlorine, has a light blue color.

If the dry phenolate of orthochlorophenol, especially the potassium phenolate, is heated, the formation of dibenzodioxine is observed at temperatures as low as 100°C by the formation of a sublimate in the condenser.

Phenolic compounds or starting materials were not found any more after heating. The yield of dibenzodioxin having a melting point of 118°C is approximately 30%. In the rabbit test it does not produce chloracne.

Powdered copper accelerates the fusion reaction so much that it may acquire an almost explosive character. Trichlorophenol shows the same behavior as monochlorophenol. Pure trichlorophenol (tested biologically) shows the same course of reaction, forming the very strongly active tetrachlorodibenzodioxime having a melting point of 288°C.

Tri- and tetrachlorodibenzofuran tested in rabbits show the typical chloracne symptoms and changes of the liver.

According to the experiments of the Clinic for Skin Diseases of the University of Hamburg, Eppendorf, compounds having a high activity in causing chloracne can, if used in high concentrations, so quickly cause the death of the experimental animal that no external symptoms of chloracne become apparent.

Chloracne dibenzodioxime tetrachlorodibenzodioxime
References hazards safety precautions accontaminatio

C. H. Boehringer Sohn (cont'd.) -2-

A single dose of one (1) milligram of tetrachlorodibenzofuran per kilogram of rabbit caused death in a very short time.

Tetrachlorodibenzodioxin

Painting the rabbit ear with a .01% solution in intervals of two days caused pronounced chloracne with changes in the liver after one week. A single dose of .5 milligram per kilogram of weight caused the death of the experimental animal.

We want to emphasize that in syntheses in the laboratory of compounds of high chloracne activity, which we expect to lie in the group of chlorinated dibenzofurans and dibenzodioxines, the very greatest precaution has to be used in order to prevent damage to the health of the person carrying out these experiments. These substances have a really sinister character. Owing to their easy sublimation they can infect whole laboratories in such a form that they become unusable for a considerable time.

For the sake of completeness we mention the following literature which gives some pertinent information:

1. G. Wittig, B. 89, (1957) 1334-50
Angewandte Chemie 69, 245 Dehydrobenzol, Anomalie bei techn. Phenolprozess,
2. A. Lüttringhausen und D. Ambros, B. 89, 463-74 (1956)
Nebenreaktion der alkalischen Chlorbenzolkhydrolyse,
vergl. hierzu auch
3. N.S. Kozlov und A.F. Achmetzin, Z. obsc. Chim. 25, Nr. 3, 485-88 (1955)
Bildung von Dibenzofuran in alkalischem Medium bei hoherer Temperatur aus o-Phenyl-phenol.
4. Sandermann, B. 90, 690
Tetrachlorodibenzodioxin als Chloracneerreg.
5. Oberarzt Dr. K.H. Schuls, Der Hautarzt, Febr. 57, Heft 2, S. 94
Klinische und experimentelle Untersuchungen zur Aetiologie der Chloracne.
Referat des Vortrags vom 23. Deutschen Dermatologen-Kongress in Wien.
in Mai 56.
6. Hofmann und Oettel: Arztl. Wschr. 1954, 965. - Leberschädigungen.

In our plant in Hamburg we have still a few milligrams of the chloracne source. Owing to the fact that the gentleman in charge is on vacation, I can obtain the substance only by the end of this week. I shall send it to you immediately after obtaining it.