UNITED STATES DISTRICT COURT

DISTRICT OF RHODE ISLAND

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EMHART INDUSTRIES, INC.,

Plaintiff,

vs.

HOME INSURANCE COMPANY, INSURANCE COMPANY OF NORTH AMERICA, LIBERTY MUTUAL INSURANCE COMPANY, NORTH RIVER INSURANCE COMPANY, ONEBEACON AMERICA INSURANCE COMPANY, and UNITED STATES FIRE INSURANCE COMPANY,

Defendants.

Civil Action No. 02-053 S

DEPOSITION OF THOMAS F. CLEARY

Monday, February 10, 2003

Mendocino, California

EXHIBITS

Reported by:
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United States Patent Office 2,814,597 Patented Nov. 26, 1957

2,814,597

GERMICIDAL SOAPS COMPOSITION

John M. Wenneis, Port Washington, Thomas F. Cleary, North Bellmore, and Saul Chodroff, Brooklyn, N. Y., assignors to Norda Essential Oil & Chemical Company, New York, N. Y., a corporation of New York

No Drawing. Application March 12, 1953, Serial No. 342,014

8 Claims. (Cl. 252—107)

This invention relates to new chemical compounds which have germicidal activity and which are relatively non-toxic, non-irritating and non-sensitizing, to methods of preparing the same, and to soaps and other detergents containing said compounds in which the desirable germicidal and other properties are retained.

An acceptable germicidal compound must meet a number of desiderata. It must have effective germicidal properties, particularly for the destruction of bacteria under normal conditions of use. If it is to destroy bacteria in contact with the human skin, it must have germicidal activity under these conditions. The germicide must be effective for this purpose in a relatively low concentration in order that it may be economically employed and also utilized in concentrations below that which would impart any adverse effect.

Such a germicide should also be non-toxic, since if it is employed in contact with the human skin it may be absorbed into the body and would be objectionable if it possessed toxic properties. The undesirability of toxic germicides, such as corrosive sublimate, is too well-known to require elaboration.

Furthermore, an acceptable germicide must be relatively non-irritating to the skin. There are many germicides which destroy bacteria and which are not objectionably toxic but which are irritating when used in contact with the skin in that they cause erythema and in extreme cases produce blisters and pustules.

In addition to being non-irritating, an acceptable germicide must be relatively non-sensitizing. A germicide may be unobjectionable, in that it is non-irritative, upon its first use, but upon repeated use the subject may become sensitive to the germicide so that it cannot be reused without adverse results.

The effect of chemical structure on any and all of the above properties is not very well understood, if at all, particularly the effect of structure on irritative properties. Changes in chemical structure which amount to no more than a difference of one chlorine atom on a ring, or in the position of a chlorine atom, markedly affect the results. Compounds so closely related as adjacent homologues similarly give marked differences in results. There is, therefore, no predictability from a consideration of chemical structure of the results obtained in the field of germicidal activity, toxicity, irritative effects, and sensitization.

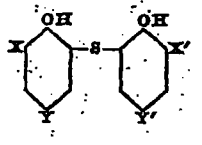
A large number of compounds have been proposed for inclusion with soap to render it germicidal. Since soap is so universally used in cleansing the skin, the inclusion of a satisfactory germicide in soap would be an ideal way of destroying bacteria in contact with the human skin. Many compounds which are recognized as germicides have been proposed for combination with soap, especially various phenolic materials, but because of the depressing action of soap upon the germicidal properties of known germicidal agents, soaps containing such agents do not have germicidal properties. This effect has been demonstrated and is reviewed at some length in U. S. Patent

No. 2,535,077, dated December 26, 1950. In view of this fact, which is now well-recognized in the art, it is not possible to predict, from the germicidal properties of a chemical compound itself, whether a soap containing it would have satisfactory germicidal activity, and would also meet the other requirements discussed above.

Because of the desirability of a germicidal soap, a great deal of research has been done, and at least one germicidal soap has been placed on the market in which the active ingredient is 2,2' - dihydroxy - 3,5,6-3',5',6' - hexachlorodiphenyl methane (also referred to as Hexachlorophene and G-11). Although a soap containing this compound is wanting in some respects, as will be pointed out, it has had wide sales and acceptance as an unusual product in which the germicidal activity is retained in the presence of the soap. In view of the fact that almost twenty-five years of extensive research on a wide variety of compounds preceded the discovery of this particular germicidal soap, it is obvious that the element of predictability is substantially nil and that the discovery of any other compound which could be incorporated in soap with equal or better results would be quite unobvious and unpredictable.

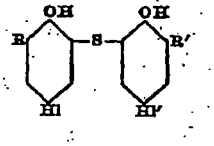
We have discovered, in accordance with our invention, that the following described compounds have germicidal properties and that these properties are retained in soap and that they meet the other desiderata enumerated above, more particularly non-toxicity, non-irritation, and non-sensitization.

These compounds have the following general formula:

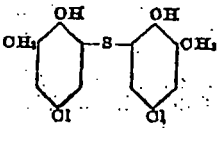


where X and X' are the same or different but are one member selected from the group consisting of (1) a halogen, especially chlorine, bromine and iodine, and preferably chlorine, and (2) an alkyl or cycloalkyl radical having 1 to 8 carbon atoms; and in which Y and Y' are the same or different but are the other members selected from the said group. More particularly, if X and X' are halogen, then Y and Y' are alkyl or cycloalkyl, and if X and X' are alkyl or cycloalkyl, then Y and Y' are halogen. The alkyl or cycloalkyl radical, for instance, may be methyl, isopropyl, octyl, hexyl, cyclohexyl, etc

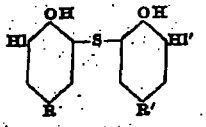
The preferred compounds have the general formula:



in which R and R' are the same or different alkyl or cycloalkyl radicals of 1 to 8 carbon atoms, and Hl and Hl' are the same or different halogens as defined above, the preferred compound of this type having the following formula:

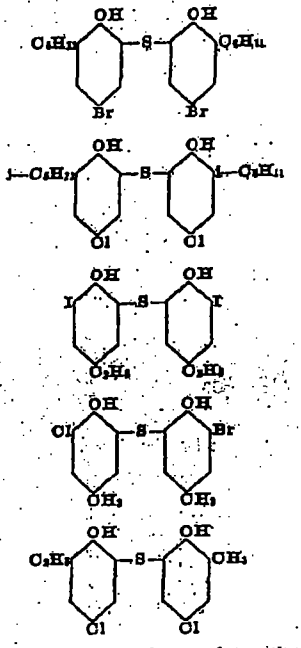


The alternative compounds would have the following formula:



where R and R' and HI and HI' are as defined above.

Other compounds falling within the invention include, for example:



A specific embodiment of our invention which we regard at the present time as the best mode that we contemplate for carrying out our invention utilizes the 2-hydroxy-3-methyl-5-chloro phenyl sulfide. This compound has a melting point of about 148–150° C., and is soluble in alcohol, benzene and warm carbon tetrachloride; it is insoluble in carbon disulfide, hexane and water. It is, however, soluble in soap at the normal pH of soap. This compound is selected as illustrative because of simplicity and economic considerations. Compounds in which the hydrocarbon radical has a larger number of carbon atoms may be preferred from a bactericidal and solubility standpoint.

The compounds of the invention may be made by condensing the appropriate halogenated alkyl or cycloalkyl phenol with sulfur dichloride. An inert solvent or reaction medium may be employed which may or may not be a solvent for the final product. The temperature is not particularly critical, as long as the reaction takes place at a rate which is controllable. Inasmuch as the reaction proceeds satisfactorily at room temperature, this is preferably employed, since it obviates the need for refrigeration or maintenance of elevated temperatures. A catalyst is not required, nor is extended refluxing essential. The final product is separated from the reaction medium by filtration and can be washed, and if necessary recrystallized to obtain a purer product.

As illustrative of the best mode of practicing the process of preparing the preferred compound of the invention, 28.4 grams of p-chloro-o-cresol and 25 cc. of solvent is placed in a flask and to it is added drop-wise, over a period of about fifteen minutes, 10.2 grams of sulfur dichloride in 10 cc. of the solvent. The mixture is stirred during the addition, which is carried out at room temperature (20–30° C.). The stirring of the mixture is continued until the evolution of hydrogen chloride ceases, which generally requires from thirty minutes to three hours. During this time, the product crystallizes if a solvent is employed in which the reaction product is insoluble. The product is filtered and washed colorless with the solvent generally in an amount of 50–100 cc. The combined filtrates may be stripped of solvent and unreacted sulfur dichloride, preferably in vacuo, to yield oily solids. However, it is difficult to salvage a clean product from such a residue.

The solvent employed in the reaction can influence the yield, ease of handling, and cleanliness of the product.

When carbon disulfide is employed as the solvent, a reaction medium commonly used for this type of reaction, the initial yield is 82%, the product having a melting point of 126° C. Upon recrystallization the yield is reduced to 56%, the product having a melting point of 148° C. The high crude yield is not indicative of the final results, since the material salvaged from the second crop of crystals cannot be successfully handled to give a clean product under usual circumstances. For practical purposes, therefore, the yield from carbon disulfide may be considered 56%.

When ethylene dichloride is used, the crude yield is 60%, the product melting at 149° C. When hexane is used as the solvent, the crude yield is 66%, the product melting at 130° C. These crude yields were washed in hexane and not recrystallized. Further losses would be obtained upon recrystallization.

In another variation of the process, the reaction medium may be an ester in which the alcohol and acid radicals have 5 carbon atoms or less, for instance isopropyl acetate. In such solvents, all of the reaction components are soluble, as well as the resulting product, including a large portion of the hydrogen chloride. At the conclusion of the reaction, the product is neutralized with sodium carbonate and stripped of hydrogen chloride. The solvent is evaporated and the resulting product may be recrystallized from any suitable solvent, such as hexane.

The preferred solvent consists of a mixture of ethylene dichloride and hexane, such as, for example, 10 to 50% by volume of ethylene dichloride and 90 to 50% hexane, preferably 22% ethylene dichloride and 72% hexane. The yield from this solvent is 63%, the product having a melting point of 148° C. This initial product is clean and does not need recrystallization. This solvent is preferred because of the higher yield as compared with the yield of recrystallized product when carbon disulfide is used as the solvent and also because of the elimination of recrystallization.

In a modification of this process in which the hydrogen chloride is swept out by bubbling with air until no more hydrogen chloride is evolved, followed by treating the reaction mixture with a slight excess of sodium carbonate solution, the product obtained by filtration and washing with hexane amounted to a yield of 72% without recrystallization.

The use of excess sulfur dichloride does not increase the yield, nor does the use of a chlorine carrier catalyst, such as aluminum chloride, result in advantages; such a catalyst, in fact, reduces the yield and gives a darker product. Refluxing does not affect the yield and leads to a darker product.

The product made by any of the above processes can be decolorized, if desired, by dissolving it in methanol, adding a small amount of activated carbon, such as Darco G–60, at elevated temperature below the boiling point of the methanol, and filtering. The product is precipitated by adding water to the hot solution and cooling gradually with stirring.

In order to demonstrate the effectiveness of the compounds of the present invention as germicides, particularly in soap, a germicidal soap composition was prepared

utilizing as the base a pure white soap of the type conventionally employed for toilet purposes (Ivory), in which was thoroughly incorporated 2% of 2-hydroxy-3-methyl-5-chloro phenyl sulfide. This was tested in comparison with a similar soap containing 2% of Hexachlorophene. These two soaps were tested to determine the skin-degerming efficiency on six subjects each, according to the method of Arthur R. Cade, "An in vivo method for determining the de-germing efficiency of soaps containing Hexachlorophene," Papers on Evaluation of Soaps and Detergents, Special Technical Publication No. 115, published by the American Society for Testing Materials, 1952.

While this test is fully described in the above publication, it may be summarized as follows: Twelve subjects were used for the test. They were divided into two groups of six subjects each, three males and three females in each group, which were used to test each of the above two soaps. Each subject was given two cakes of soap corresponding to his or her group, one for use at home and the other at work. No subject had used any germicidal soap for at least two weeks prior to the test. The test was started on a Monday and ended on the second Friday following, during which time the subjects used their allotted soap when washing their hands. The transient and resident bacterial population on the hands of each subject was determined on the first day prior to starting the use of the experimental soap. The transient and resident bacterial population on the hands of each subject was also determined on the Friday of the first week, after four days' use of the soap, and on the Thursday and Friday of the second week, after nine and ten days' use of the soap.

The details of the method are given in the publication referred to above. Briefly, the method consists in having each subject wash his hands with a bland, non-germicidal, neutral soap, five consecutive times, the first, fourth and fifth times, in separate basins containing 2 liters of lukewarm water. The second and third times the hands were washed under running lukewarm tap water. Bacterial counts were taken on the wash waters in the basins, which represent the first, fourth and fifth washings. The counts on the first washing are considered to be predominantly the transient bacterial population of the skin, whereas the counts on the fourth and fifth washings are considered to be predominantly the resident bacterial population of the skin.

Since the effectiveness of a germicidal soap will be demonstrated primarily by the reduction in the resident bacterial population rather than the transient, the results are expressed as the reduction obtained on the fifth washing. The mean figure is obtained by discarding the two highest and the two lowest values and averaging the remaining two. The mean does not take into consideration a subject who may be out of line with the other subjects. The results are given in the following table:

Reduction in the resident bacterial population (5th washing)

Germicidal agent in soap	Fourth day		Ninth day		Tenth day	
	Average, percent	Mean, percent	Average, percent	Mean, percent	Average, percent	Mean, percent
2-hydroxy-3-methyl-5-chloro phenyl sulfide	72	74	79	81	82	84
Hexachlorophene	68	79	78	81	84	82

It will be obvious that considering both the mean and the average, the soap made in accordance with the invention is as good, and in some instances better than the soap containing Hexachlorophene, which may be considered as the standard reference. As has been explained heretofore, the discovery of Hexachlorophene as a germicide for soap was the result of years of research and is widely accepted as an unusual development in the germicidal soap field. The development of any other soap which equalled this at this stage of the art would be quite unexpected.

The toxicity of the preferred compound of the invention, namely, 2-hydroxy-3-methyl-5-chloro phenyl sulfide, was determined by administering the compound orally to rats. The method employed is the LD_{50} test which may be defined as the amount which, when administered orally as a single dose, will probably kill 50% of the animals to which it is administered. In carrying out the test, normal healthy white albino rats, paired for sex, fasted for 24 hours, were administered various dosages of the compound (dissolved in corn oil) by stomach tube. All animals were observed for at least two weeks following the administration of the dosage, unless death occurred before that time.

The results are given in the following table:

Dose per 100 grams body weight of rat	Number of animals			Percent mortality
	Tested	Living	Dead	
30 milligrams	5	4	1	20
40 milligrams	5	5	0	0
60 milligrams	5	5	0	0
90 milligrams	5	4	1	20
120 milligrams	5	3	2	40
150 milligrams	5	2	3	60
180 milligrams	5	0	5	100

When the results were plotted on semilogarithmic paper, with the percent mortality on the ordinate and the dose on the abscissa (logarithmic scale), the LD_{50} of the compound was found to be approximately 1.3 grams of the compound per kilogram body weight.

As will be obvious to one skilled in the art, this low toxicity, when measured by this standard test, is assurance that the compound is sufficiently safe for use as a germicide in soap.

In order to determine the irritative properties of 2-hydroxy-3-methyl-5-chloro phenyl sulfide, and particularly to compare it with the irritative properties of Hexachlorophene, these two compounds were tested, as well as the sodium salt of both compounds, since the sodium salt probably corresponds to the form of the compound present in soap. The solutions tested were as follows:

Solution A: 0.5% 2-hydroxy-3-methyl-5-chloro phenyl sulfide in aqueous isopropyl alcohol

Solution B: 0.5% Hexachlorophene in aqueous isopropyl alcohol

Solution C: 0.5% sodium salt of 2-hydroxy-3-methyl-5-chloro phenyl sulfide in aqueous isopropyl alcohol

Solution D: 0.5% sodium salt of Hexachlorophene in aqueous isopropyl alcohol

Each solution was tested by the well-known patch test to determine if the compounds would produce contact dermatitis on primary contact. In this test 55 human subjects, 34 females and 21 males, ranging from ten to sixty-three years, were employed. Discs approximately 1 cm. in diameter were cut from white blotting paper and different discs saturated with the four solutions described above. The saturated discs were applied to the flexor surface of either the forearm or the upper arm of each subject, utilizing four patches for each subject. All patches were covered with an Elastopatch. After twenty-four hours of primary contact with the patches, they were removed and the subjects examined. The reactions obtained on every subject following examination were noted, and the severity of reaction was based on an arbitrary scoring system, as follows:

0=No reaction.

1=Slight erythema or discoloration lasting at least four hours after removal of the patch.

2=Rather severe erythema or discoloration lasting at least two days after removal of the patch.

3=Severe circumscribed irritation with blisters or pustules.

The results are given in the following table, which lists the number of subjects in each reaction category:

	Solution A	Solution B	Solution C	Solution D
Number of 0	12×0= 0	6×0= 0	34×0= 0	23×0= 0
Number of 1	21×1=21	14×1=14	21×1=21	25×1=25
Number of 2	21×2=42	32×2=64	0×2= 0	7×2=14
Number of 3	1×3= 3	3×3= 9	0×3= 0	0×3= 0
Total	55 66	55 87	55 21	55 39
Average	1.20	1.58	0.38	0.71

From a consideration of the above results, it will be obvious that the compound of the invention, as well as the sodium salt thereof, are much less irritating than the Hexachlorophene. This is particularly true in the case of the sodium salt, the form in which the compound would exist in soap, where the Hexachlorophene is found to be almost again as irritating as the compound of the invention.

In order to determine the sensitizing properties, the irritation test was repeated on each of the subjects by applying patches with the same solution to the same subject, each patch being applied at the site previously used for that particular patch. The patches were again worn for twenty-four hours and the subjects examined in the same manner as described above. The results are given in the following table:

	Solution A	Solution B	Solution C	Solution D
Number of 0	14×0= 0	9×0= 0	39×0= 0	27×0= 0
Number of 1	25×1=25	18×1=18	16×1=16	25×1=25
Number of 2	16×2=32	30×2=60	0×2= 0	3×2= 6
Number of 3	0×3= 0	0×3= 0	0×3= 0	0×3= 0
Total	55 57	55 78	55 16	55 31
Average	1.04	1.42	0.29	0.56

From this it will be seen that as compared with Hexachlorophene the compounds of the invention cause less sensitization, and that this is particularly true in the case of the sodium salt of the compound, where the Hexachlorophene is shown to be almost twice as objectionable as the preferred compound of the invention from the standpoint of sensitization.

A low sensitization level is an extremely important aspect of compounds used in germicidal soaps because of the repeated use of such soaps under normal living conditions. It will be obvious that a soap is useless for normal toilet use if it cannot be utilized over long periods of time. To substantiate the non-sensitizing properties of the preferred compound of the invention, the sensitization was determined on white male guinea-pigs by the method described in an article entitled "Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes," John H. Draize, Geoffrey Woodard and Herbert O. Calvery, Journal of Pharmacology and Experimental Therapeutics, vol. 82, No. 4, pages 386–388, December 1944. In this method, ten white male guinea-pigs, weighing 325–450 grams, were used. The hair was removed from the back by close clipping. A 0.1% suspension of the compound in water was injected intracutaneously, using a 26-gauge needle. A total of ten injections were made at random in an area about three to four centimeters square, just below the midline of the back. The first injection was 0.05 ml., while the remaining injections were 0.1 ml. Two weeks after the tenth injection, a test injection of 0.05 ml. of a freshly-prepared suspension was made on the flank, slightly below the sensitizing area. Twenty-four hours later, a reading of the diameter, height and color of the reaction was made and compared with similar readings taken after the first injection.

As a result of this test, it was found that on all ten animals the values for the test readings were no greater than those for the initial readings, and it is concluded that when tested by the above procedure the preferred compound of the invention cannot be considered to be a sensitizer.

The compounds of the invention may be used in soaps, in the so-called non-soap synthetic organic detergents, or in combination with any "organic detergent." This expression is intended to include the soaps which are the salts of higher fatty acids and the so-called non-soap synthetic detergents. All of these compounds are characterized by an organic radical having at least 8 carbon atoms and a group or grouping imparting sufficient hydrophilic, water-solubilizing or water-dispersible properties to give the detergent satisfactory washing properties in water. These organic detergents are to be distinguished from the inorganic detergents, such as the silicates, phosphates, etc., which possess detergent properties but which do not ordinarily have the property of inhibiting the germicidal activity of germicides as do the soaps and synthetic non-soap detergents.

The soap may be any of those commercially utilized in the household or in industry. These are generally the sodium soaps of fatty acids having 12 to 18 carbon atoms, such as lauric, myristic, palmitic, oleic, stearic, etc., or mixtures thereof. The mixtures of fatty acids derived from tallow and coconut oil are illustrative. A portion of the sodium soap may be replaced by potassium soap. As a specific illustrative example, the soap may consist of 75% tallow fatty acids and 25% coconut oil fatty acids saponified with sodium hydroxide. In another specific example, 10% of the sodium hydroxide is replaced by potassium hydroxide. The soap may contain antioxidants, pigments, dyes, perfume, etc., as is conventional.

The non-soap organic detergents may be of the so-called anionic, nonionic or cationic type. Illustrative detergents of this type are described in Industrial and Engineering Chemistry, vol. 35, page 107 et seq. and page 126 et seq. (1943). As specific examples may be mentioned sodium lauryl sulfate (Duponol) and sodium polypropylene benzene sulfonate in which the polypropylene radical contains 10 to 15 carbon atoms (Oronite). Others include the sulfonated monoglycerides of fatty acids, the sodium fatty acid taurides, and methyl taurides such as sodium oleic methyl tauride (Igepon T), coconut fatty alkyl dimethylbenzylammonium chloride (Triton K–60), coconut fatty acid diethanolamide (Ninol), and similar detergents.

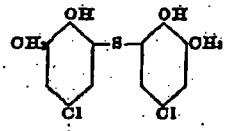
The amount of the compound to be incorporated in the detergent will be controlled somewhat by economic considerations and the extent of the germicidal activity desired in the detergent. Amounts as low as a fraction of 1%, for example 0.25 to 0.5%, show a significant improvement in germicidal action. Larger amounts, however, of the order of 1.5 to 3.0% are preferred, 2.0% appearing to be an optimum. Amounts larger than 3% to 5% are uneconomical, and the use properties are not sufficiently important under the usual circumstances to justify such larger amounts.

The compounds of the invention may be included in soap or detergents in any form, such as in cakes or bars of the type generally sold and used for the toilet, in the all-purpose type, such as the white floating bar, or in powders, liquids, flakes, beads, and similar forms.

The compounds may be incorporated in the soap in any manner. If the soap is a liquid, the compound may simply be dissolved therein; if it is a solid, the compound may be incorporated at any stage of the manufacture, such as in the kettle, the mill, the plodder, the crutcher, etc. so long as uniform distribution is obtained.

We claim:

1. The compound having the following formula:



2. A method of preparing the compound of claim 1 which comprises reacting sulfur dichloride with p-chloro-o-cresol in approximately stoichiometric proportions at a temperature within the range of 20 to 30° C., the sulfur dichloride being added gradually to the p-chloro-o-cresol, both the sulfur dichloride and the p-chloro-o-cresol being dissolved in a reaction medium consisting essentially of from 10 to 50% by volume of ethylene dichloride and from 90 to 50% by volume of hexane, the reaction being carried out with stirring during the addition of the sulfur dichloride until the evaporation of hydrogen chloride ceases.

3. The method of claim 2 in which the reaction is followed by bubbling air through the reaction mixture to strip hydrogen chloride therefrom.

4. The method of claim 2 in which the reaction medium comprises about 22% ethylene dichloride and about 72% hexane.

5. The method of claim 2 in which the reaction medium is about 22% ethylene dichloride and about 72% hexane, and in which the reaction is followed by bubbling air through the reaction mixture to strip hydrogen chloride therefrom.

6. A germicidal detergent composition comprising a fatty acid soap and an amount of the compound of claim 1 to render the composition germicidal.

7. The composition of claim 6 in which the fatty acid soap is a toilet soap in bar form.

8. The composition of claim 7 in which the amount of the compound incorporated is about 2%.

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McClement et al.: Jour. Chem. Soc., London (1937), pp. 1016–21.

United States Patent Office 3,456,020 Patented July 15, 1969

3,456,020

PRODUCTION OF 2,2'-METHYLENE BIS(3,4,6-TRICHLOROPHENOL)

Thomas F. Cleary, Summit, N.J., assignor to Centerchem Inc., New York, N.Y., a corporation of New York

No Drawing. Continuation-in-part of application Ser. No. 489,036, Sept. 21, 1965. This application Nov. 28, 1967, Ser. No. 686,290

Int. Cl. C07c 37/00

U.S. Cl. 260—619 3 Claims

ABSTRACT OF THE DISCLOSURE

This invention is directed to the production of hexachlorophene by a two stage process in which one mol of 2,4,5-trichlorophenol and one mol of formaldehyde are reacted under the influence of an acid catalyst, after which the reaction product is condensed with one mol of 2,4,5-trichlorophenol through the agency of chlorosulfonic acid or fluorosulfonic acid.

RELATED APPLICATION

This application is a continuation-in-part of my copending application Ser. No. 489,036, now abandoned, filed Sept. 21, 1965, and having the same title as this application.

THE INVENTION

This invention relates generally to new and useful improvements for the production of 2,2'-methylene bis-(3,4,6-trichlorophenol), commonly called hexachlorophene, and particularly seeks to provide a novel two stage process for producing same.

The known processes for the preparation of hexachlorophene (2,2'-methylene bis(3,4,6-trichlorophenol)) involve the condensation of two mols of 2,4,5-trichlorophenol with one mol of formaldehyde (as Formalin or paraformaldehyde). The usual condensing agent is concentrated sulfuric acid or weak oleum, and the reaction may be carried out in the presence or absence of a solvent which is inert to the reactants and to the condensing agent.

In these processes it is customary to mix all of the reactants (and the solvent, if any) at once and to heat the mixture, with agitation, for a certain time. Conditions such as these are disadvantageous in the production of hexachlorophene in that:

(1) They tend to promote the formation of color bodies which make difficult the purification of the product;

(2) They tend to promote the formation of the by-product 2,4,5-trichlorobenzodioxolane with an attendant loss of yield;

(3) They require, if acceptable yields are to be obtained, extreme care that the 2,4,5-trichlorophenol and formaldehyde be present in exactly the molar ratio 2.00:1.00. Since the composition of Formalin or of formaldehyde is usually imprecise, and since a certain amount of formaldehyde is lost from the reaction mixture by volatilization, this is a difficult requirement to realize in practice.

However, through the use of this invention the above mentioned disadvantages in prior processes have been overcome.

Therefore, an object of this invention is to provide a new method of producing hexachlorophene from previously known source materials which is simpler, more effective and results in higher yields by comparison with prior processes.

Another object of this invention is to provide a process of the character stated in which one mol of 2,4,5-trichlorophenol and one mol of formaldehyde are reacted

under the influence of an acidic catalyst to form a novel intermediate product, which in turn is condensed with one mol of 2,4,5-trichlorophenol through the agency of chlorosulfonic acid or fluorosulfonic acid to produce high yields of pure hexachlorophene.

With these and other objects, the nature of which will be apparent, the invention will be more fully understood by reference to the accompanying detailed description and the appended claims.

In accordance with this invention it has been discovered that:

(1) One mol of 2,4,5-trichlorophenol and one mol of formaldehyde will react, under the influence of acidic catalysts such as benzenesulfonic acid, anhydrous hydrogen, and diluted sulfuric acid, to form quantitatively and exclusively, a compound which has a melting point of 78° C. The compound has a chlorine content 46.5%, occurs in long colorless prisms, and definitely is not 2,4,5-trichlorosaligenin.

(2) The compound formed as in (1) can be condensed with 2,4,5-trichlorophenol, through the agency of chlorosulfonic acid or fluorosulfonic acid, to produce high yields of pure hexachlorophene.

Both of these reactions are surprising. The only hitherto known reaction product of equimolar amounts of 2,4,5-trichlorophenol and formaldehyde is 2,4,5-trichlorosaligenin, which is formed under alkaline conditions and has a melting point of 128° C. 2,4,5-trichlorophenol, which is relatively inert to concentrated sulfuric acid and to oleum, will react readily with chlorosulfonic acid and fluorosulfonic acid to form 2,4,5-trichlorophenol-6-sulfonic acid.

The following examples will illustrate this invention.

Example 1

197.5 grams of 2,4,5-trichlorophenol having a melting point of 66° C. is dissolved in 1000 grams of perchloroethylene and the solution is warmed to 50° C. with agitation. To this solution is added 50 grams of 90° sulfuric acid. 30 grams of paraformaldehyde is added slowly over a period of one hour with sufficient cooling to maintain the temperature between 60° C. and 70° C. The reaction is exothermic. The mixture is stirred for an additional two hours at 70° C. The perchloroethylene solution is then separated from the dilute acid layer. Upon evaporating a small sample to dryness a crystalline product is obtained which has a melting point of 78° C. There is no free formaldehyde remaining either in the dilute acid layer or in the perchloroethylene solution. There is no hexachlorophene present at this point in the reaction mixture, nor any unreacted 2,4,5-trichlorophenol.

The perchloroethylene solution of the product of the reaction between 2,4,5-trichlorophenol and paraformaldehyde is mixed with a solution of 197.5 grams of 2,4,5-trichlorophenol in 1000 grams of perchloroethylene and the mixture is heated with agitation to 75° C. There is then introduced dropwise over a period of three hours 116 grams of chlorosulfonic acid. The addition of chlorosulfonic acid is accompanied by a mild exothermic reaction and by the evolution of HCl. The temperature is maintained at 75° C. throughout the chlorosulfonic acid addition and is then held at 75° C. to 80° C. for an additional two hours. Agitation is stopped, the remaining sulfuric acid layer is allowed to settle and is separated. The hot perchloroethylene solution is stirred with 10 grams of activated charcoal and is filtered. The reaction product, 2,2'-methylene bis(3,4,6-trichlorophenol), crystallizes upon cooling and is separated by filtration. The yield is 310 grams having a melting point of 162° C. Upon concentration of the mother liquors there is obtained an additional 65 grams of product having the same melting point.

Example 2

197.5 grams of 2,4,5-trichlorophenol having a melting point of 62° C. is dissolved in 2000 ml. of chloroform, and the solution is warmed to 50° C. with agitation. Dry hydrogen chloride is bubbled through the solution at a rate of 5 grams per minute, and over a period of one hour, 31.6 grams of 95% paraformaldehyde is added. Hydrogen chloride addition is continued for 30 minutes, and the mixture is then heated to reflux for one hour.

A small sample of the reaction mixture, evaporated to dryness, yields a white crystalline compound, having a melting point of 78° C. It contains no 2,4,5-trichlorophenol or formaldehyde.

To the reaction mixture is then added a solution of 197.5 grams of 2,4,5-trichlorophenol, having a melting point of 62° C., in 2000 ml. of chloroform. The mixture is heated to 65° C., under a reflux condenser and with good agitation, 100 grams of fluorosulfonic acid is added dropwise, over a period of three hours. Agitation and heating at 65° C. are continued for three hours more, then agitation is stopped, the acid layer is settled and separated. The hot chloroform solution is stirred with 10 grams activated charcoal, filtered and cooled to 10° C. The crystallized 2,2'-methylene bis(3,4,6-trichlorophenol) is filtered off, washed with cold chloroform and dried. The yield is 310 grams having a melting point of 164° C. Evaporation of the mother liquor yields an additional 70 grams of product.

Example 3

To 1000 ml. of benzene is added, slowly, 58 grams of chlorosulfonic acid, and the solution is then heated to reflux until all HCl is driven off. There is thus produced a benzene solution containing 79 grams benzenesulfonic acid. To this solution is added 197.5 grams 2,4,5-trichlorophenol having a melting point of 62° C. The solution is then heated just to the point of reflux, and with good agitation, 85 grams of 37% Formalin is added over two hours, while the water introduced with the Formalin is taken off as an azeotrope with benzene. The condensed benzene is returned to the reaction mixture. Reflux is then continued for one hour, after which 500 ml. of water is added. The mixture stirred 15 minutes at 60° C., and settled. The water layer which contains the benzenesulfonic acid, is separated and discarded.

A small sample of the benzene solution evaporated to dryness, yields a white crystalline product having a melting point of 78° C. It contains no 2,4,5-trichlorophenol or formaldehyde.

The benzene solution is added to 2000 ml. of perchloroethylene, and the benzene is removed from the mixture by fractional distillation.

To the remaining perchloroethylene solution of the reaction product of 2,4,5-trichlorophenol with Formalin is added 197.5 grams 2,4,5-trichlorophenol having a melting point of 62° C. The solution is heated to 75° C., and with vigorous agitation is added, over five hours, 116 grams chlorosulfonic acid. Stirring is continued at 75° C. for two hours and the acid layer is then settled and separated. The hot perchloroethylene solution is stirred with ten grams activated charcoal, filtered and cooled to 10° C. The crystallized 2,2'-methylene bis(3,4,6-trichlorophenol) is filtered off, washed with cold perchloroethylene and dried. The yield is 280 grams having a melting point of 163° C. Evaporation of the mother liquor yields an additional 85 grams of product.

I claim:

1. In a method for producing hexachlorophene the steps of, supplying a solution of 2,4,5-trichlorophenol and formaldehyde at a 1 to 1 molar ratio in a solvent selected from the group consisting of perchloroethylene, chloroform and benzene, reacting said 2,4,5-trichlorophenol and formaldehyde in the pressure of an acid catalyst selected from the group consisting of benzene-sulfonic acid, anhydrous hydrogen chloride and diluted sulfuric acid to form a solution of a compound which, when dry, has a melting point of 78° C. and a chlorine content of 46.5%, then adding a solution of 1 mol of 2,4,5-trichlorophenol to the solution containing the reaction product of the preceding step, and effecting condensation therebetween by the addition of a sulfonic acid selected from the group consisting of chlorosulfonic acid and fluorosulfonic acid to produce pure hexachlorophene.

2. A reatcion product between 2,4,5-trichlorophenol and formaldehyde, having a melting point of 78° C. and a chlorine content of 46.5%, produced by supplying a solution of 2,4,5-trichlorophenol and formaldehyde at a 1 to 1 molar ratio in a solvent selected from the group consisting of perchloroethylene, chloroform and benzene, reacting said 2,4,5-trichlorophenol and formaldehyde in the presence of an acid catalyst selected from the group consisting of benzenesulfonic acid, anhydrous hydrogen chloride and diluted sulfuric acid, and separating the solvent solution containing the reaction product from the acid.

3. In a method for producing hexachlorophene the steps of; dissolving a molar equivalent of 2,4,5-trichlorophenol in a solvent selected from the group consisting of perchlorethylene, chloroform and benzene; adding to said solution an acid catalyst selected from the group consisting of benzenesulfonic acid, anhydrous hydrogen chloride and diluted sulfuric acid; then adding a molar equivalent of formaldehyde and maintaining the temperature between about 60° C. and about 70° C. during the exothermic reaction produced as the result of such addition to produce a reaction product which, when dry, has a melting point of 78° C. and a chlorine content of 46.5%; separating the solvent solution from the acid; adding a molar equivalent of 2,4,5-trichlorophenol dissolved in said solvent to said separated solvent solution; effecting condensation between said added molar equivalent of said 2,4,5-trichlorophenol and the reaction product in said separated solvent solution by the addition of an acid selected from the group consisting of chlorosulfonic acid and fluorosulfonic acid; then removing the solvent solution containing the condensed product and recovering pure hexachlorophene therefrom by cooling and filtering same.

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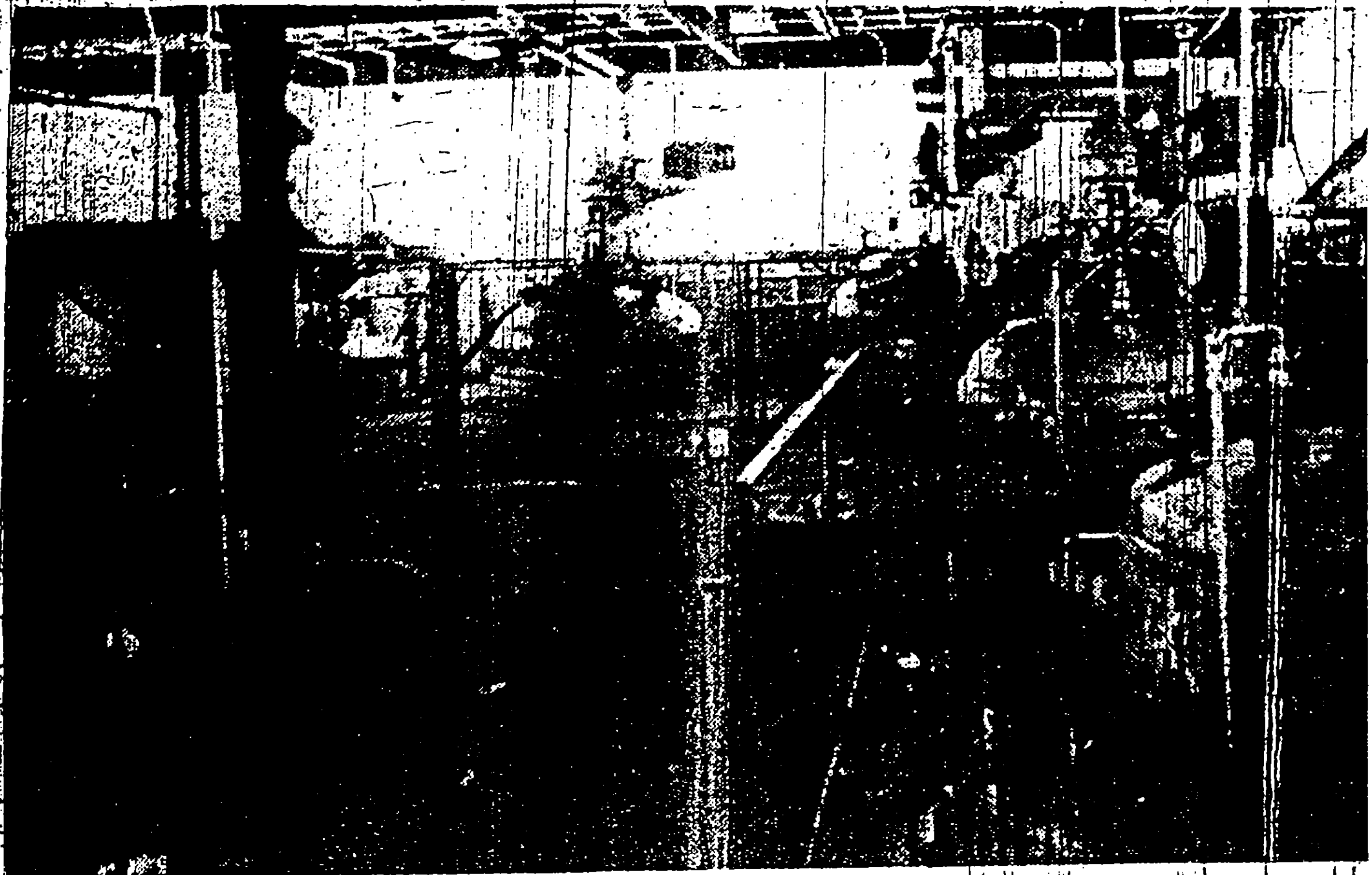
LEON ZITVER, Primary Examiner

N. MORGENSTERN, Assistant Examiner

JS-30-65.B22



Upper level of new hexachlorophene plant at Metro-Atlantic, Inc., Centredale, showing a number of its stainl

Pharmaceutical Products Adde

By ARTHUR S. RESEIGH
Journal-Bulletin Business Writer

An entrance into the pharmaceutical field has been achieved by Metro-Atlantic, Inc. of Centredale as a result of a product development program in which it has been active for the past three years.

The chemicals manufacturer, originally a producer of chemical products for the textile industry, has erected a new 2,000 square foot plant for the production of its newest product -- hexachlorophene.

The new facility, erected at a reported cost of a quarter of a million dollars, provides Metro-Atlantic with the equipment necessary to produce the new product by means of its newly patented process.

Joseph E. Buonanno, president, said the facility contains enough equipment to produce a complete line of chemical products. It could produce the equivalent of 15 million pounds per year if used for general chemicals production, he said.

The many different pieces of equipment in the new plant, however, are performing single steps in the production of hexa- [illegible]

ed he counted 34 different products containing hexachlorophene.

"We are not setting out to capture the market for this product, but only to acquire a share of it," Mr. Buonanno said. He expressed the opinion that the use of hexachlorophene is on the increase and that another manufacturer will be able to find ample market for his output.

Metro Atlantic was led into the pharmaceutical chemicals field as a result of a project on which it worked with Eli Lilly Co. of Indianapolis.

The big pharmaceuticals manufacturer needed a large-scale manufacturer for trifluralin, designated in chemical terms as "a,a,a-trifloro-2,6-dinitro-N,N-di-proply-y-toludine," while it was building its own production ability for the prod-

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By ARTHUR D. [illegible]
Journal-Bulletin Business Writer

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The many different pieces of equipment in the new plant, however, are performing single steps in the production of hexachlorophene. The final product, according to George C. Huse, the firm's chemical director, involves a number of highly complicated chemical reactions. The process starts with raw materials and includes such chemical processes as purification, crystallization, recovery of the reactor media, drying, grinding and packaging.

Raw materials are fed from large storage tanks outside the plant. Process equipment includes a dozen different stainless steel, glass-lined low and high temperature reactors—each of them limited to one step of the production cycle.

Product Is Bactericide

Hexachlorophene is a bactericide used in soaps, shaving creams, tooth paste, medical soaps and all kinds of creams and salves for hospital use.

Making the production of hexachlorophene particularly interesting to Metro-Atlantic was the large number of preparations in which it is used and the fact that its production was limited to one manufacturer.

Mr. Huse reports that in one section of a drugstore he visited he counted 34 different products containing hexachlorophene.

"We are not setting out to capture the market for this product, but only to acquire a share of it," Mr. Buonanno said. He expressed the opinion that the use of hexachlorophene is on the increase and that another manufacturer will be able to find ample market for his output.

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Signed for Production

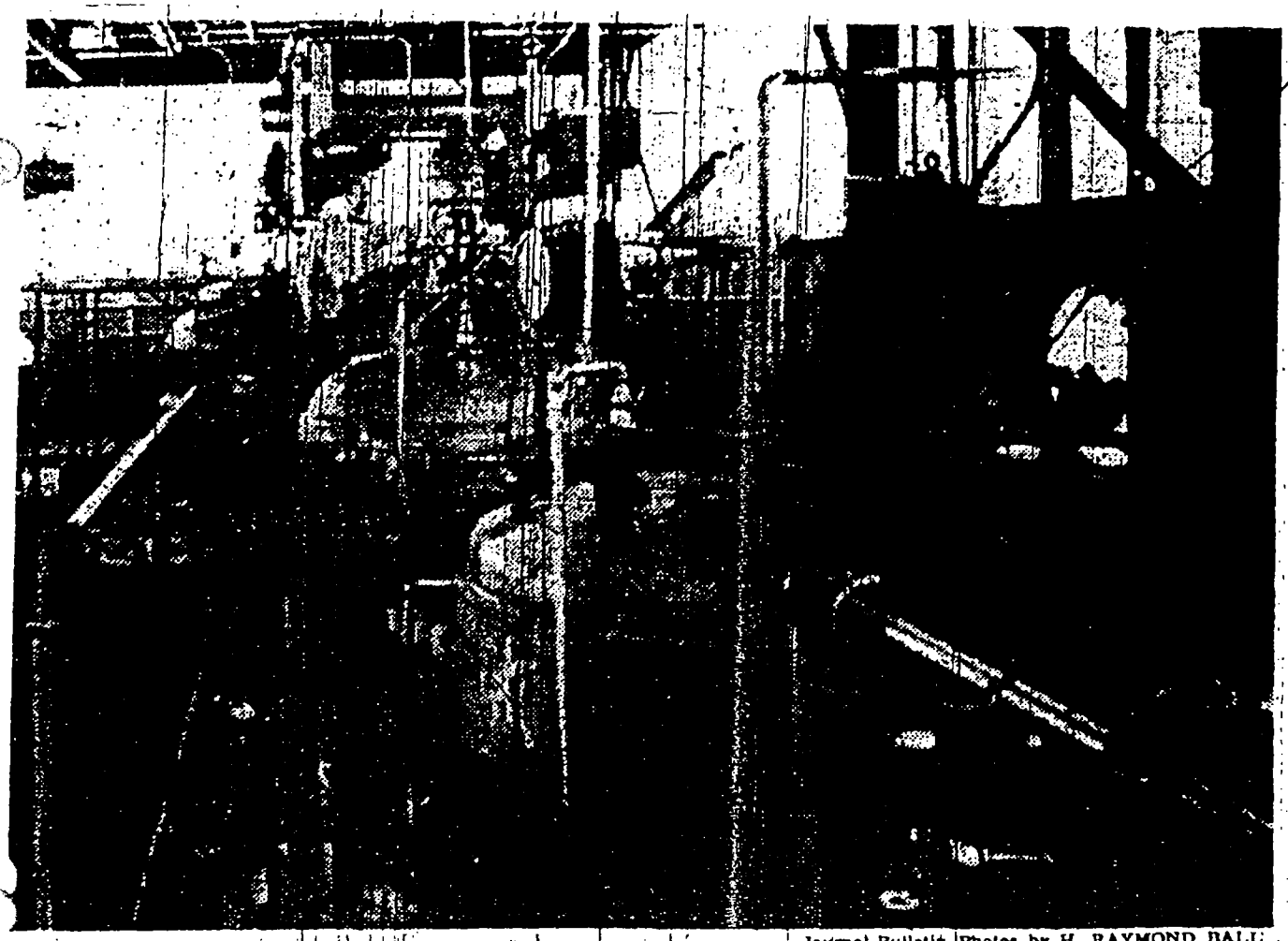
They contacted Metro-Atlantic and set up an arrangement for carrying on the required research and also for producing close to half a million pounds of the product.

The Centredale company worked on the project in collaboration with Eli Lilly Co. for about a year. In that time research was completed, a pilot plant set up and production started. Patents on the product—a post emergence weed killer—were procured and later turned over to the Lilly company.

With the completion of a multi-million-dollar plant, Lilly took over the production of the product. It is designed for specific use on cotton and soybean plantations.

The research and subsequent manufacture of about 500,000 pounds of the product served to interest Metro-Atlantic in the pharmaceutical side of the chemical business.

The facilities used for the trifluralin project became the beginning of the new facility now being used exclusively for the



—Journal-Bulletin Photos by H. RAYMOND BALL

lantic, Inc., Centredale, showing a number of its stainless steel low and high temperature reactors.

l Products Added

CTHUR S. RESEIGH
l-Bulletin Business Writer

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production of hexachlorophene.

Two other programs are currently in progress at the Centredale plant. When completed, the operation there will be about 25 per cent pharmaceuticals, Mr. Buonanno said. It is our intention, he added, to increase the line of new products

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and show progress for age. Business or sales background helpful. In requesting personal interview, please submit resume stating personal history, education, and business experience.

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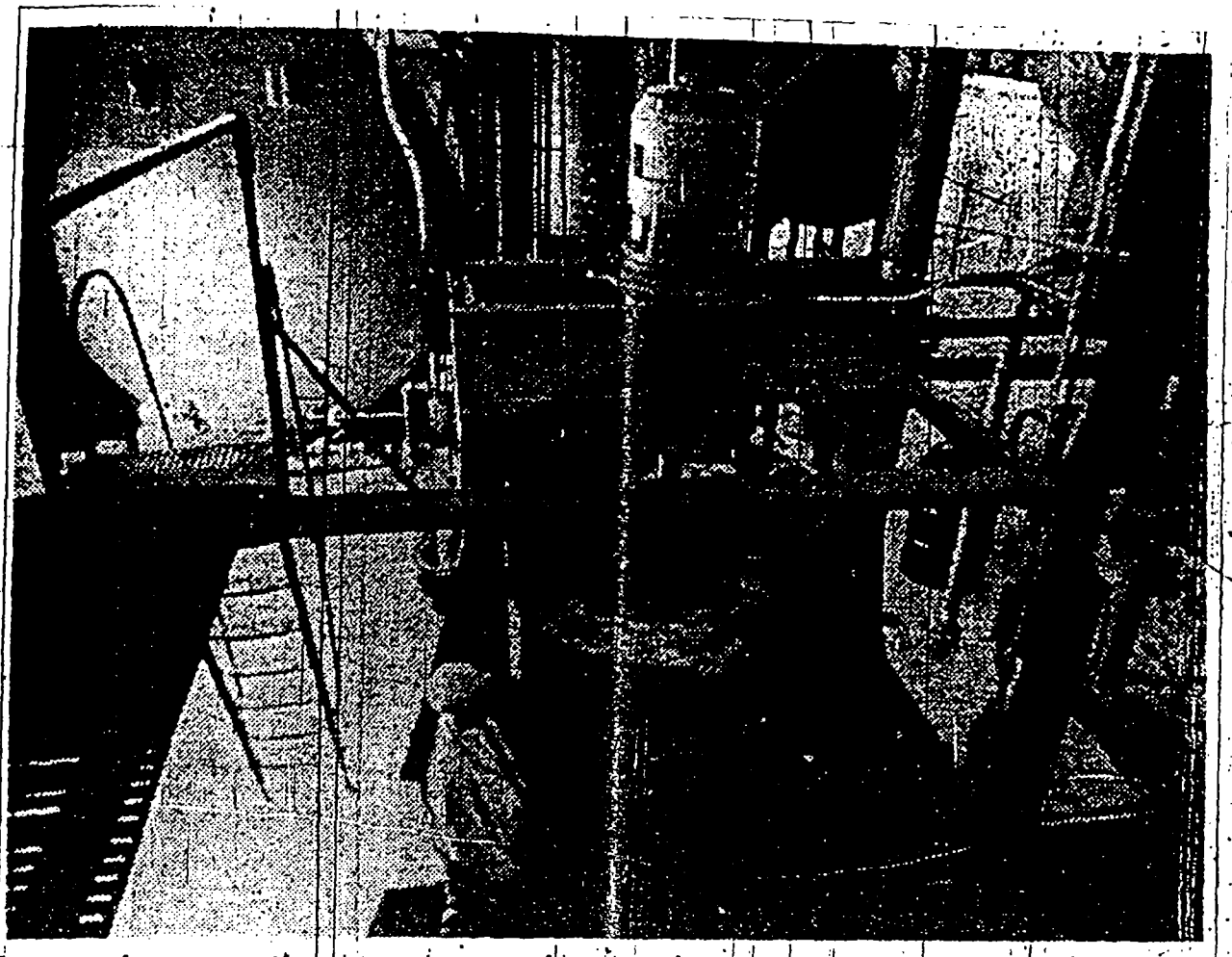

Large perforate centrifuge located in new plant provides company a means of crystal recovery.

CONTINUED from preceding page

Proposed Line of Metro-Atlantic To Be Half Non-Textile Products

until the operation is 50 per cent non-textile.

During the development of non-textile products, the company's volume in its normal textile chemicals has been holding up well, management reported. New products also have been added. These include several textile finishing products, including wash and wear, permanent crease and water repellency items.

The company also is active in chemicals for the metals field. It is making products used for metal finishing and stripping. On some of these, Metro-Atlantic is one of the first two suppliers in the country, Mr. Buonanno said. The line is made in bulk and sold to manufacturers of metal finishes who package and distribute them.

The company also has developed a chrome complex type of water repellent used chiefly in the paper trade. It is expected to be one of Metro's big items.

The company has become one of the first firms of its size to produce mallamine resins—used in textiles to give stiffness and crispness to a fabric.

New Facility Planned

Earlier this month, Metro-Atlantic announced plans to build a $400,000 plant at Don-

about five years, has recently been increased to 50 per cent.

The facility is operated jointly with a Swiss firm and produces dye stuffs. The plant supplies the Centerdale operation, the value of the imported product being 50 per cent American and 50 per cent European.

Operated for about 18 years is a Canadian facility, utilized chiefly for selling, but including some textile chemicals manufacture.

Metro-Atlantic additionally is working currently under license arrangements with manufacturing companies for the packaging and distribution of some of the products the firm produces

Military

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New Facility Planned

Earlier this month, Metro-Atlantic announced plans to build a $400,000 plant at Donaldson Center, Greenville, S.C., for production of a complete line of textile and paper chemicals. Also planned for this facility, scheduled for completion in the fall, is a line of printing inks for use in the paper trade, a new operation for the company.

Metro also has facilities abroad. One of these is a compounding plant in Brussels, designed to serve the European Common Market. It presently uses chemicals produced in this country, but plans are being considered for the addition of some manufacturing there.

One of its other foreign operations is an interest in the Virgin Islands Chemical Co., St. Croix, Christiansted, V.I. Its interest in the firm, dating back about five years, has recently been increased to 50 per cent.

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Military Surplus Sales

Inspection may be made and bids submitted up to dates indicated for useable surplus property and scrap for sale at New England military installations. Further information, including location, free sales catalogs and bid instructions, may be obtained from the Defense Surplus Sales Office, Dept. P, P.O. Box 160, Bldg. 115, Newport; telephone 841-3558. Requests should specify sales catalog number for prompt response.

Steel Scrap. June 4—(1 p.m.)—16-S-65-97. Steel scrap unprepared, galvanized (net panels).

Electronics and Aeronautical. June 8—(1 p.m.)—16-S-65-98. Current regulators, magnetron tubes, receivers transmitters, amplifiers, fuel tanks; spinner, stabilizer and strut assemblies, valves, shafts, hydraulic pumps, aircraft heaters, water separators, cylinders, linear actuators, accumulators and lighting fixtures. Original cost: $446,052.

Platinum Tipped Spark Plugs. June 9—(1 p.m.)—16-S-65-99. Platinum tipped spark plugs. Original cost: $11,739.

Varied Material. June 10—(1 p.m.)—16-S-65-100. Engine, turret and woodworking lathes, milling machine, wood surfacer; titanium bars, boring bars, cutters, lube oil, sealing compound, leather dressing, clothing and laundry and restaurant equipment. Original cost: $350,023.

NEW CREDIT CARDS

Ft. Lauderdale, Fla. — (UPI) — A new all-purpose credit card is being launched by Credit Card Acceptance Corporation, according to J. C. Behringer, president. The Gold Medal credit cards will be honored initially by approximately 3,000 member establishments in more than 40 states.

Behringer believes that these feature will revolutionize the credit card industry.

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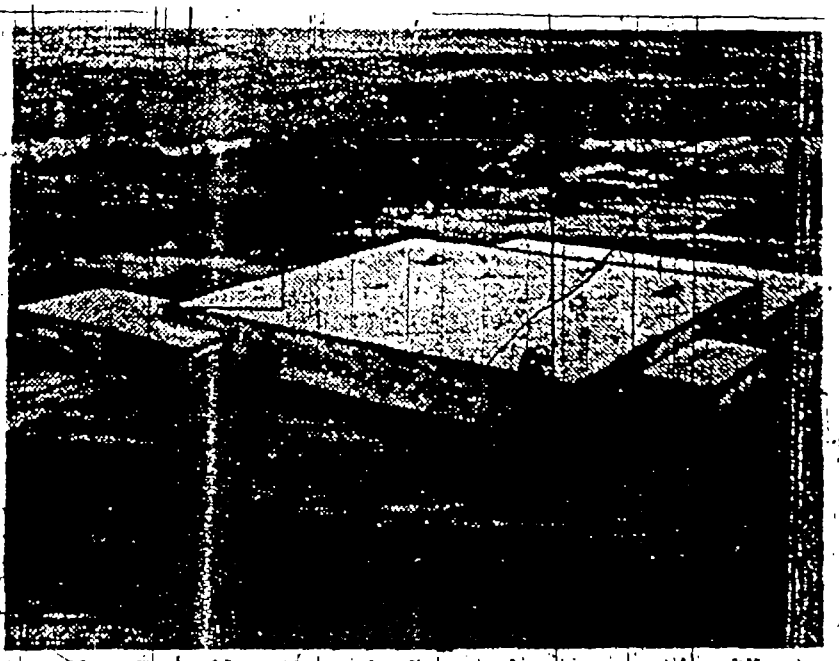

New line of printing inks for use in paper trade will be manufactured in this plant at Greenville, S.C.

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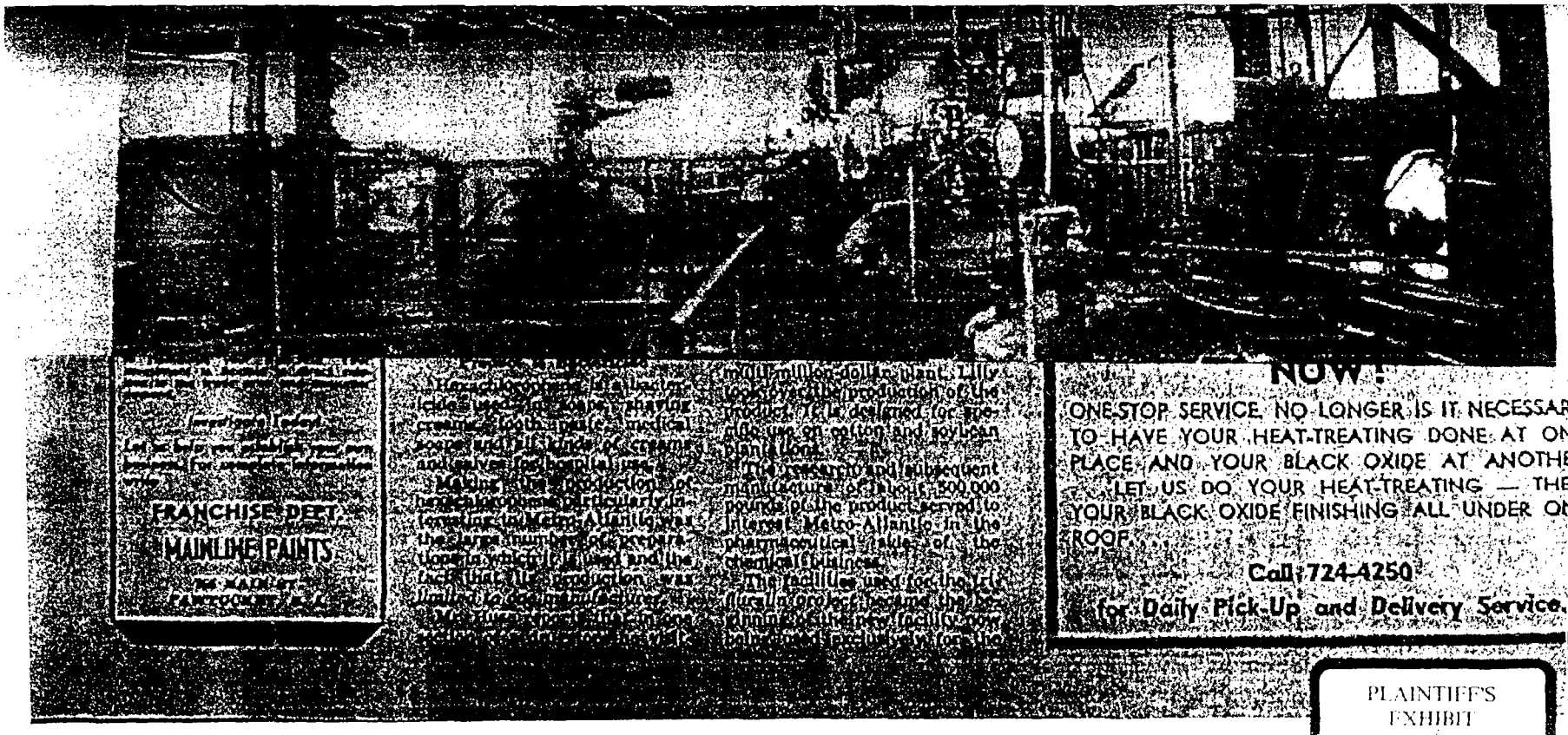
Operated for about 18 years is a Canadian facility, utilized chiefly for selling, but including some textile chemicals manufacture.

Metro-Atlantic additionally is working currently under license arrangements with manufacturing companies for the packaging and distribution of some of the products the firm produces in bulk. A household bleach, spot remover and spray glue are among these items.

The varied programs of the 25-year-old company are working together to bring expansion to the firm, Mr. Buonanno said. Employment has climbed to 130 throughout the organization with about 80 affiliated with the Centredale operation.

"We are looking forward to growth, especially from our entrance into the manufacture of products for the pharmaceutical trade, but we are striving also for a continuation of our employment stability record," Mr. Buonanno said. He reported that throughout its 25 years of operation the company has never laid off anyone.



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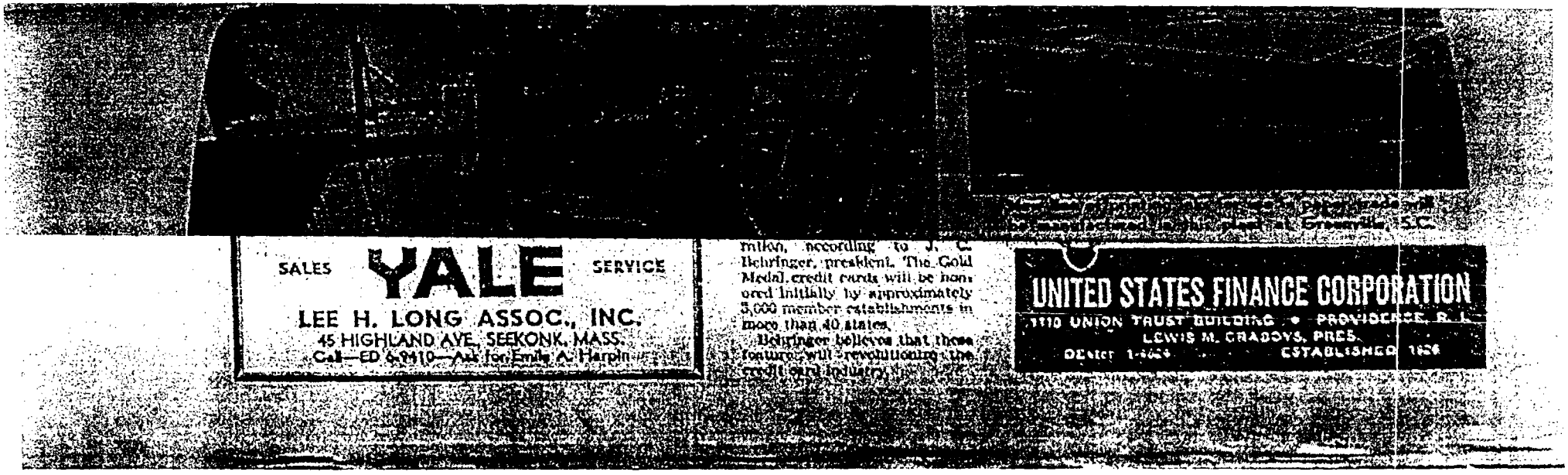
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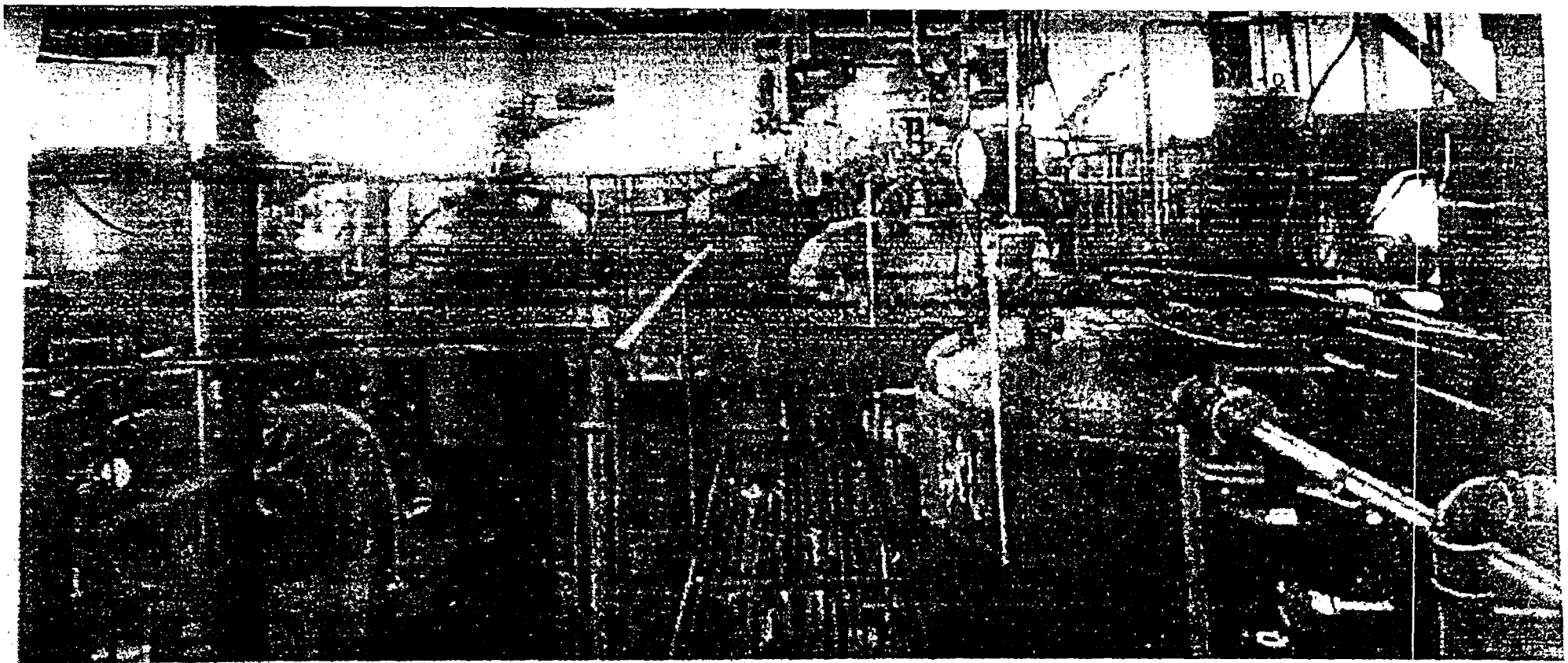
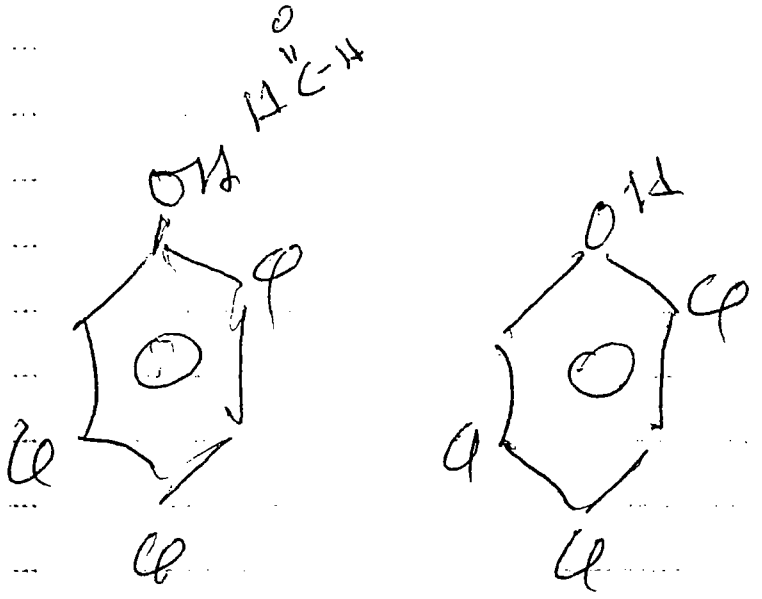


—Journal-Bulletin Photos by H. RAYMOND BATT

Upper level of new hexachlorophene plant at Metro-Atlantic, Inc., Centredale, showing a number of its stainless steel low and high temperature reactors.

PLAINTIFF'S EXHIBIT 5

Large perforate centrifuge located in new plant provides company a means of crystal recovery.



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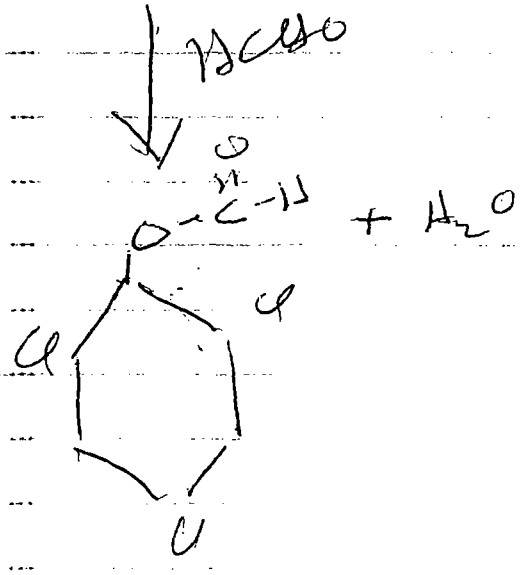

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ZEP Manufacture

Phase #1:

Purification Equipment:

Steel tank equipped with cooling jacket and gate type agitator and centrifuge.

Basic Charge:

Lbs.	Materials
--	Sodium TCP (Concentration 36-38%) So as to contain 1000 lbs. TCP contained
5280	30% Caustic Soda
800	30% Caustic Soda (Wash)
450	66° Be' Sulfuric Acid (Precipitating acid)
370	66° Be' Sulfuric Acid (Purification acid)
4800	Perchloroethylene
10	Nuchar
10	Fiber Flo
1000	Theo. Yield (Total Isomers)
787	Minimum Yield TCP
880	Maximum Yield TCP
65°C	Melting Point (Minimum)

This is Geo Hoses
B.U of Materials for
Purification of Trichlorophenol

"Zep" was our nickname
for Hexachlorophene.

To: Mr. Vincent Buonanno, c/o Temple Steel Co.; from Tom Cleary

CLARITY, INC. 45451 SOUTH CASPAR DRIVE / BOX 949 MENDOCINO, CALIFORNIA 95460 / TEL. 707 964-7065
FAX 707-937-2631

Vinny—

Among perhaps relevant matters not covered, 12/3:

Several years ago, the Newark, N.J. premises of Diamond-Alkali - long inactive and vacant, I believe, were declared to be a "superfund site", and were eventually cleaned up.

The person who knows the history and fate of D.-A. is John Burton, who resides in Washington, N.J. Tel. No. 908-689-6645. Burton was mgr. of that D.-A. plant when Mat.-Al. was purchasing their TCP. He was seriously injured there ('60?) in a reactor explosion of a kind that also occurred also at Monsanto, Thompson, and the notorious Seveso, Italy event ('76 - Givaudan/Roche)

I presume Burton also knows who paid for cleaning up that property, in Newark.

Question: If party A sells and ships Poison X to Party B, who is unaware of it, who is responsible for the harm done by Poison X?

I look forward to receiving your "chemical list." I had been intending to request it, and I'll respond to it as soon as I'm able.

TOM

PLAINTIFF'S EXHIBIT 9
CLEARY - 2/10/03

To: Mr. Vincent Cummings c/o Temple Steel Co., From Tom Cleary

CLARITY, INC. 45451 SOUTH CASPAR DRIVE / BOX 949 MENDOCINO, CALIFORNIA 95460 / TEL. 707 964-7065

Dear Vinny,

You're aware I'm sure of my conversation some time ago with Dominic S. concerning the soil analyses at Centredale. It might be well to report my chemist-to-lawyer impressions with chemist-to-representing-man reports:

1. I was startled by the number of substances that showed up in these samples.
2. The only ones I have knowledge of are Dioxin and Perchloroethylene.
3. The only Metro operation I was familiar with was "Reserve Salt", which I sold for them. This consumed large amounts of Nitrobenzene, NOT found.
4. No trace of the Lilly work, i.e. "Tretlan" or its Dinitro intermediate or its raw materials were found.

Except for "Reserve Salt" and the two projects I was involved with, I knew nothing about the operations, products, raw materials used at Metro.

I have no knowledge of the origin of PCB's, etc. etc. found in these samples.

Best regards,

Tom

PLAINTIFF'S EXHIBIT 10
CLEARY - 2/10/03

PLAINTIFF'S EXHIBIT
11
CLEARY - 2/10/03

State of California)
County of Mendocino) ss:

AFFIDAVIT OF THOMAS F. CLEARY

Thomas F. Cleary, being duly sworn, deposes and states as follows:

1. I have personal knowledge of the facts set forth in this affidavit and, if called as a witness, I could and would competently testify to the facts set forth below.

2. I am retired after a career working for several companies as an organic chemist.

3. I currently reside at 45451 S. Caspar Dr., Mendocino, CA 95460, phone 707-964-7065.

4. I have a B.S. in chemistry from Rutgers University.

5. Before my retirement, I was employed at Centerchem, Inc. between approximately 1960 to 1980 as an organic chemist and as President and Chief Executive Officer after 1977.

6. While working for Centerchem, Inc., I would solicit custom chemical manufacturing contracts for small chemical manufacturing companies.

7. As part of that work, I would assist the chemical manufacturers with development of the manufacturing processes used to fill their custom chemical manufacturing contracts.

8. In the 1960s I was acquainted with Metro-Atlantic, Inc., a chemical manufacturer located in North Providence, Rhode Island.

9. Metro-Atlantic was owned and run by Joseph Buonanno, now deceased.

10. I was acquainted with purchasing agents of Eli Lilly and Company of Indianapolis, IN and would attempt to assist in the development of contracts for the custom manufacture of chemicals for Eli Lilly by custom chemical manufacturing companies like Metro-Atlantic.

EXHIBIT
1

11. My primary contacts at Eli Lilly in the 1960s were Robert G. "Bob" Weigel, Eli Lilly's purchasing agent, now deceased, and assistant purchasing agent Robert Dille, also deceased.

12. In approximately 1963 or 1964, I became aware of Eli Lilly's development of a pesticide known as treflan or trifluralin.

13. When starting production of treflan, Eli Lilly needed time to design, build and start up the process equipment in its Tippecanoe, IN plant.

14. I suggested to Joseph Buonanno that Metro-Atlantic might be able to manufacture treflan for Eli Lilly.

15. I assisted Metro-Atlantic in developing the process to manufacture treflan at its North Providence, Rhode Island plant and Metro-Atlantic erected a building specifically to house that process at that time.

16. Eli Lilly entered into an agreement with Metro-Atlantic by which Metro-Atlantic made treflan for Eli Lilly at the Metro-Atlantic North Providence plant.

17. The treflan process at the North Providence plant consisted of converting the substrate parachlorobenzotrifluoride or PCBT, obtained from Hooker Chemical in Niagara Falls, N.Y., into treflan, first by dinitration then amination of the resulting 3.5-Dinitro-4-chlorobenzotifluoride with dipropylamime. The treflan active substance was formulated with solvents and emulsifiers supplied by and under the direction of Eli Lilly.

18. After a short period of production, no more than a few months at most, Eli Lilly began production of treflan at its Tippecanoe, IN plant and treflan production at the Metro-Atlantic North Providence, R.I. plant ceased.

19. The Metro-Atlantic production facility built for treflan production was not used for

some time after the treflan production ceased; I then worked with Joseph Buonanno to set up a process to manufacture hexachlorophene in the building formerly used to manufacture treflan.

20. The hexachlorophene produced by Metro-Atlantic was sold on the open market, with Sterling Winthrop being one of the largest purchasers.

21. To my knowledge, Eli Lilly had no relationship to the production of hexachlorophene at the Metro-Atlantic North Providence plant.

Further affiant sayeth not.

[name]

Subscribed to and sworn to before me this
8 day of ~~September~~ November, 2001.

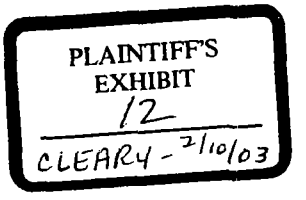
My commission expires: 10-5-03

JACK R. DRUCKER
COMM. 1238809 MEN. RC81
NOTARY PUBLIC
CALIFORNIA
MENDOCINO COUNTY
MY COMM. EXPIRES OCT. 5, 2003

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
REGION I
ONE CONGRESS STREET SUITE 1100
BOSTON, MASSACHUSETTS 02114-2023

Memorandum

DRAFT



Date: November 26, 2002

Subj: Notes of Conversation with Thomas Cleary

From: Ann Gardner
Paralegal

To: Centredale Manor Site File

On Thursday November 14, 2002 I placed a call to Thomas Cleary of Mendocino, CA to inquire if he recalled how Metro-Atlantic produced hexachlorophene. These notes have been reviewed by Mr. Cleary for accuracy and is a summary of our conversation.

Background

Mr. Cleary was an organic and production chemist which means that he supplied chemical companies with the production "know-how" for specific chemicals. He would work closely with the companies during the process development stage.

He was aware that the Eli Lilly company had developed a chemical called Treflan and was looking for a place to manufacture this substance until a permanent facility was constructed. Mr. Cleary was aware of the Metro-Atlantic facility and brokered a deal for Metro-Atlantic to produce Treflan for Eli Lilly. According to Mr. Cleary, Metro-Atlantic

constructed a separate building for the production of Treflan. When asked why Metro-Atlantic went to the effort and expense of constructing a building for a temporary production process, Mr. Cleary thought that the building was not a big investment and that it was profitable for Metro-Atlantic. Mr. Cleary estimated that the production of Treflan at the Metro-Atlantic facility was less than a year.

Hexachlorophene production

After the Treflan production ceased, Mr. Cleary worked with Metro-Atlantic to produce hexachlorophene. At the time, there was only one company that produced hexachlorophene and companies were looking for additional suppliers.

Hexachlorophene is manufactured using 2,4,5-trichlorophenol. At the time Metro-Atlantic began hexachlorophene production, the U.S. Army was using large quantities of trichlorophenol in the production of Agent Orange making quantities of pure 2,4,5-trichlorophenol unavailable. Metro-Atlantic purchased a crude form of 2,4,5-trichlorophenol from Diamond Alkali. This was a dark liquid brought into the facility by tanker trucks. Before the 2,4,5-trichlorophenol could be used in hexachlorophene production, it needed to be purified. This was accomplished by adding sodium hydroxide and methyl alcohol to 2,4,5-trichlorophenol. There was not 100% recovery from the purification process and some 2,4,5-trichlorophenol became a waste or by-product. Mr. Cleary believes that this waste 2,4,5-trichlorophenol is the origin of the dioxin at the

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
REGION 1
1 CONGRESS STREET, SUITE 1100
BOSTON, MASSACHUSETTS 02114-2023

CERTIFIED MAIL - RETURN RECEIPT REQUESTED

November 26, 2002

Thomas Cleary
45451 S. Caspar Drive
Mendocino, CA 95460

Dear Mr. Cleary,

Enclosed is a draft summary of my conversation with you concerning the Metro-Atlantic facility, formerly located in North Providence, RI. Our discussion centered around their use of 2,4,5-trichlorophenol in the production of hexachlorophene. Because of the chemistry involved, you agreed to review my notes to ensure that I had the facts correct. Please make corrections wherever necessary. If there is any information you would like to add, please do so. I have enclosed a self-addressed, stamped envelope so you may return the letter to us

Thank you very much for you time. If you would like to discuss this memo or any other issue concerning the Metro-Atlantic facility, New England Container Company, or the Centredale Manor Restoration Project, please contact me at (617) 918-1895 and I will return your call, or you can reach me via e-mail at gardner.ann@epa.gov.

Sincerely,

617-918-1895

Ann L. Gardner,
Paralegal

Enclosure

PLAINTIFF'S EXHIBIT 13
CLEARY - 2/10/03

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
REGION 1
1 CONGRESS STREET, SUITE 1100
BOSTON, MASSACHUSETTS 02114-2023

CERTIFIED MAIL -
RETURN RECEIPT REQUESTED

January 14, 2003

Thomas Cleary
45451 South Caspar Dr.
Mendocino, CA 95460

Re: Notes concerning use of 2,4,5-trichlorophenol at Centredale Manor Site File, North Providence, RI

Dear Mr. Cleary,

Enclosed you will find a copy of my draft memo to the file concerning our phone conversation in November 2002. In addition, I have also enclosed a photocopy of the notes and corrections you sent back to me.

When I revise my draft memo, I will send you that version for your review and comment.

Thank you for your time and assistance in this matter. If you have any questions, do not hesitate to call me at (617) 918-1895.

Sincerely,

Ann L. Gardner

Ann L. Gardner
Paralegal

Enclosure

PLAINTIFF'S EXHIBIT
14
CLEARY - 2/10/03

12/02/02

Dear Ms. Gardner

Here with a number of corrections to your notes, and some additional pertinent material.

(1) This is misleading. The dioxin, unknown and unsuspected, was already present in the crude TCP product shipped from Diamond Alkali Co. It was not chemically or physically possible that additional Dioxin could have been generated at the Centredale site.

(4) Co-option of the TCP supply began several months AFTER Hex production began at Centredale. What the USG bought was not TCP, but its downstream derivative, Trichlorophenylacetic Acid, all of which was made directly from Crude, unpurified TCP.

The amount of TCP supplied to 14-A by Diamond Alkali, probably didn't exceed 25,000 Kgs.

PLAINTIFF'S EXHIBIT 15
CLEARY - 2/10/03

Centredale Superfund Site. However, Mr. Cleary is very puzzled as to why phenols are not present in the sampling results.

Mr. Cleary explained how Diamond Alkali produced the 2,4,5-trichlorophenol. The raw material, 1,2,4,5-tetrachlorobeneze was put into an autoclave, a ~~machine~~ vessel that puts substances under very high temperatures and pressure, and converts the 1,2,4,5-tetrachlorobenzene into 2,4,5-trichlorophenol. Mr. Cleary suggested we contact John Burton, formerly with Diamond Alkali, to ask questions about this process and the 2,4,5-trichlorophenol delivered to Metro-Atlantic.

Tel: 908-659-6648

Once the 2,4,5-trichlorophenol was purified, it was ~~mixed~~ reacted with formaldehyde to create hexachlorophene. Mr. Cleary has a patent on this production of hexachlorophene. Mr. Cleary was certain that the hexachlorophene production resulted in the dioxin at the site. As previously mentioned, the 2,4,5-trichlorophenol purification process did not recapture all of the 2,4,5-trichlorophenol and some was lost as a waste by-product. This waste would contain, among other things, dioxin and phenols. He repeatedly stated he was puzzled as to why no phenols were appearing in the test results.

I asked Mr. Cleary about the Metro-Atlantic plant and who might have knowledge of the hexachlorophene process. Apparently, hexachlorophene was really the only chemical they produced; the other chemical work done by Metro-Atlantic was primarily mixing and

re-formulating products. Other than Mr. Cleary, all the individuals who were familiar with the hexachlorophene production are deceased. Joseph ("Joe") Buonanno, Sr. was the head of Metro-Atlantic and became a good friend of Mr. Cleary's. George ~~Ewes (sp?)~~ HUSE was active in managing the hexachlorophene production and moved to South Caroiina * when Metro-Atlantic opened the plant there. Unfortunately both are deceased. Joseph Buonanno, Jr. was in the sales department and did not or would not have any detailed knowledge of the production process. Mr. Cleary recalled Joe Buonanno had two partners: Hugh Bonino and Bernard ("Bernie") Buonanno. Bernie would be at the plant but Mr. Cleary did not recall what he did. Mr. Bonino moved to South Carolina when Metro-Atlantic opened a plant there but has since passed away.

* Prior to the move to Greenville, S.C. Metro-Atlantic merged with Crown Chemical Co, A similar business in R.I. The merged entity, Known As "Crown-Metro" was purchased by United Shoe Machinery Corp and then by a succession of other owners, including, finally, Black & Decker.
TC

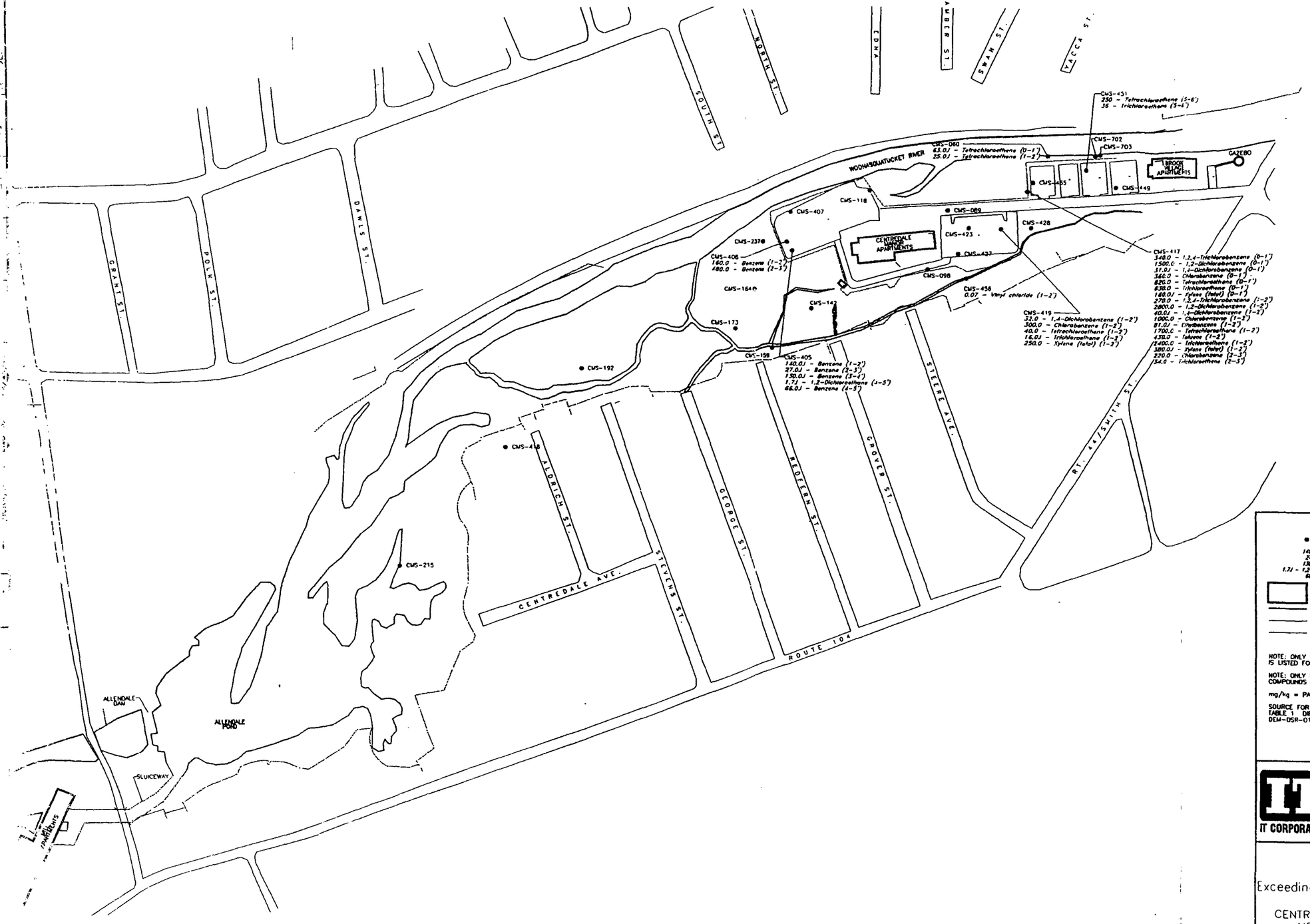
(2) Metro-Atlantic had in fact for some years, produced meta-Nitro-benzene Sodium Sulfonate by the Sulfonation of Nitrobenzene. I had been selling this product for another company. It was the cessation of that source that led to my acquaintance with Mr. Buoniano and Metro-Atlantic in about '61.

The soil analyses at Centredal show no trace of this operation.

Also, there was no trace found there of Raw materials, intermediates or product, Related to the Trefiny operation for Lilly.

Volatile Organic Compounds
Exceeding Rhode Island Residential Standards
(June to November 1999)

PLAINTIFF'S EXHIBIT 17 CLEARY - 7/10/03



LEGEND:

- SOIL BORING LOCATION
  - EX.: CMS-118 - SOIL BORING IDENTIFICATION
  - 140.0J - Benzene (1-2') - SAMPLE RESULT AND COMPOUND IN mg/kg - SAMPLE DEPTH RANGE
  - 27.0J - Benzene (2-3') - SAMPLE RESULT AND COMPOUND IN mg/kg - SAMPLE DEPTH RANGE
  - 130.0J - Benzene (3-4') - SAMPLE RESULT AND COMPOUND IN mg/kg - SAMPLE DEPTH RANGE
  - 1.7J - 1,2-Dichloroethane (4-5') - SAMPLE RESULT AND COMPOUND IN mg/kg - SAMPLE DEPTH RANGE
  - 66.0J - Benzene (4-5') - SAMPLE RESULT AND COMPOUND IN mg/kg - SAMPLE DEPTH RANGE
- BUILDING OUTLINE
- WATERWAY OR POND
- ROADWAY EDGE
- FENCE

NOTE: ONLY THE MAXIMUM CONCENTRATION FOR EACH COMPOUND EXCEEDANCE IS LISTED FOR EACH BORING LOCATION.

NOTE: ONLY BORING LOCATIONS SAMPLED FOR VOLATILE ORGANIC COMPOUNDS ARE SHOWN.

mg/kg = PARTS PER MILLION

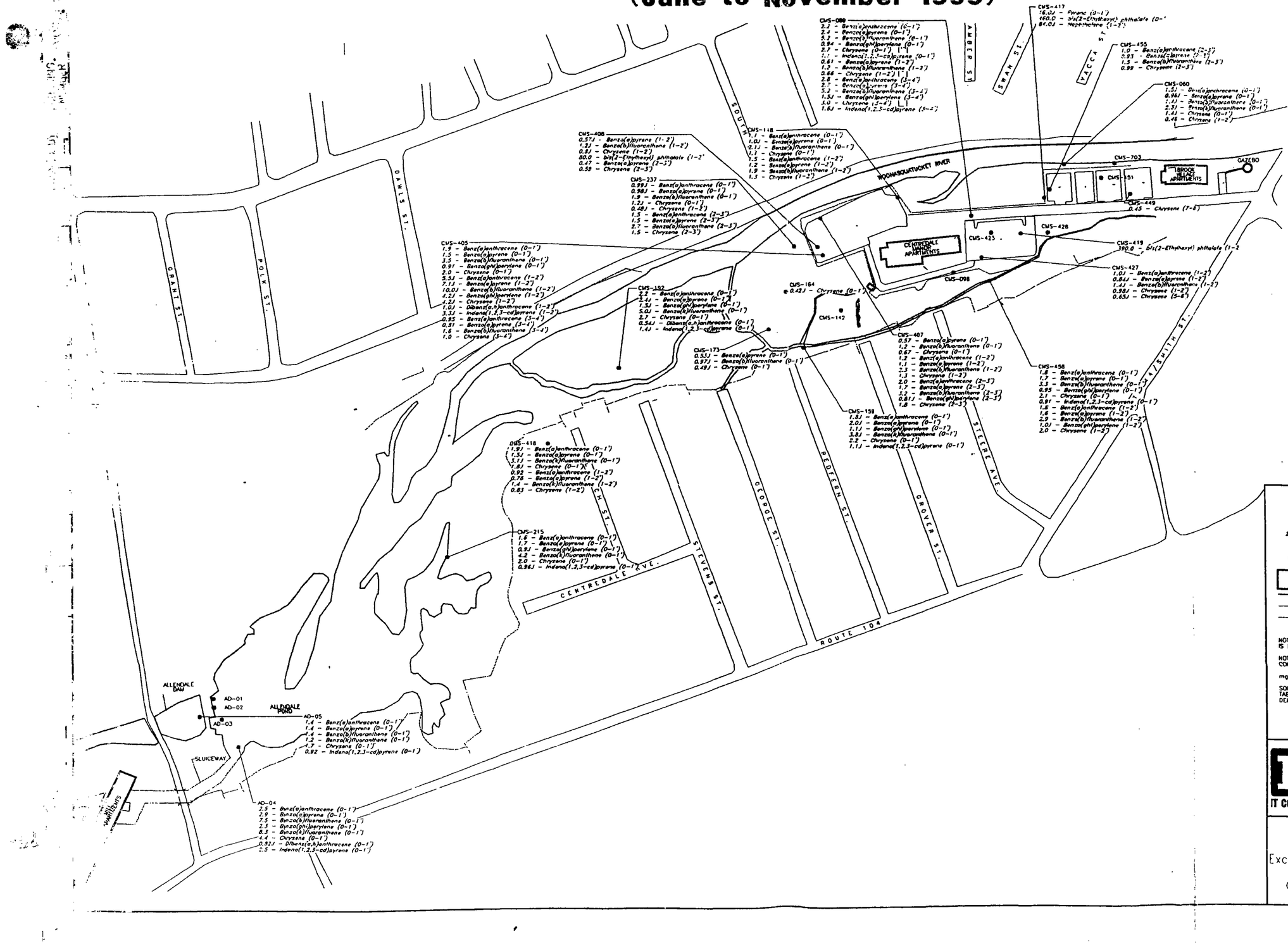
SOURCE FOR RHODE ISLAND STANDARDS:
TABLE 1 DIRECT EXPOSURE CRITERIA, REMEDIATION REGULATIONS.
DEM-DSR-01-93, 31 MARCH 1993, AMENDED AUGUST 1996

SCALE
0 125 250 375 FEET

IT CORPORATION
88C ELM STREET
HOPKINTON, MASSACHUSETTS
(508) 435-9561

FIGURE 2
Volatile Organic Compounds
Exceeding Rhode Island Residential Standards
(June to November 1999)
CENTREDALE MANOR RESTORATION PROJECT
NORTH PROVIDENCE, RHODE ISLAND

Semi Volatile Organic Compounds
Exceeding Rhode Island Residential Standards
(June to November 1999)



LEGEND:

- SOIL BORING LOCATION
  - EX.: CMS-118 – SOIL BORING IDENTIFICATION
  - 1.1 – Benz(a)anthracene (0-1') – SAMPLE RESULT AND COMPOUND IN mg/kg – SAMPLE DEPTH RANGE
  - 1.0J – Benzo(a)pyrene (0-1') – SAMPLE RESULT AND COMPOUND IN mg/kg – SAMPLE DEPTH RANGE
  - 2.1J – Benzo(b)fluoranthene (0-1') – SAMPLE RESULT AND COMPOUND IN mg/kg – SAMPLE DEPTH RANGE
  - 1.1 – Chrysene (0-1') – SAMPLE RESULT AND COMPOUND IN mg/kg – SAMPLE DEPTH RANGE
  - 1.5 – Benz(a)anthracene (1-2') – SAMPLE RESULT AND COMPOUND IN mg/kg – SAMPLE DEPTH RANGE
  - 1.2 – Benzo(a)pyrene (1-2') – SAMPLE RESULT AND COMPOUND IN mg/kg – SAMPLE DEPTH RANGE
  - 1.9 – Benzo(b)fluoranthene (1-2') – SAMPLE RESULT AND COMPOUND IN mg/kg – SAMPLE DEPTH RANGE
  - 1.5 – Chrysene (1-2') – SAMPLE RESULT AND COMPOUND IN mg/kg – SAMPLE DEPTH RANGE
- BUILDING OUTLINE
- WATERWAY OR POND
- ROADWAY EDGE
- FENCE

NOTE: ONLY THE MAXIMUM CONCENTRATION FOR EACH COMPOUND EXCEEDANCE IS LISTED FOR EACH BORING LOCATION.

NOTE: ONLY BORING LOCATIONS SAMPLED FOR SEMI VOLATILE ORGANIC COMPOUNDS ARE SHOWN.

mg/kg = PARTS PER MILLION

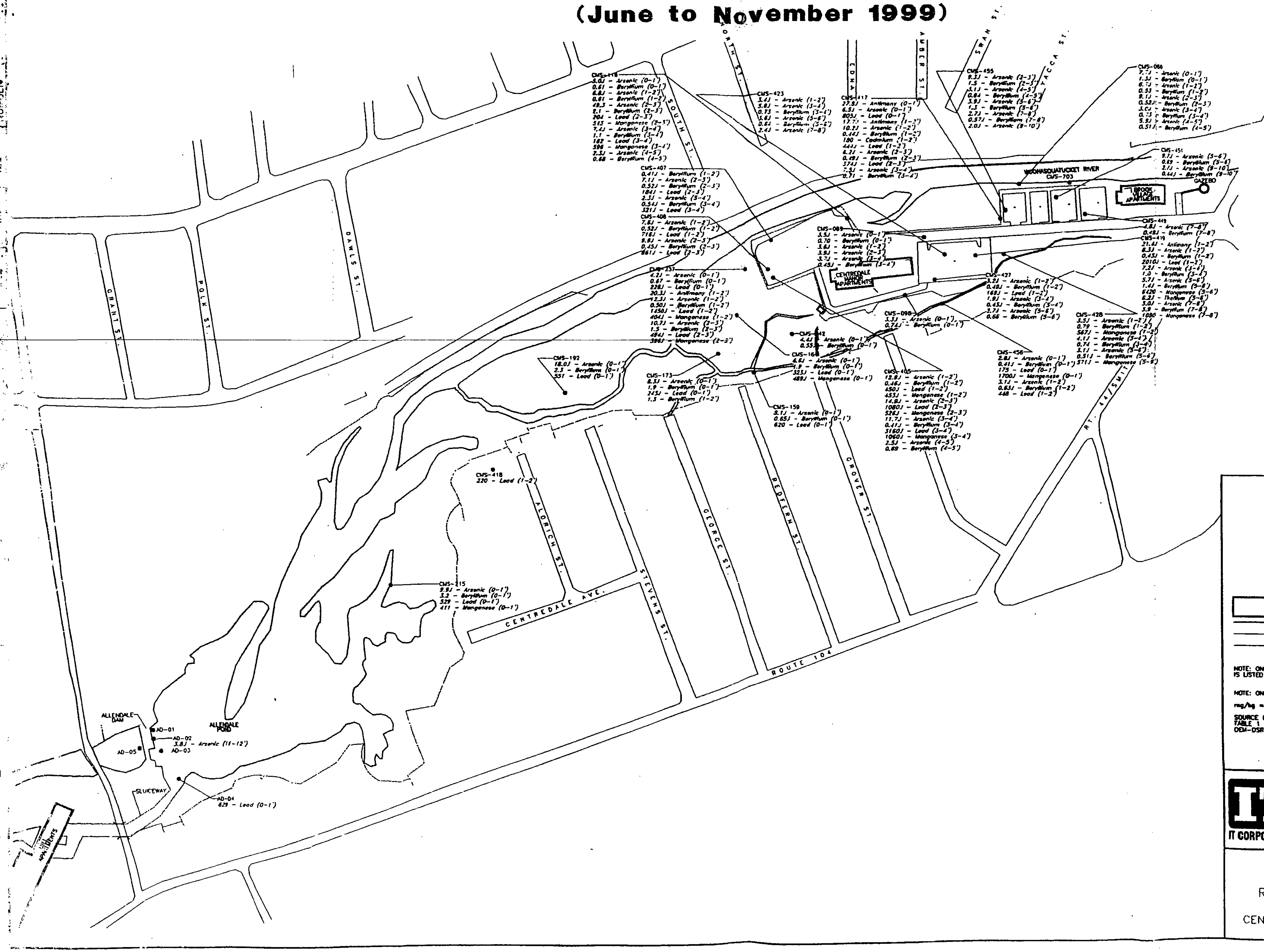
SOURCE FOR RHODE ISLAND STANDARDS:
TABLE 1 DIRECT EXPOSURE CRITERIA, REMEDIATION REGULATIONS,
DEM-DSR-01-93, 31 MARCH 1993, AMENDED AUGUST 1996

SCALE
0 125 250 375 FEET

IT CORPORATION
88C ELM STREET
HOPKINTON, MASSACHUSETTS
(508) 435-9561

FIGURE 3
Semi Volatile Organic Compounds
Exceeding Rhode Island Residential Standards
(June to November 1999)
CENTREDALE MANOR RESTORATION PROJECT
NORTH PROVIDENCE, RHODE ISLAND

RCRA Metals Exceeding Rhode Island Residential Standards (June to November 1999)



LEGEND:

- • SOIL BORING LOCATION
- BUILDING OUTLINE
- WATERWAY OR POND
- ROADWAY EDGE
- FENCE

NOTE: ONLY THE MAXIMUM CONCENTRATION FOR EACH COMPOUND EXCEEDANCE IS LISTED FOR EACH BORING LOCATION.

NOTE: ONLY BORING LOCATIONS SAMPLED FOR RCRA METALS ARE SHOWN.

mg/kg = PARTS PER MILLION

SOURCE FOR RHODE ISLAND STANDARDS: TABLE 1 DIRECT EXPOSURE CRITERIA, REMEDIATION REGULATIONS. DEM-DSR-01-93, 31 MARCH 1993, AMENDED AUGUST 1996

SCALE: 0 — 125 — 250 — 375 FEET

IT CORPORATION

8BC ELM STREET
HOPKINTON, MASSACHUSETTS
(508) 435-9561

FIGURE 4
RCRA Metals Exceeding
Rhode Island Residential Standards
(June to November 1999)
CENTREDALE MANOR RESTORATION PROJECT
NORTH PROVIDENCE, RHODE ISLAND

Total SVOC Results
(June to November 1999)

LEGEND:

- SOIL BORING LOCATION
  EX.: CMS-118 - SOIL BORING IDENTIFICATION
  13.0J - (0-1') - SAMPLE RESULT AND COMPOUND IN mg/kg - SAMPLE DEPTH RANGE
  20.0 - (1-2') - SAMPLE RESULT AND COMPOUND IN mg/kg - SAMPLE DEPTH RANGE
  4.3 - (2-3') - SAMPLE RESULT AND COMPOUND IN mg/kg - SAMPLE DEPTH RANGE
  1.0 - (3-4') - SAMPLE RESULT AND COMPOUND IN mg/kg - SAMPLE DEPTH RANGE
  0.3 - (4-5') - SAMPLE RESULT AND COMPOUND IN mg/kg - SAMPLE DEPTH RANGE
- BUILDING OUTLINE
- WATERWAY OR POND
- ROADWAY EDGE
- FENCE

NOTE: ONLY THE MAXIMUM CONCENTRATION FOR EACH COMPOUND EXCEEDANCE IS LISTED FOR EACH BORING LOCATION.

NOTE: ONLY BORING LOCATIONS SAMPLED FOR SEMI VOLATILE ORGANIC COMPOUNDS ARE SHOWN.

mg/kg = PARTS PER MILLION

SCALE
0 125 250 375 FEET

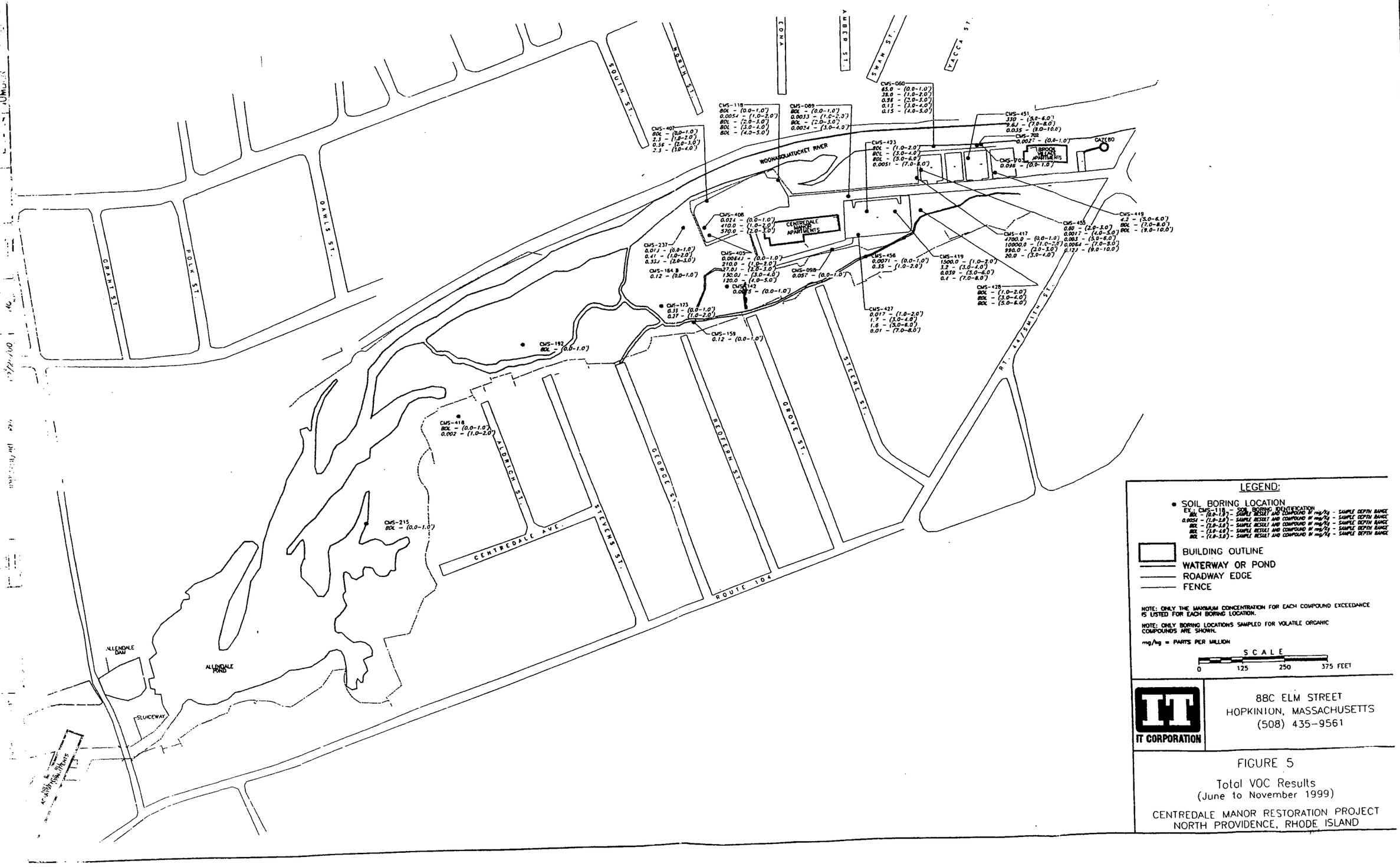
IT CORPORATION
88C ELM STREET
HOPKINTON, MASSACHUSETTS
(508) 435-9561

FIGURE 6

Total SVOC Results
(June to November 1999)

CENTREDALE MANOR RESTORATION PROJECT
NORTH PROVIDENCE, RHODE ISLAND

Total VOC Results
(June to November 1999)



LEGEND:

- SOIL BORING LOCATION
  - EX.: CMS-118 - SOIL BORING IDENTIFICATION
  - BDL - (0.0-1.0') - SAMPLE RESULT AND COMPOUND IN mg/kg - SAMPLE DEPTH RANGE
  - 0.0054 - (1.0-2.0') - SAMPLE RESULT AND COMPOUND IN mg/kg - SAMPLE DEPTH RANGE
  - BDL - (2.0-3.0') - SAMPLE RESULT AND COMPOUND IN mg/kg - SAMPLE DEPTH RANGE
  - BDL - (3.0-4.0') - SAMPLE RESULT AND COMPOUND IN mg/kg - SAMPLE DEPTH RANGE
  - BDL - (4.0-5.0') - SAMPLE RESULT AND COMPOUND IN mg/kg - SAMPLE DEPTH RANGE
- BUILDING OUTLINE
- WATERWAY OR POND
- ROADWAY EDGE
- FENCE

NOTE: ONLY THE MAXIMUM CONCENTRATION FOR EACH COMPOUND EXCEEDANCE IS LISTED FOR EACH BORING LOCATION.

NOTE: ONLY BORING LOCATIONS SAMPLED FOR VOLATILE ORGANIC COMPOUNDS ARE SHOWN.

mg/kg = PARTS PER MILLION

SCALE
0 125 250 375 FEET

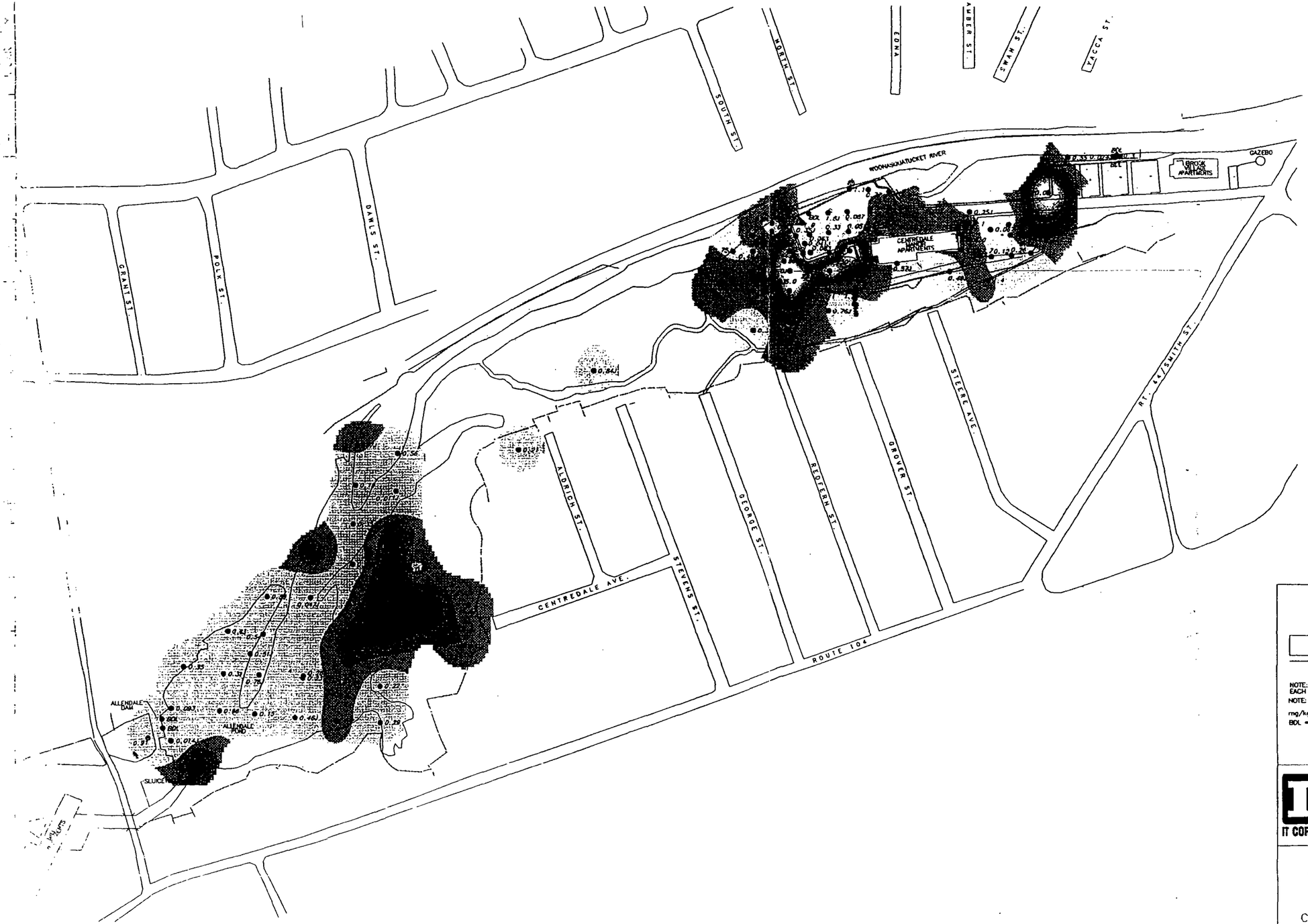
IT CORPORATION
88C ELM STREET
HOPKINTON, MASSACHUSETTS
(508) 435-9561

FIGURE 5

Total VOC Results
(June to November 1999)

CENTREDALE MANOR RESTORATION PROJECT
NORTH PROVIDENCE, RHODE ISLAND

PCB Concentration Distribution in Soil
(0-1 feet below ground surface)
(June to November 1999)



LEGEND:

- SOIL BORING LOCATION
  4.1 = SAMPLE RESULT IN mg/Kg
- BUILDING OUTLINE
- FENCE

NOTE: ONLY THE MAXIMUM CONCENTRATION DETECTED IS LISTED FOR EACH BORING LOCATION.

NOTE: ONLY BORING LOCATIONS SAMPLED FOR PCBS ARE SHOWN.

mg/kg = PARTS PER MILLION

BDL = BELOW DETECTION LIMIT

SCALE

0 125 250 375 FEET

IT CORPORATION

88C ELM STREET
HOPKINTON, MASSACHUSETTS
(508) 435-9561

FIGURE 7a
PCB Concentration Distribution in Soil
(0-1 feet below ground surface)
(June to November 1999)
CENTREDALE MANOR RESTORATION PROJECT
NORTH PROVIDENCE, RHODE ISLAND

PCB Concentration Distribution in Soil
(1-2 feet below ground surface)
(June to November 1999)

5000
4000
3000
2000
1000
900
800
700
600
500
400
300
200
100
90
80
70
60
50
40
30
20
10
9
8
7
6
5
4
3
2
1
0

Concentrations in milligrams per kilogram (mg/Kg)

LEGEND:

- ● SOIL BORING LOCATION
  ST. 0 - SAMPLE RESULT IN mg/Kg
- BUILDING OUTLINE
- FENCE

NOTE: ONLY THE MAXIMUM CONCENTRATION DETECTED IS LISTED FOR EACH BORING LOCATION.
NOTE: ONLY BORING LOCATIONS SAMPLED FOR PCBS ARE SHOWN.
mg/kg = PARTS PER MILLION
BDL = BELOW DETECTION LIMIT

SCALE
0 125 250 375 FEET

IT CORPORATION
88C ELM STREET
HOPKINTON, MASSACHUSETTS
(508) 435-9561

FIGURE 7b
PCB Concentration Distribution in Soil
(1-2 feet below ground surface)
(June to November 1999)
CENTREDALE MANOR RESTORATION PROJECT
NORTH PROVIDENCE, RHODE ISLAND

PCB Concentration Distribution in Soil
(2-3 feet below ground surface)
(June to November 1999)

5000
4000
3000
2000
1000
900
800
700
600
500
400
300
200
100
90
80
70
60
50
40
30
20
10
9
8
7
6
5
4
3
2
1
0

Concentrations in milligrams per kilogram (mg/Kg)

LEGEND:

- SOIL BORING LOCATION
  0.33J - SAMPLE RESULT IN mg/Kg
- BUILDING OUTLINE
- FENCE

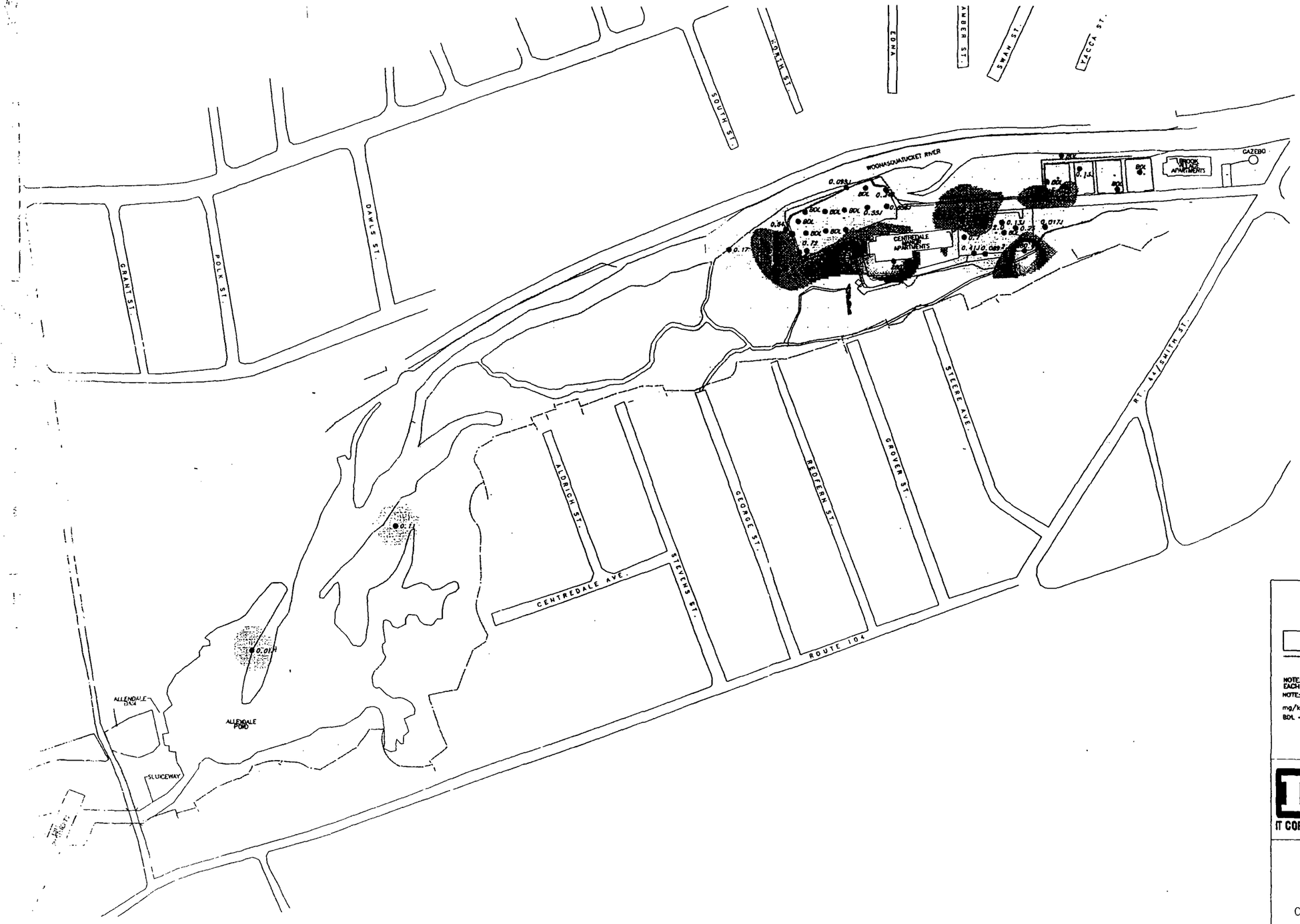
NOTE: ONLY THE MAXIMUM CONCENTRATION DETECTED IS LISTED FOR EACH BORING LOCATION.
NOTE: ONLY BORING LOCATIONS SAMPLED FOR PCBS ARE SHOWN.
mg/kg = PARTS PER MILLION
BDL = BELOW DETECTION LIMIT

SCALE
0 125 250 375 FEET

IT CORPORATION
88C ELM STREET
HOPKINTON, MASSACHUSETTS
(508) 435-9561

FIGURE 7c
PCB Concentration Distribution in Soil
(2-3 feet below ground surface)
(June to November 1999)
CENTREDALE MANOR RESTORATION PROJECT
NORTH PROVIDENCE, RHODE ISLAND

PCB Concentration Distribution in Soil
(3-4 feet below ground surface)
(June to November 1999)



LEGEND:

- ● SOIL BORING LOCATION
  2.4 - SAMPLE RESULT in mg/Kg
- BUILDING OUTLINE
- FENCE

NOTE: ONLY THE MAXIMUM CONCENTRATION DETECTED IS LISTED FOR EACH BORING LOCATION.
NOTE: ONLY BORING LOCATIONS SAMPLED FOR PCBS ARE SHOWN.
mg/kg = PARTS PER MILLION
BDL = BELOW DETECTION LIMIT

SCALE
0 125 250 375 FEET

IT CORPORATION
88C ELM STREET
HOPKINTON, MASSACHUSETTS
(508) 435-9561

FIGURE 7d
PCB Concentration Distribution in Soil
(3-4 feet below ground surface)
(June to November 1999)
CENTREDALE MANOR RESTORATION PROJECT
NORTH PROVIDENCE, RHODE ISLAND

PCB Concentration Distribution in Soil
(4-8 feet below ground surface)
(June to November 1999)

LEGEND:

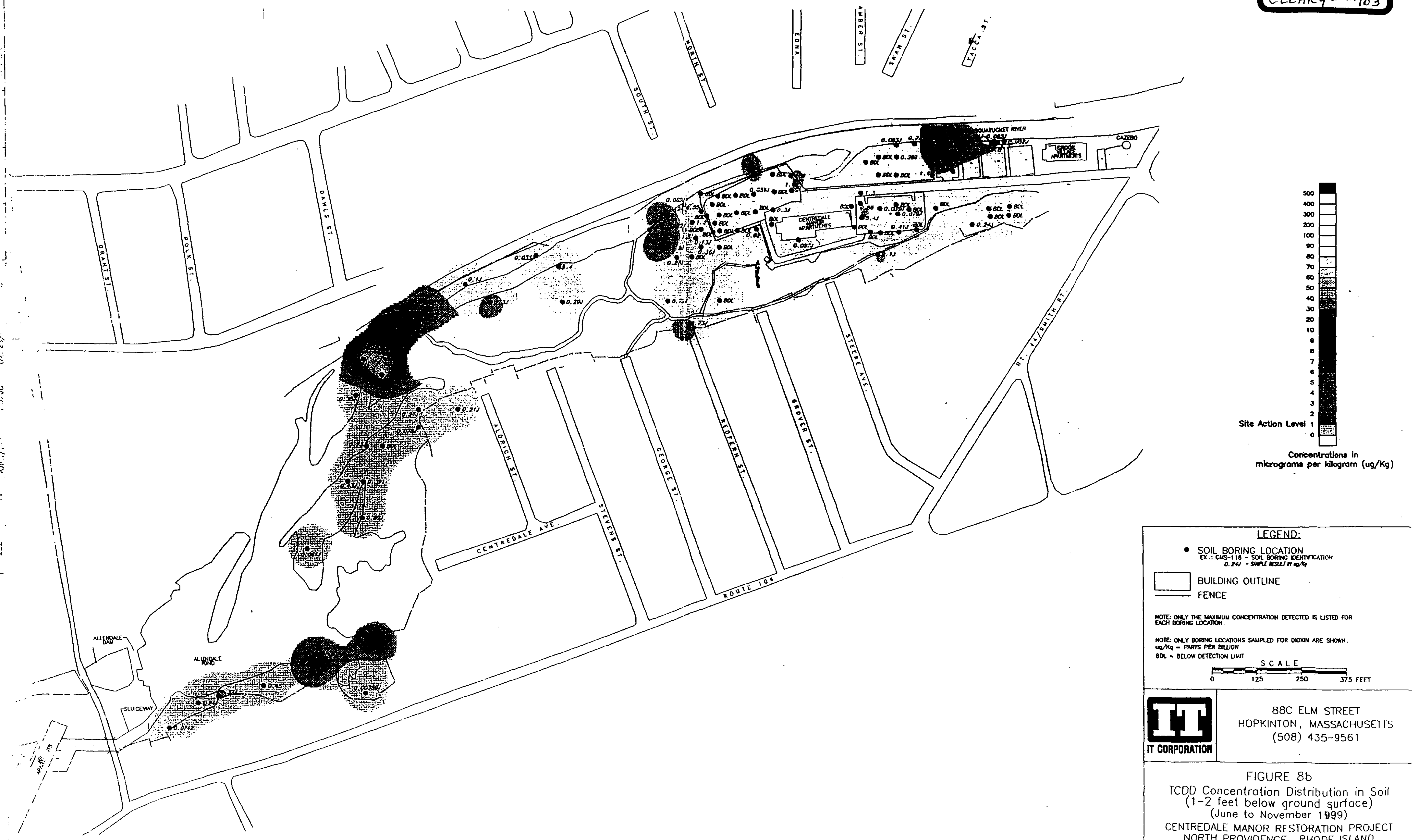
- ● SOIL BORING LOCATION
  EX.: CMS-155 - SOIL BORING IDENTIFICATION
- 1 ppm
- 10 ppm
- RED 4-5 FEET
- GREEN 5-6 FEET
- BLUE 6-7 FEET
- CYAN 7-8 FEET
- BUILDING OUTLINE
- FENCE

SCALE
0 125 250 375 FEET

IT CORPORATION
88C ELM STREET
HOPKINTON, MASSACHUSETTS
(508) 435-9561

FIGURE 7e
PCB Concentration Distribution in Soil
(4-8 feet below ground surface)
(June to November 1999)
CENTREDALE MANOR RESTORATION PROJECT
NORTH PROVIDENCE, RHODE ISLAND

TCDD Concentration Distribution in Soil
(1-2 feet below ground surface)
(June to November 1999)



LEGEND:

- SOIL BORING LOCATION
  EX.: CMS-118 – SOIL BORING IDENTIFICATION
  0.24J – SAMPLE RESULT IN ug/Kg
- BUILDING OUTLINE
- FENCE

NOTE: ONLY THE MAXIMUM CONCENTRATION DETECTED IS LISTED FOR EACH BORING LOCATION.

NOTE: ONLY BORING LOCATIONS SAMPLED FOR DIOXIN ARE SHOWN.
ug/Kg = PARTS PER BILLION
BDL = BELOW DETECTION LIMIT

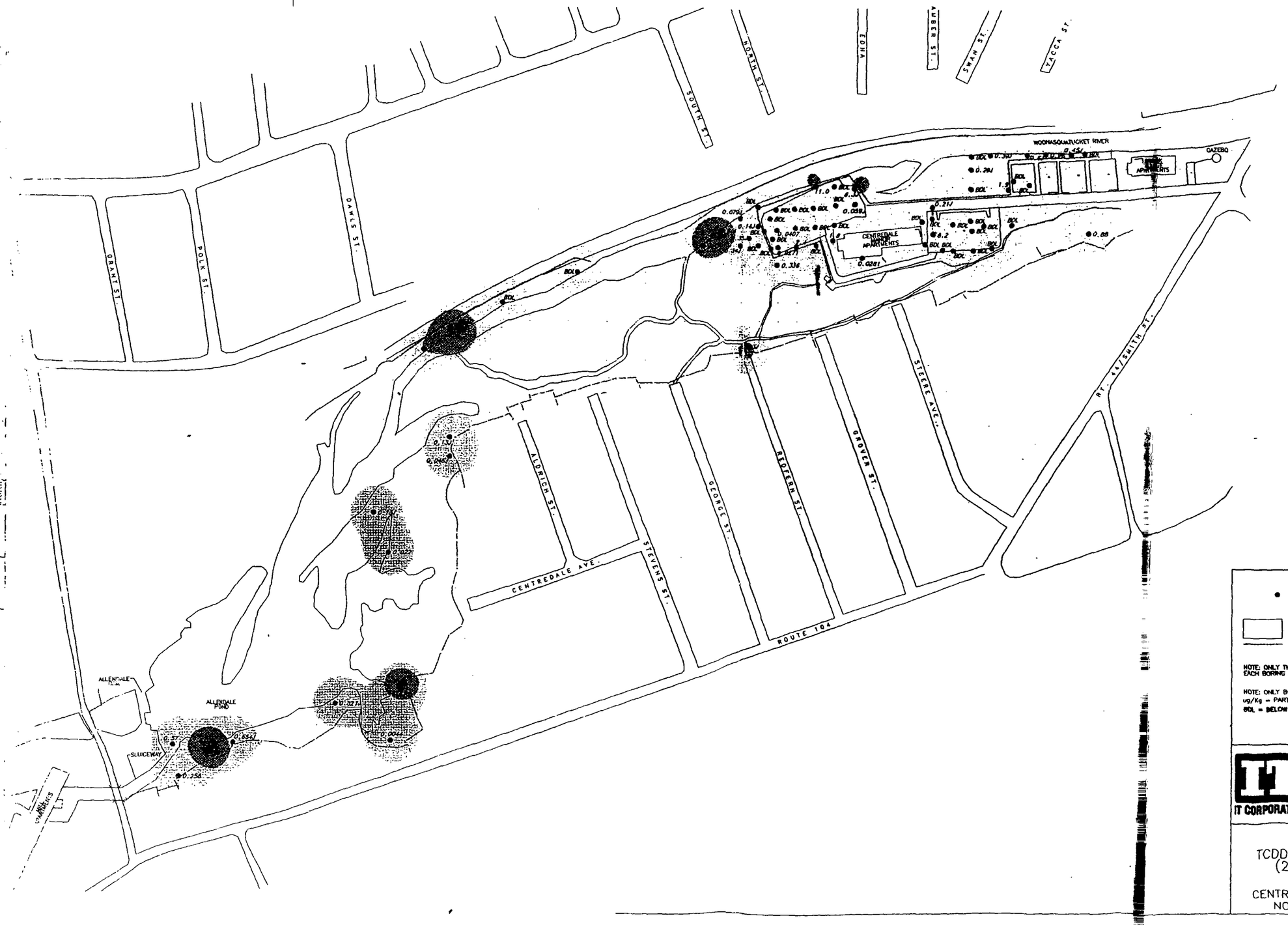
SCALE
0 125 250 375 FEET

IT CORPORATION

88C ELM STREET
HOPKINTON, MASSACHUSETTS
(508) 435-9561

FIGURE 8b
TCDD Concentration Distribution in Soil
(1-2 feet below ground surface)
(June to November 1999)
CENTREDALE MANOR RESTORATION PROJECT
NORTH PROVIDENCE, RHODE ISLAND

TCDD Concentration Distribution in Soil
(2-3 feet below ground surface)
(June to November 1999)



500
400
300
200
100
90
80
70
60
50
40
30
20
10
9
8
7
6
5
4
3
2
1
0

Site Action Level

Concentrations in micrograms per kilogram (ug/Kg)

LEGEND:

- SOIL BORING LOCATION
  EX.: CMS-118 - SOIL BORING IDENTIFICATION
  0.88 - SAMPLE RESULT in ug/Kg
- BUILDING OUTLINE
- FENCE

NOTE: ONLY THE MAXIMUM CONCENTRATION DETECTED IS LISTED FOR EACH BORING LOCATION.

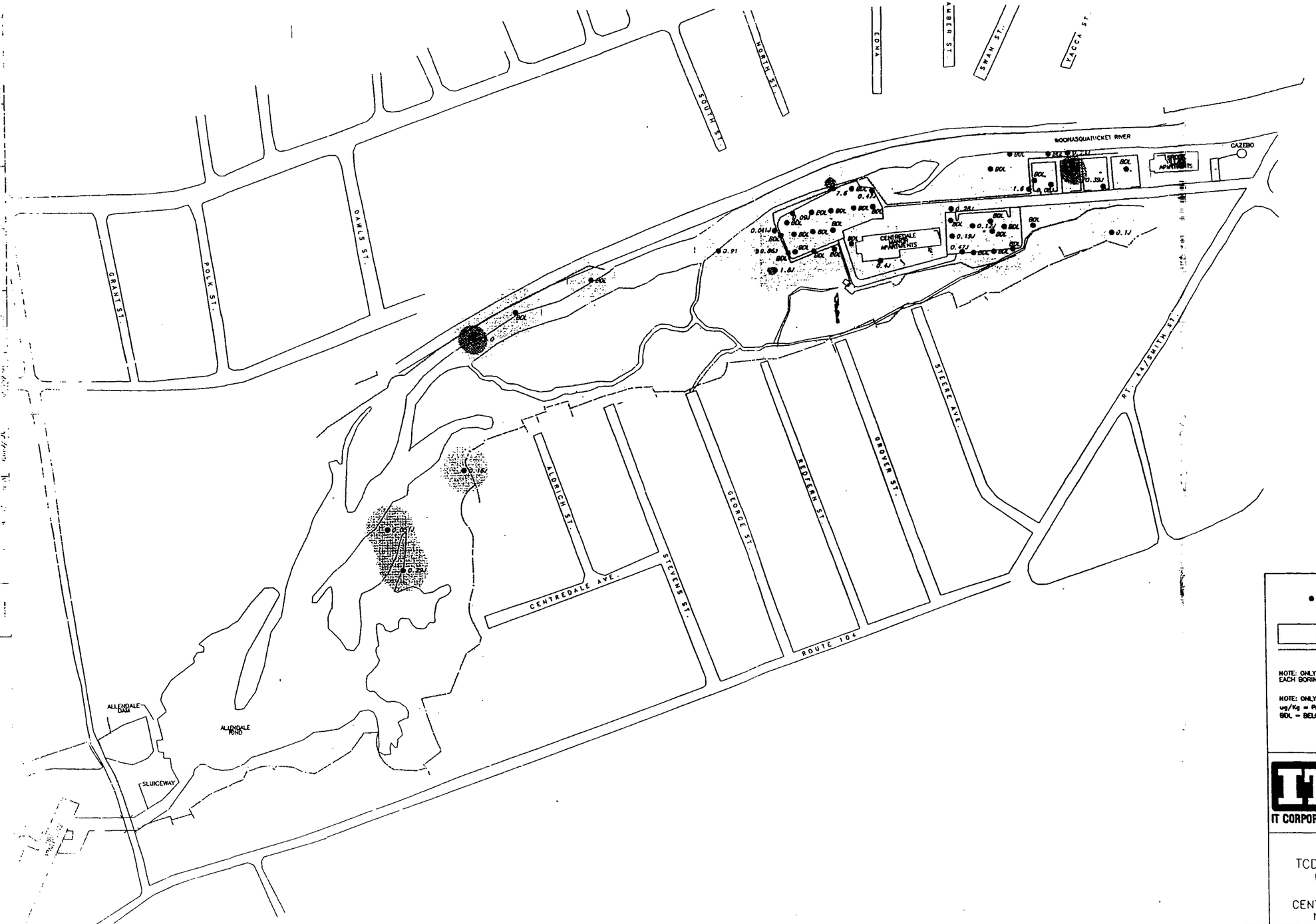
NOTE: ONLY BORING LOCATIONS SAMPLED FOR DIOXIN ARE SHOWN.
ug/Kg = PARTS PER BILLION
BDL = BELOW DETECTION LIMIT

SCALE
0 125 250 375 FEET

IT CORPORATION
88C ELM STREET
HOPKINTON, MASSACHUSETTS
(508) 435-9561

FIGURE 8c
TCDD Concentration Distribution in Soil
(2-3 feet below ground surface)
(June to November 1999)
CENTREDALE MANOR RESTORATION PROJECT
NORTH PROVIDENCE, RHODE ISLAND

TCDD Concentration Distribution in Soil
(3-4 feet below ground surface)
(June to November 1999)



Site Action Level

500 400 300 200 100 90 80 70 60 50 40 30 20 10 9 8 7 6 5 4 3 2 1 0

Concentrations in micrograms per kilogram (ug/Kg)

LEGEND:

- SOIL BORING LOCATION
  1.6 - SAMPLE RESULT IN ug/Kg
- BUILDING OUTLINE
- FENCE

NOTE: ONLY THE MAXIMUM CONCENTRATION DETECTED IS LISTED FOR EACH BORING LOCATION.

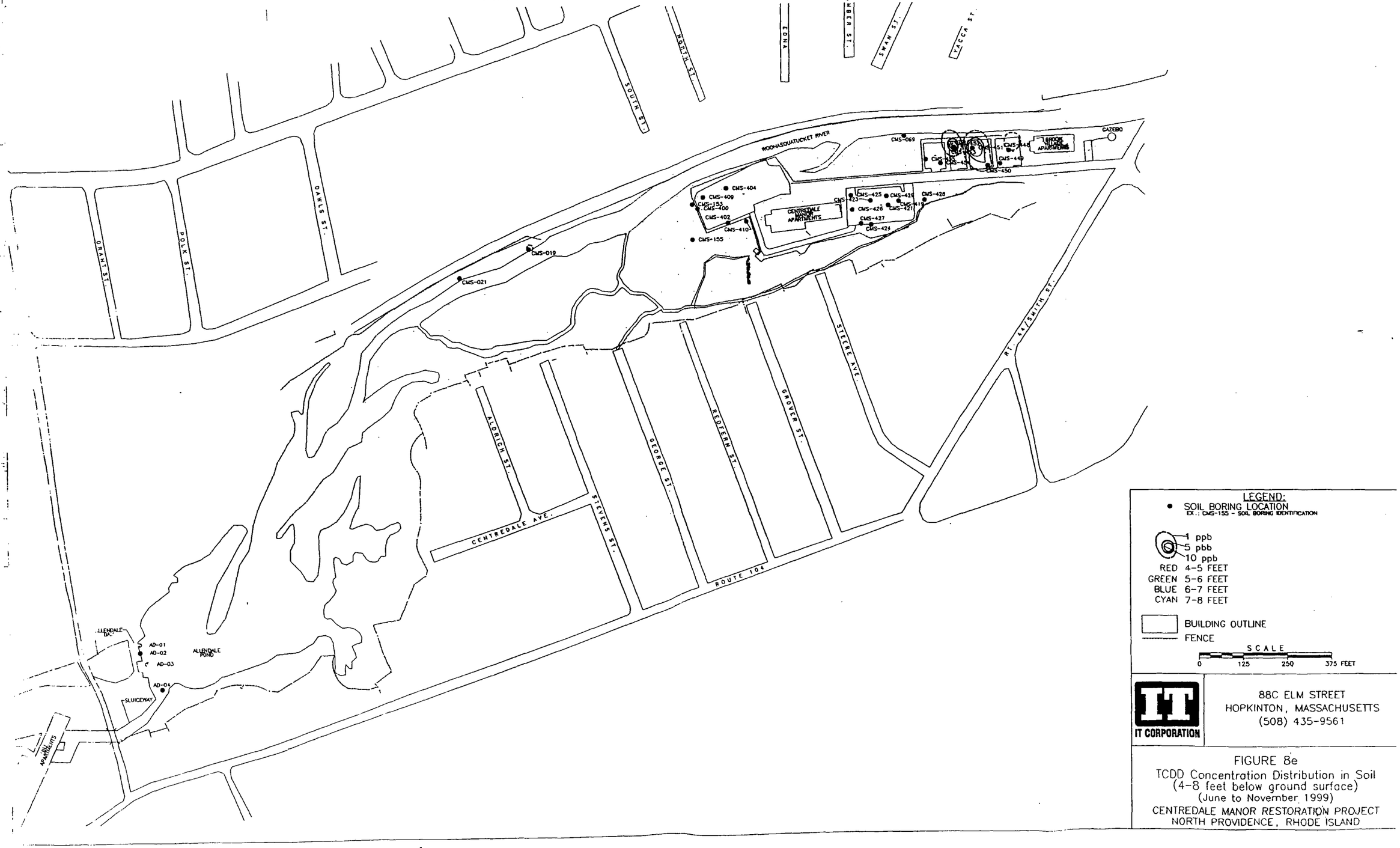
NOTE: ONLY BORING LOCATIONS SAMPLED FOR DIOXIN ARE SHOWN.
ug/Kg = PARTS PER BILLION
BOL = BELOW DETECTION LIMIT

SCALE
0 125 250 375 FEET

IT CORPORATION
88C ELM STREET
HOPKINTON, MASSACHUSETTS
(508) 435-9561

FIGURE 8d
TCDD Concentration Distribution in Soil
(3-4 feet below ground surface)
(June to November 1999)
CENTREDALE MANOR RESTORATION PROJECT
NORTH PROVIDENCE, RHODE ISLAND

TCDD Concentration Distribution in Soil
(4-8 feet below ground surface)
(June to November 1999)



LEGEND:

- SOIL BORING LOCATION
  EX.: CMS-155 - SOIL BORING IDENTIFICATION
- 1 ppb
- 5 ppb
- 10 ppb
- RED 4-5 FEET
- GREEN 5-6 FEET
- BLUE 6-7 FEET
- CYAN 7-8 FEET
- BUILDING OUTLINE
- FENCE

SCALE
0 125 250 375 FEET

IT CORPORATION
88C ELM STREET
HOPKINTON, MASSACHUSETTS
(508) 435-9561

FIGURE 8e
TCDD Concentration Distribution in Soil
(4-8 feet below ground surface)
(June to November 1999)
CENTREDALE MANOR RESTORATION PROJECT
NORTH PROVIDENCE, RHODE ISLAND

Dioxin/PCB
Concentration Summary Map
(February 1999 and June to November 1999)

TCDD
- BLANK = NO SAMPLE FOR TCDD
- ≥ 10ppb
- < 1ppb

PCBs
- BLANK = NO SAMPLE FOR PCBs
- ≥ 50ppm
- < 1ppm

* – LOCATION MOVED FOR CLARITY
LEADER DENOTES ACTUAL LOCATION

SCALE
0 125 250 375 FEET

IT CORPORATION
88C ELM STREET
HOPKINTON, MASSACHUSETTS
(508) 435-9561

FIGURE 9
Dioxin/PCB
Concentration Summary Map
(February 1999 and June to November 1999)

CENTREDALE MANOR RESTORATION PROJECT
NORTH PROVIDENCE, RHODE ISLAND

PLAINTIFF'S EXHIBIT 18 CLEARY-2/10/03

State of California)
County of Marin) ss:

AFFIDAVIT OF THOMAS F. CLEARY

Thomas F. Cleary, being duly sworn, deposes and states as follows:

1. I have personal knowledge of the facts set forth in this affidavit and, if called as a witness, I could and would competently testify to the facts set forth below.

2. I am retired after a career working for several companies as an organic chemist.

3. I currently reside at 45451 S. Caspar Dr., Mendocino, CA 95460, phone 707-964-7065.

4. I have a B.S. in chemistry from Rutgers University.

5. Before my retirement, I was employed at Centerchem, Inc. between approximately 1960 to 1980 as an organic chemist and as President and Chief Executive Officer after 1977.

6. While working for Centerchem, Inc., I would solicit custom chemical manufacturing contracts for small chemical manufacturing companies.

7. As part of that work, I would assist the chemical manufacturers with development of the manufacturing processes used to fill their custom chemical manufacturing contracts.

8. In the 1960s I was acquainted with Metro-Atlantic, Inc., a chemical manufacturer located in North Providence, Rhode Island.

9. Metro-Atlantic was owned and run by Joseph Buonanno, now deceased.

10. I was acquainted with purchasing agents of Eli Lilly and Company of Indianapolis, IN and would attempt to assist in the development of contracts for the custom manufacture of chemicals for Eli Lilly by custom chemical manufacturing companies like Metro-Atlantic.

EXHIBIT 1

11. My primary contacts at Eli Lilly in the 1960s were Robert G. "Bob" Weigel, Eli Lilly's purchasing agent, now deceased, and assistant purchasing agent Robert Dille, also deceased.

12. In approximately 1963 or 1964, I became aware of Eli Lilly's development of a pesticide known as treflan or trifluralin.

13. When starting production of treflan, Eli Lilly needed time to design, build and start up the process equipment in its Tippecanoe, IN plant.

14. I suggested to Joseph Buonanno that Metro-Atlantic might be able to manufacture treflan for Eli Lilly.

15. I assisted Metro-Atlantic in developing the process to manufacture treflan at its North Providence, Rhode Island plant and Metro-Atlantic erected a building specifically to house that process at that time.

16. Eli Lilly entered into an agreement with Metro-Atlantic by which Metro-Atlantic made treflan for Eli Lilly at the Metro-Atlantic North Providence plant.

17. The treflan process at the North Providence plant consisted of converting the substrate parachlorobenzotrifluoride or PCBT, obtained from Hooker Chemical in Niagara Falls, N.Y., into treflan, first by dinitration then amination of the resulting 3,5-Dinitro-4-chlorobenzotifluoride with dipropylamine. The treflan active substance was formulated with solvents and emulsifiers supplied by and under the direction of Eli Lilly.

18. After a short period of production, no more than a few months at most, Eli Lilly began production of treflan at its Tippecanoe, IN plant and treflan production at the Metro-Atlantic North Providence, R.I. plant ceased.

19. The Metro-Atlantic production facility built for treflan production was not used for

some time after the treflan production ceased; I then worked with Joseph Buonanno to set up a process to manufacture hexachlorophene in the building formerly used to manufacture treflan.

20. The hexachlorophene produced by Metro-Atlantic was sold on the open market, with Sterling Winthrop being one of the largest purchasers.

21. To my knowledge, Eli Lilly had no relationship to the production of hexachlorophene at the Metro-Atlantic North Providence plant.

Further affiant sayeth not.

[name]

Subscribed to and sworn to before me this
6 day of ~~September~~ November, 2001.

My commission expires: 10-5-03

JACK R. BRUCKER
COMM. #1288609 - MEN. RC01
NOTARY PUBLIC
CALIFORNIA
MENDOCINO COUNTY
MY COMM. EXPIRES OCT. 5, 2003

DOCUMENTS TO BE PRODUCED

(1) any and all documents concerning the manufacture and/or sale of hexachlorophene by Metro-Atlantic, Inc, including any efforts to establish a process for such manufacture and/or sale of hexachlorophene, as referenced in paragraphs 19 and 20 of the affidavit of Thomas F. Cleary dated November 8, 2001 (a copy of which is attached), and (2) any and all documents concerning the chemical composition of the hexachlorophene manufactured and/or sold by Metro-Atlantic, Inc.

United States Patent Office

3,456,020

Patented July 15, 1969

3,456,020

PRODUCTION OF 2,2'-METHYLENE BIS(3,4,6-TRICHLOROPHENOL)

Thomas F. Cleary, Summit, N.J., assignor to Centerchem Inc., New York, N.Y., a corporation of New York

No Drawing. *Continuation-in-part of application Ser. No. 489,036, Sept. 21, 1965. This application Nov. 28, 1967, Ser. No. 686,290*

Int. Cl. C07c *37/00*

U.S. Cl. 260—619 3 Claims

ABSTRACT OF THE DISCLOSURE

This invention is directed to the production of hexachlorophene by a two stage process in which one mol of 2,4,5-trichlorophenol and one mol of formaldehyde are reacted under the influence of an acid catalyst, after which the reaction product is condensed with one mol of 2,4,5-trichlorophenol through the agency of chlorosulfonic acid or fluorosulfonic acid.

RELATED APPLICATION

This application is a continuation-in-part of my copending application Ser. No. 489,036, now abandoned, filed Sept. 21, 1965, and having the same title as this application.

THE INVENTION

This invention relates generally to new and useful improvements for the production of 2,2'-methylene bis-(3,4,6-trichlorophenol), commonly called hexachlorophene, and particularly seeks to provide a novel two stage process for producing same.

The known processes for the preparation of hexachlorophene (2,2'-methylene bis(3,4,6-trichlorophenol)) involve the condensation of two mols of 2,4,5-trichlorophenol with one mol of formaldehyde (as Formalin or paraformaldehyde). The usual condensing agent is concentrated sulfuric acid or weak oleum, and the reaction may be carried out in the presence or absence of a solvent which is inert to the reactants and to the condensing agent.

In these processes it is customary to mix all of the reactants (and the solvent, if any) at once and to heat the mixture, with agitation, for a certain time. Conditions such as these are disadvantageous in the production of hexachlorophene in that:

(1) They tend to promote the formation of color bodies which make difficult the purification of the product;

(2) They tend to promote the formation of the by-product 2,4,5-trichlorobenzodioxolane with an attendant loss of yield;

(3) They require, if acceptable yields are to be obtained, extreme care that the 2,4,5-trichlorophenol and formaldehyde be present in exactly the molar ratio 2.00:1.00. Since the composition of Formalin or of formaldehyde is usually imprecise, and since a certain amount of formaldehyde is lost from the reaction mixture by volatilization, this is a difficult requirement to realize in practice.

However, through the use of this invention the above mentioned disadvantages in prior processes have been overcome.

Therefore, an object of this invention is to provide a new method of producing hexachlorophene from previously known source materials which is simpler, more effective and results in higher yields by comparison with prior processes.

Another object of this invention is to provide a process of the character stated in which one mol of 2,4,5-trichlorophenol and one mol of formaldehyde are reacted under the influence of an acidic catalyst to form a novel intermediate product, which in turn is condensed with one mol of 2,4,5-trichlorophenol through the agency of chlorosulfonic acid or fluorosulfonic acid to produce high yields of pure hexachlorophene.

With these and other objects, the nature of which will be apparent, the invention will be more fully understood by reference to the accompanying detailed description and the appended claims.

In accordance with this invention it has been discovered that:

(1) One mol of 2,4,5-trichlorophenol and one mol of formaldehyde will react, under the influence of acidic catalysts such as benzenesulfonic acid, anhydrous hydrogen, and diluted sulfuric acid, to form quantitatively and exclusively, a compound which has a melting point of 78° C. The compound has a chlorine content 46.5%, occurs in long colorless prisms, and definitely is not 2,4,5-trichlorosaligenin.

(2) The compound formed as in (1) can be condensed with 2,4,5-trichlorophenol, through the agency of chlorosulfonic acid or fluorosulfonic acid, to produce high yields of pure hexachlorophene.

Both of these reactions are surprising. The only hitherto known reaction product of equimolar amounts of 2,4,5-trichlorophenol and formaldehyde is 2,4,5-trichlorosaligenin, which is formed under alkaline conditions and has a melting point of 128° C. 2,4,5-trichlorophenol, which is relatively inert to concentrated sulfuric acid and to oleum, will react readily with chlorosulfonic acid and fluorosulfonic acid to form 2,4,5-trichlorophenol-6-sulfonic acid.

The following examples will illustrate this invention.

Example 1

197.5 grams of 2,4,5-trichlorophenol having a melting point of 66° C. is dissolved in 1000 grams of perchloroethylene and the solution is warmed to 50° C. with agitation. To this solution is added 50 grams of 90° sulfuric acid. 30 grams of paraformaldehyde is added slowly over a period of one hour with sufficient cooling to maintain the temperature between 60° C. and 70° C. The reaction is exothermic. The mixture is stirred for an additional two hours at 70° C. The perchloroethylene solution is then separated from the dilute acid layer. Upon evaporating a small sample to dryness a crystalline product is obtained which has a melting point of 78° C. There is no free formaldehyde remaining either in the dilute acid layer or in the perchloroethylene solution. There is no hexachlorophene present at this point in the reaction mixture, nor any unreacted 2,4,5-trichlorophenol.

The perchloroethylene solution of the product of the reaction between 2,4,5-trichlorophenol and paraformaldehyde is mixed with a solution of 197.5 grams of 2,4,5-trichlorophenol in 1000 grams of perchloroethylene and the mixture is heated with agitation to 75° C. There is then introduced dropwise over a period of three hours 116 grams of chlorosulfonic acid. The addition of chlorosulfonic acid is accompanied by a mild exothermic reaction and by the evolution of HCl. The temperature is maintained at 75° C. throughout the chlorosulfonic acid addition and is then held at 75° C. to 80° C. for an additional two hours. Agitation is stopped, the remaining sulfuric acid layer is allowed to settle and is separated. The hot perchloroethylene solution is stirred with 10 grams of activated charcoal and is filtered. The reaction product, 2,2'-methylene bis(3,4,6-trichlorophenol), crystallizes upon cooling and is separated by filtration. The yield is 310 grams having a melting point of 162° C. Upon concentration of the mother liquors there is obtained an additional 65 grams of product having the same melting point.

Example 2

197.5 grams of 2,4,5-trichlorophenol having a melting point of 62° C. is dissolved in 2000 ml. of chloroform, and the solution is warmed to 50° C. with agitation. Dry hydrogen chloride is bubbled through the solution at a rate of 5 grams per minute, and over a period of one hour, 31.6 grams of 95% paraformaldehyde is added. Hydrogen chloride addition is continued for 30 minutes, and the mixture is then heated to reflux for one hour.

A small sample of the reaction mixture, evaporated to dryness, yields a white crystalline compound, having a melting point of 78° C. It contains no 2,4,5-trichlorophenol or formaldehyde.

To the reaction mixture is then added a solution of 197.5 grams of 2,4,5-trichlorophenol, having a melting point of 62° C., in 2000 ml. of chloroform. The mixture is heated to 65° C., under a reflux condenser and with good agitation, 100 grams of fluorosulfonic acid is added dropwise, over a period of three hours. Agitation and heating at 65° C. are continued for three hours more, then agitation is stopped, the acid layer is settled and separated. The hot chloroform solution is stirred with 10 grams activated charcoal, filtered and cooled to 10° C. The crystallized 2,2'-methylene bis(3,4,6-trichlorophenol) is filtered off, washed with cold chloroform and dried. The yield is 310 grams having a melting point of 164° C. Evaporation of the mother liquor yields an additional 70 grams of product.

Example 3

To 1000 ml. of benzene is added, slowly, 58 grams of chlorosulfonic acid, and the solution is then heated to reflux until all HCl is driven off. There is thus produced a benzene solution containing 79 grams benzenesulfonic acid. To this solution is added 197.5 grams 2,4,5-trichlorophenol having a melting point of 62° C. The solution is then heated just to the point of reflux, and with good agitation, 85 grams of 37% Formalin is added over two hours, while the water introduced with the Formalin is taken off as an azeotrope with benzene. The condensed benzene is returned to the reaction mixture. Reflux is then continued for one hour, after which 500 ml. of water is added. The mixture stirred 15 minutes at 60° C., and settled. The water layer which contains the benzenesulfonic acid, is separated and discarded.

A small sample of the benzene solution evaporated to dryness, yields a white crystalline product having a melting point of 78° C. It contains no 2,4,5-trichlorophenol or formaldehyde.

The benzene solution is added to 2000 ml. of perchloroethylene, and the benzene is removed from the mixture by fractional distillation.

To the remaining perchloroethylene solution of the reaction product of 2,4,5-trichlorophenol with Formalin is added 197.5 grams 2,4,5-trichlorophenol having a melting point of 62° C. The solution is heated to 75° C., and with vigorous agitation is added, over five hours, 116 grams chlorosulfonic acid. Stirring is continued at 75° C. for two hours and the acid layer is then settled and separated. The hot perchloroethylene solution is stirred with ten grams activated charcoal, filtered and cooled to 10° C. The crystallized 2,2'-methylene bis(3,4,6-trichlorophenol) is filtered off, washed with cold perchloroethylene and dried. The yield is 280 grams having a melting point of 163° C. Evaporation of the mother liquor yields an additional 85 grams of product.

I claim:

1. In a method for producing hexachlorophene the steps of, supplying a solution of 2,4,5-trichlorophenol and formaldehyde at a 1 to 1 molar ratio in a solvent selected from the group consisting of perchloroethylene, chloroform and benzene, reacting said 2,4,5-trichlorophenol and formaldehyde in the pressure of an acid catalyst selected from the group consisting of benzene-sulfonic acid, anhydrous hydrogen chloride and diluted sulfuric acid to form a solution of a compound which, when dry, has a melting point of 78° C. and a chlorine content of 46.5%, then adding a solution of 1 mol of 2,4,5-trichlorophenol to the solution containing the reaction product of the preceding step, and effecting condensation therebetween by the addition of a sulfonic acid selected from the group consisting of chlorosulfonic acid and fluorosulfonic acid to produce pure hexachlorophene.

2. A reaction product between 2,4,5-trichlorophenol and formaldehyde, having a melting point of 78° C. and a chlorine content of 46.5%, produced by supplying a solution of 2,4,5-trichlorophenol and formaldehyde at a 1 to 1 molar ratio in a solvent selected from the group consisting of perchloroethylene, chloroform and benzene, reacting said 2,4,5-trichlorophenol and formaldehyde in the presence of an acid catalyst selected from the group consisting of benzenesulfonic acid, anhydrous hydrogen chloride and diluted sulfuric acid, and separating the solvent solution containing the reaction product from the acid.

3. In a method for producing hexachlorophene the steps of; dissolving a molar equivalent of 2,4,5-trichlorophenol in a solvent selected from the group consisting of perchlorethylene, chloroform and benzene; adding to said solution an acid catalyst selected from the group consisting of benzenesulfonic acid, anhydrous hydrogen chloride and diluted sulfuric acid; then adding a molar equivalent of formaldehyde and maintaining the temperature between about 60° C. and about 70° C. during the exothermic reaction produced as the result of such addition to produce a reaction product which, when dry, has a melting point of 78° C. and a chlorine content of 46.5%; separating the solvent solution from the acid; adding a molar equivalent of 2,4,5-trichlorophenol dissolved in said solvent to said separated solvent solution; effecting condensation between said added molar equivalent of said 2,4,5-trichlorophenol and the reaction product in said separated solvent solution by the addition of an acid selected from the group consisting of chlorosulfonic acid and fluorosulfonic acid; then removing the solvent solution containing the condensed product and recovering pure hexachlorophene therefrom by cooling and filtering same.

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Wegler et al.: MaKromol. Chem. 9, pp. 1–9, 16–21 (1952).

LEON ZITVER, Primary Examiner

N. MORGENSTERN, Assistant Examiner

United States Patent Office

3,499,045

Patented Mar. 3, 1970

3,499,045

PURIFICATION OF 2,4,5-TRICHLOROPHENOL

Thomas F. Cleary, Summit, N.J., assignor to Centerchem, Inc., New York, N.Y., a corporation of New York

No Drawing. Filed Oct. 20, 1966, Ser. No. 587,991
Int. Cl. C07c 39/32
U.S. Cl. 260—623 1 Claim

ABSTRACT OF THE DISCLOSURE

This invention is directed to a method for purifying crude 2,4,5-trichlorophenol by treating it with an aqueous alkali hydroxide to form an alkali salt of the crude product, adding an additional quantity of the alkali hydroxide, then crystallizing and separating the alkali salt of 2,4,5-trichlorophenol and recovering essentially pure 2,4,5-trichlorophenol from the separated alkali salt by treating the salt with an acid.

This invention relates to new and useful improvements in the production of essentially pure 2,4,5-trichlorophenol and particularly seeks to provide a novel method for purifying crude 2,4,5-trichlorophenol.

2,4,5-trichlorophenol is produced conventionally by the reaction of 1,2,4,5-tetrachlorobenzene with methyl alcoholic or aqueous methyl alcoholic sodium hydroxide at an elevated temperature and pressure. The resulting crude product when isolated contains only about 88–92% of the desired 2,4,5-trichlorophenol and is inevitably accompanied by at least three impurities consisting of the methyl ether of 2,4,5-trichlorophenol, the 2,4-5-trichlorophenyl ether of 2,4,5-trichlorophenol, and 2,4-dichlorophenol. The latter impurity results from trichlorobenzene which is present as an impurity in the tetrachlorobenzene. There are also traces of several other impurities which occur as by-products or as substances present in the starting reactants.

Heretofore a degree of purification has been effected in a costly manner by a single distillation which raises the 2,4,5-trichlorophenol content to about 94–96% while a second distillation will raise it only slightly more to about 97–98% and even this degree of purity is inadequate for certain end uses. Furthermore, the yield of purified 2,4,5-trichlorophenol obtained by distillation is not very high because a very careful fractionation must be carried out.

However, in accordance with this invention it is possible to simply and inexpensively separate essentially pure 2,4,5-trichlorophenol from the crude reaction mixture.

Therefore, an object of this invention is to provide a novel process for purifying 2,4,5-trichlorophenol.

Another object of this invention is to provide a process of the character stated in which at least 95% of the 2,4,5-trichlorophenol present in the crude product is recovered in at least a 99.5% pure state and has a melting point of 65 to 67° C.

Another object of this invention is to provide a process of the character stated that is based upon the separation of 2,4,5-trichlorophenol from an aqueous medium as its sodium or potassium salt, in the presence of an excess of an alkali hydroxide, followed by liberation of free 2,4,5-trichlorophenol by acidification of the salt.

The following examples are illustrative of the invention:

EXAMPLE I

200 grams of a commercial grade of 2,4,5-trichlorophenol containing 94% of the 2.4,5-isomer was dissolved in 600 grams of 10% sodium hydroxide solution, and this solution was heated to 60° C. Any insoluble matter which was apparent in this solution was filtered off and there

was then added 600 grams of 50% sodium hydroxide solution, and the mixture was stirred while external cooling was applied. Over a period of 3 hours the mixture was cooled to 15° C., whereupon a heavy crystal mass of the sodium salt of 2,4,5-trichlorophenol had formed. The crystals were filtered off and washed with a small quantity of cold 30% sodium hydroxide solution. The pure white crystals were dissolved in 2 liters of water, and with stirring and cooling, the solution was adjusted to a pH of 3.0 with dilute hydrochloric acid. The 2,4,5-trichlorophenol which precipitated, was filtered off, washed with water, and dried. The yield of purified 2,4,5-trichlorophenol, having an assay of 99.6% and a melting point of 65.5 C. was 179 grams, representing a recovery of 95% of the 2,4,5-trichlorophenol which was present in the starting crude material.

EXAMPLE II

430 grams of commercial grade 1,2,4,5-tetrachlorobenzene was dissolved in 1,000 cc. of methyl alcohol, and 400 grams of 50% sodium hydroxide solution was added. This mixture was heated in an autoclave at 160° for 6 hours. The reaction mixture was then cooled to 30° C., and 500 cc. of water was added. The methyl alcohol was then distilled off and the residue was subjected to steam distillation until no organic matter was evident in the steam distillate. To the residue was then added 1,200 grams of 50% sodium hydroxide solution and the entire mixture was heated to 60° C. An additional 500 cc. of water was added, and the mixture was cooled over a period of 6 hours to 15° C., whereupon a heavy crystal mass of the sodium salt of 2,4,5-trichlorophenol formed. The crystals were removed by filtration, and washed with a small quantity of cold 30% sodium hydroxide solution. The crystals were dissolved in 1 liter of water and the solution was warmed to 70° C., and acidified to pH 3 with dilute hydrochloric acid. The 2,4,5-trichlorophenol separated from the warm mixture as an oil, and was removed from the water layer. The product had a setting point of 65° C., and an assay of 99.5% 2,4,5-trichlorophenol. The yield was 320 grams which represents a yield of 80.8% of the theoretical amount of pure 2,4,5-trichlorophenol from 1,2,4,5-tetrachlorobenzene.

EXAMPLE III

200 grams of a crude technical grade of 2,4,5-trichlorophenol, having an assay of 92.5% of the 2,4,5-isomer is dissolved in 600 cc. of 10% potassium hydroxide solution. The solution is heated to 60° C., and 800 grams of 50% potassium hydroxide solution is added. The mixture is cooled with stirring over a period of 8 hours to 12° C. The formed crystals of the potassium salt of 2,4,5-trichlorophenol are filtered off and washed with a small quantity of cold 25% potassium hydroxide solution. The crystals are dissolved in 1 liter of water, and 300 cc. of chloroform is added. With stirring, the mixture is acidified to a pH of 2.0 with dilute sulfuric acid. The chloroform solution is separated and clarified by filtration. The chloroform is distilled off, leaving a residue of 177 grams of 2,4,5-trichlorophenol having an assay of 99.7%, and a melting point of 66.5° C. This represents a recovery of 95% of the 2,4,5-trichlorophenol which was present in the crude starting material.

In the foregoing examples the excess alkali hydroxide should be present in an amount ranging from 1 to 3 times the weight of the 2,4,5-trichlorophenol.

Although only hydrochloric and sulfuric acids have been disclosed as the acidifying agents, it will be appreciated that many other acids could be used for this purpose as long as they are capable of reducing the pH to 4.5 or lower.

The phrase "essentially pure" is intended to indicate a purity of at least 99.5%.

I claim:

1. In a process for obtaining essentially pure 2,4,5-trichlorophenol from a crude product, wherein the crude product is obtained from the hydrolysis of 1,2,4,5-tetrachlorobenzene, the steps of forming an alkali salt of 2,4,5-trichlorophenol by treating said crude product with an aqueous alkali hydroxide selected from the group consisting of sodium and potassium hydroxides in which an excess of said alkali hydroxide is added at the ratio of about 1 to 3 weight units for each weight unit of 2,4,5-trichlorophenol present, cooling to crystallize said alkali salt and thereafter separating the said crystalized alkali salt of 2,4,5-trichlorophenol from solution by filtration, and recovering 2,4,5-trichlorophenol from the said alkali salt thereof by treating said alkali salt with an acid selected from the group consisting of hydrochloric and sulfuric acid.

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United States Patent Office

3,456,020
Patented July 15, 1969

3,456,020

PRODUCTION OF 2,2'-METHYLENE BIS(3,4,6-TRICHLOROPHENOL)

Thomas F. Cleary, Summit, N.J., assignor to Centerchem Inc., New York, N.Y., a corporation of New York

No Drawing. Continuation-in-part of application Ser. No. 489,036, Sept. 21, 1965. This application Nov. 28, 1967, Ser. No. 686,290

Int. Cl. C07c 37/00

U.S. Cl. 260—619 3 Claims

ABSTRACT OF THE DISCLOSURE

This invention is directed to the production of hexachlorophene by a two stage process in which one mol of 2,4,5-trichlorophenol and one mol of formaldehyde are reacted under the influence of an acid catalyst, after which the reaction product is condensed with one mol of 2,4,5-trichlorophenol through the agency of chlorosulfonic acid or fluorosulfonic acid.

RELATED APPLICATION

This application is a continuation-in-part of my copending application Ser. No. 489,036, now abandoned, filed Sept. 21, 1965, and having the same title as this application.

THE INVENTION

This invention relates generally to new and useful improvements for the production of 2,2'-methylene bis-(3,4,6-trichlorophenol), commonly called hexachlorophene, and particularly seeks to provide a novel two stage process for producing same.

The known processes for the preparation of hexachlorophene (2,2'-methylene bis(3,4,6-trichlorophenol)) involve the condensation of two mols of 2,4,5-trichlorophenol with one mol of formaldehyde (as Formalin or paraformaldehyde). The usual condensing agent is concentrated sulfuric acid or weak oleum, and the reaction may be carried out in the presence or absence of a solvent which is inert to the reactants and to the condensing agent.

In these processes it is customary to mix all of the reactants (and the solvent, if any) at once and to heat the mixture, with agitation, for a certain time. Conditions such as these are disadvantageous in the production of hexachlorophene in that:

(1) They tend to promote the formation of color bodies which make difficult the purification of the product;

(2) They tend to promote the formation of the by-product 2,4,5-trichlorobenzodioxolane with an attendant loss of yield;

(3) They require, if acceptable yields are to be obtained, extreme care that the 2,4,5-trichlorophenol and formaldehyde be present in exactly the molar ratio 2.00:1.00. Since the composition of Formalin or of formaldehyde is usually imprecise, and since a certain amount of formaldehyde is lost from the reaction mixture by volatilization, this is a difficult requirement to realize in practice.

However, through the use of this invention the above mentioned disadvantages in prior processes have been overcome.

Therefore, an object of this invention is to provide a new method of producing hexachlorophene from previously known source materials which is simpler, more effective and results in higher yields by comparison with prior processes.

Another object of this invention is to provide a process of the character stated in which one mol of 2,4,5-trichlorophenol and one mol of formaldehyde are reacted under the influence of an acidic catalyst to form a novel intermediate product, which in turn is condensed with one mol of 2,4,5-trichlorophenol through the agency of chlorosulfonic acid or fluorosulfonic acid to produce high yields of pure hexachlorophene.

With these and other objects, the nature of which will be apparent, the invention will be more fully understood by reference to the accompanying detailed description and the appended claims.

In accordance with this invention it has been discovered that:

(1) One mol of 2,4,5-trichlorophenol and one mol of formaldehyde will react, under the influence of acidic catalysts such as benzenesulfonic acid, anhydrous hydrogen, and diluted sulfuric acid, to form quantitatively and exclusively, a compound which has a melting point of 78° C. The compound has a chlorine content 46.5%, occurs in long colorless prisms, and definitely is not 2,4,5-trichlorosaligenin.

(2) The compound formed as in (1) can be condensed with 2,4,5-trichlorophenol, through the agency of chlorosulfonic acid or fluorosulfonic acid, to produce high yields of pure hexachlorophene.

Both of these reactions are surprising. The only hitherto known reaction product of equimolar amounts of 2,4,5-trichlorophenol and formaldehyde is 2,4,5-trichlorosaligenin, which is formed under alkaline conditions and has a melting point of 128° C. 2,4,5-trichlorophenol, which is relatively inert to concentrated sulfuric acid and to oleum, will react readily with chlorosulfonic acid and fluorosulfonic acid to form 2,4,5-trichlorophenol-6-sulfonic acid.

The following examples will illustrate this invention.

Example 1

197.5 grams of 2,4,5-trichlorophenol having a melting point of 66° C. is dissolved in 1000 grams of perchloroethylene and the solution is warmed to 50° C. with agitation. To this solution is added 50 grams of 90° sulfuric acid. 30 grams of paraformaldehyde is added slowly over a period of one hour with sufficient cooling to maintain the temperature between 60° C. and 70° C. The reaction is exothermic. The mixture is stirred for an additional two hours at 70° C. The perchloroethylene solution is then separated from the dilute acid layer. Upon evaporating a small sample to dryness a crystalline product is obtained which has a melting point of 78° C. There is no free formaldehyde remaining either in the dilute acid layer or in the perchloroethylene solution. There is no hexachlorophene present at this point in the reaction mixture, nor any unreacted 2,4,5-trichlorophenol.

The perchloroethylene solution of the product of the reaction between 2,4,5-trichlorophenol and paraformaldehyde is mixed with a solution of 197.5 grams of 2,4,5-trichlorophenol in 1000 grams of perchloroethylene and the mixture is heated with agitation to 75° C. There is then introduced dropwise over a period of three hours 116 grams of chlorosulfonic acid. The addition of chlorosulfonic acid is accompanied by a mild exothermic reaction and by the evolution of HCl. The temperature is maintained at 75° C. throughout the chlorosulfonic acid addition and is then held at 75° C. to 80° C. for an additional two hours. Agitation is stopped, the remaining sulfuric acid layer is allowed to settle and is separated. The hot perchloroethylene solution is stirred with 10 grams of activated charcoal and is filtered. The reaction product, 2,2'-methylene bis(3,4,6-trichlorophenol), crystallizes upon cooling and is separated by filtration. The yield is 310 grams having a melting point of 162° C. Upon concentration of the mother liquors there is obtained an additional 65 grams of product having the same melting point.

Example 2

197.5 grams of 2,4,5-trichlorophenol having a melting point of 62° C. is dissolved in 2000 ml. of chloroform, and the solution is warmed to 50° C. with agitation. Dry hydrogen chloride is bubbled through the solution at a rate of 5 grams per minute, and over a period of one hour, 31.6 grams of 95% paraformaldehyde is added. Hydrogen chloride addition is continued for 30 minutes, and the mixture is then heated to reflux for one hour.

A small sample of the reaction mixture, evaporated to dryness, yields a white crystalline compound, having a melting point of 78° C. It contains no 2,4,5-trichlorophenol or formaldehyde.

To the reaction mixture is then added a solution of 197.5 grams of 2,4,5-trichlorophenol, having a melting point of 62° C., in 2000 ml. of chloroform. The mixture is heated to 65° C., under a reflux condenser and with good agitation, 100 grams of fluorosulfonic acid is added dropwise, over a period of three hours. Agitation and heating at 65° C. are continued for three hours more, then agitation is stopped, the acid layer is settled and separated. The hot chloroform solution is stirred with 10 grams activated charcoal, filtered and cooled to 10° C. The crystallized 2,2'-methylene bis(3,4,6-trichlorophenol) is filtered off, washed with cold chloroform and dried. The yield is 310 grams having a melting point of 164° C. Evaporation of the mother liquor yields an additional 70 grams of product.

Example 3

To 1000 ml. of benzene is added, slowly, 58 grams of chlorosulfonic acid, and the solution is then heated to reflux until all HCl is driven off. There is thus produced a benzene solution containing 79 grams benzenesulfonic acid. To this solution is added 197.5 grams 2,4,5-trichlorophenol having a melting point of 62° C. The solution is then heated just to the point of reflux, and with good agitation, 85 grams of 37% Formalin is added over two hours, while the water introduced with the Formalin is taken off as an azeotrope with benzene. The condensed benzene is returned to the reaction mixture. Reflux is then continued for one hour, after which 500 ml. of water is added. The mixture stirred 15 minutes at 60° C., and settled. The water layer which contains the benzenesulfonic acid, is separated and discarded.

A small sample of the benzene solution evaporated to dryness, yields a white crystalline product having a melting point of 78° C. It contains no 2,4,5-trichlorophenol or formaldehyde.

The benzene solution is added to 2000 ml. of perchloroethylene, and the benzene is removed from the mixture by fractional distillation.

To the remaining perchloroethylene solution of the reaction product of 2,4,5-trichlorophenol with Formalin is added 197.5 grams 2,4,5-trichlorophenol having a melting point of 62° C. The solution is heated to 75° C., and with vigorous agitation is added, over five hours, 116 grams chlorosulfonic acid. Stirring is continued at 75° C. for two hours and the acid layer is then settled and separated. The hot perchloroethylene solution is stirred with ten grams activated charcoal, filtered and cooled to 10° C. The crystallized 2,2'-methylene bis(3,4,6-trichlorophenol) is filtered off, washed with cold perchloroethylene and dried. The yield is 280 grams having a melting point of 163° C. Evaporation of the mother liquor yields an additional 85 grams of product.

I claim:

1. In a method for producing hexachlorophene the steps of: supplying a solution of 2,4,5-trichlorophenol and formaldehyde at a 1 to 1 molar ratio in a solvent selected from the group consisting of perchloroethylene, chloroform and benzene, reacting said 2,4,5-trichlorophenol and formaldehyde in the pressure of an acid catalyst selected from the group consisting of benzene-sulfonic acid, anhydrous hydrogen chloride and diluted sulfuric acid to form a solution of a compound which, when dry, has a melting point of 78° C. and a chlorine content of 46.5%, then adding a solution of 1 mol of 2,4,5-trichlorophenol to the solution containing the reaction product of the preceding step, and effecting condensation therebetween by the addition of a sulfonic acid selected from the group consisting of chlorosulfonic acid and fluorosulfonic acid to produce pure hexachlorophene.

2. A reaction product between 2,4,5-trichlorophenol and formaldehyde, having a melting point of 78° C. and a chlorine content of 46.5%, produced by supplying a solution of 2,4,5-trichlorophenol and formaldehyde at a 1 to 1 molar ratio in a solvent selected from the group consisting of perchloroethylene, chloroform and benzene, reacting said 2,4,5-trichlorophenol and formaldehyde in the presence of an acid catalyst selected from the group consisting of benzenesulfonic acid, anhydrous hydrogen chloride and diluted sulfuric acid, and separating the solvent solution containing the reaction product from the acid.

3. In a method for producing hexachlorophene the steps of; dissolving a molar equivalent of 2,4,5-trichlorophenol in a solvent selected from the group consisting of perchlorethylene, chloroform and benzene; adding to said solution an acid catalyst selected from the group consisting of benzenesulfonic acid, anhydrous hydrogen chloride and diluted sulfuric acid; then adding a molar equivalent of formaldehyde and maintaining the temperature between about 60° C. and about 70° C. during the exothermic reaction produced as the result of such addition to produce a reaction product which, when dry, has a melting point of 78° C. and a chlorine content of 46.5%; separating the solvent solution from the acid; adding a molar equivalent of 2,4,5-trichlorophenol dissolved in said solvent to said separated solvent solution; effecting condensation between said added molar equivalent of said 2,4,5-trichlorophenol and the reaction product in said separated solvent solution by the addition of an acid selected from the group consisting of chlorosulfonic acid and fluorosulfonic acid; then removing the solvent solution containing the condensed product and recovering pure hexachlorophene therefrom by cooling and filtering same.

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LEON ZITVER, Primary Examiner

N. MORGENSTERN, Assistant Examiner

ERRATUM

SPECIFICATION No. 1,016,080
Amendment No. 1

Page 4, Table 1, Column 8, *line* $\frac{CH_3OH}{TcB}$

for "$\frac{12.5}{1}$" *read* "$\frac{11}{1}$"

THE PATENT OFFICE
3rd October 1966

1,016,080

PATENT SPECIFICATION

NO DRAWINGS

1,016,080

Date of Application and filing Complete Specification: May 17, 1963.

No. 19781/63.

Application made in United States of America (No. 196,507) on May 21, 1962.

Complete Specification Published: Jan. 5, 1966.

Index at acceptance:—C2 C1E5K3

Int. Cl.:—C 07 c

COMPLETE SPECIFICATION

Improvements in or relating to Alkali Metal Polyhalo-Phenates

We, DIAMOND ALKALI COMPANY, of 300 Union Commerce Building, Cleveland 14, Ohio, United States of America, a corporation organised and existing under the laws of the State of Delaware, United States of America, (Assignees of JEWEL HEBER PERKINS, Jr., JACK A. BORROR and RAYMOND AUGUST GUIDI) do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a new and improved method of preparing polyhalophenates, and more specifically refers to improvements in the preparation of sodium 2,4,5-trichlorophenate.

Polyhalophenates, such as sodium 2,4,5-trichlorophenates, are used as raw materials in the production of polyhalophenoxycarboxylic acids which are widely used as herbicides, and there has been a continuing desire to produce such starting materials economically, safely and efficiently.

Referring particularly to the preparation of sodium 2,4,5-trichlorophenate as an illustration, it is known to prepare this material by reacting molten tetrachlorobenzene with a mixture of sodium hydroxide and methanol or water or glycol, by adding all the reactants together as a charge to a reaction vessel, then heating them under pressure to 100°—250° C. to produce the required reactions. This method involves a danger due to the creation of conditions causing runaway reactions and the formation of chloracnegens, and is generally less efficient than the method of this invention. The known method requires the heating of a large amount of a caustic-tetrachlorobenzene mixture which may result in condensation reactions, causing a reduction in efficiency.

It is an object of the present invention to provide an improved method of producing a polyhalophenate, notably sodium 2,4,5-trichlorophenate, in high yield, in a manner which avoids the hazardous condition of reacting large amounts of hot alkali and alcohol with tetrachlorobenzene.

According to the invention, an alkali metal polyhalophenate is prepared by heating a 1,2,4,5-tetrahalobenzene in a closed vessel to a temperature in the range of 140° to 250° C., adding a mixture of an alcohol and an alkali metal hydroxide at a controlled rate, the mol ratio of alcohol to alkali metal hydroxide being from 2:1 to 20:1, and maintaining the reaction temperature in the range of 140° to 250° C. under a superatmospheric pressure which is at least equal to the autogenous pressure of the reaction mixture, the amount of alcohol-alkali mixture being such as to provide a mol ratio of alkali to tetrahalobenzene of from 2:1 to 4:1.

The desired reaction product is obtained in high yield and, at the same time, the undesired dangerous condition of large quantities of unreacted tetrachlorobenzene and alkali-alcohol mixture together in a pressurized high-temperature container is avoided.

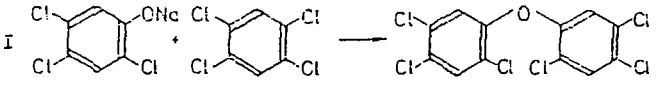
The terms "polyhalophenate" and "tetrahalobenzene" refer respectively to various halogen derivatives of phenol, such as tetrachlorophenol, and of benzene. While chlorine derivatives are preferred, other halogen derivatives are contemplated such as bromo, fluoro, iodo; and mixed halogen products such as bromochlorophenol.

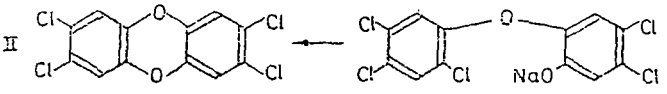
The term "alkali", as used in the specification, refers especially to an alkali metal hydroxide, preferably sodium hydroxide, although other alkali metal hydroxides, e.g., potassium hydroxide and/or lithium hydroxide can be used. It is intended to refer

also to other sources of alkali, which, under the conditions of reaction, are suitable to yield the desired high conversion characterizing the practice of this invention, and otherwise to be satisfactory. An alkali metal hydroxide, notably sodium hydroxide, is especially preferred.

The term "alcohol" means primary, secondary and tertiary alcohols. Methanol is the preferred alcohol.

It is an essential feature of the present invention that a polyhalobenzene, preferably tetrachlorobenzene, is placed in a reaction vessel in a molten or solid state in the absence of any other reactants. The desired reaction is then carried out by the gradual addition of an alkali in alcohol mixture to the molten tetrachlorobenzene. The addition, at a controllable rate, is seen to be inherently safer than adding all the reactants at once and heating the mass to the relatively high temperatures required for the reaction. Another significant advantage of this invention is that less alkali is required. Previous methods require 3.0 mol of alkali per mol of tetrachlorobenzene. The proposed process provides nearly 100% yield at 2.4 mol of alkali per mol of tetrachlorobenzene. Formerly, large amounts of alkali present caused the following condensation reactions which resulted in a corresponding loss of the product and reduction in efficiency.

I 

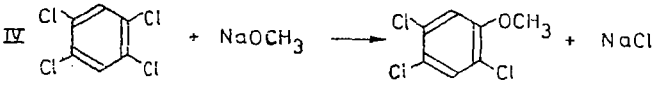
II 

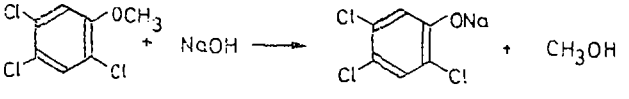
This undesirable condition is minimized by the controlled addition of small quantities of alkali-alcohol mixtures. The end product of the above reactions is termed a "chloracnegen". Condensation products of this class create the occupational hazard of skin disease known to those employed in the art as "chlor-acne". This disorder has been prevalent among operators of prior processes and the absence of the "chloracnegen" renders the method of this invention more desirable than previous processes.

In previous processes, large quantities of alcohol, present in the reaction vessel at the start of the reaction, are subjected to high temperatures before the reaction can be completed, resulting in losses through formation of dimethyl ether. The controlled addition of alkali-alcohol mixture to the reaction vessel, in accordance with the teachings of this invention, reduces losses in alcohol by formation of dimethyl ether by-product.

The sequence of reaction steps of this invention is set forth structurally in the following series of equations, it being understood that the alkali-alcohol mixture is added at a rate pre-determined to produce the most efficient reaction possible. It will then be appreciated that the reaction proceeds only as the reactants become available in the reaction vessel.

III $NaOH + CH_3OH \rightleftharpoons NaOCH_3 + H_2O$

IV 



With the practice of the invention, as outlined in the foregoing equations, conversion of greater than 90% of 1,2,4,5-tetrachlorobenzene to sodium 2,4,5-trichlorophenate is obtained. The reaction temperature varies from 140° C. to 250° C., preferably maintained at 175° C. and a superatmospheric pressure is provided which is at least equal to the autogenous pressure of the reaction mixture. The reaction time typically is 3 to 6 hours, although in commercial operations a longer reaction time of up to 8 hours is not disadvantageous with respect to high yields obtained.

The proportions of the reactants generally can be varied. Thus, molar ratios in the alkali-alcohol mix can be from 1:2 to 1:20 mols of alkali to alcohol. The overall molar ratios of alkali to tetrachlorobenzene can be from 2:1 to 4:1. The overall molar ratios of alcohol to tetrachlorobenzene can be in the range of 4:1 to 80:1. It is the preferred method to add 2.04 pounds of alkali-alcohol solution per pound of 1,2,4,5-tetrachlorobenzene into the reactor at a uniform rate over a period of 2 hours, maintaining the temperature at approximately 175° C. Steel equipment is employed in the examples of this invention, and steel is the preferred material of construction.

In order that those skilled in the art may more completely understand the present invention and the preferred method by which the same may be carried into effect, the following specific examples are offered.

Tetrachlorobenzene is weighed into a pressure reactor, such as an autoclave, melted and brought up to the reaction temperature, e.g., 175° C. An alkali methanol solution is heated to 55°—65° C. and added to the reactor over a period which may vary from 40 minutes to 5 hours, preferably at a controlled rate of addition which is within the range of 0.4 to 11 mol per hour. When all of the alkali methanol solution has been charged, the reactor temperature is held constant, e.g. at 175° C., for a period which may vary from 40 minutes to 3 hours. During the reaction, the pressure within the reactor will be in the range of 250 p.s.i.g. to 700 p.s.i.g., due to the autogenous pressure of the alcohol, and will vary according to the amount of alcohol added. When the reaction is complete, the charge is cooled to reduce pressure. Steam is applied to the reaction vessel to distill off all the unreacted methanol which is collected through a condenser system and recovered. When all the methanol has been removed, water is added to the reaction mass which is now a crude sodium trichlorophenate. The crude sodium trichlorophenate is transferred to a distillation vessel, where by steam distillation the intermediate reaction product, trichloroanisole, is removed and recovered. The steam-stripped sodium trichlorophenate is then pumped through an enclosed filter, which removes the salts, and is then diluted and stored for later use in the 2,4,5-trichlorophenoxyacetic acid production.

By way of illustration, the process of the invention is carried out by heating 1,2,4,5-tetrachlorobenzene in the closed reaction vessel to a temperature of 175° C., adding 11 mol per hour of sodium hydroxide contained in a mixture with methanol, the mol ratio of methanol to sodium hydroxide being 5.4:1, and maintaining the reaction temperature of 175° C. for a period of 3 hours, under a pressure of 270 to 490 p.s.i.g., the amount of methanol sodium hydroxide mixture being such as to provide a mol ratio of sodium hydroxide to tetrachlorobenzene of about 2.2:1.

In the following examples, carried out in the manner indicated, the results are indexed comparatively:

TABLE I

	1	2	3	4	5	6	7	8	9	10	11	12	13
Mole Ratio													
$\frac{NaOH}{CH_3OH}$	$\frac{1}{5}$	$\frac{1}{5}$	$\frac{1}{5}$	$\frac{1}{5}$	$\frac{1}{5}$	$\frac{1}{5}$	$\frac{1}{5}$	$\frac{1}{5}$	$\frac{1}{5}$	$\frac{1}{5}$	$\frac{1}{5}$	$\frac{1}{5}$	$\frac{1}{5}$
$\frac{NaOH}{TCB^*}$	$\frac{2.2}{1}$	$\frac{2.2}{1}$	$\frac{2.2}{1}$	$\frac{2.2}{1}$	$\frac{2.5}{1}$	$\frac{2.5}{1}$	$\frac{2.5}{1}$	$\frac{2.2}{1}$	$\frac{2.2}{1}$	$\frac{2.2}{1}$	$\frac{2.2}{1}$	$\frac{2.2}{1}$	$\frac{2.2}{1}$
$\frac{CH_3OH}{TCB^*}$	$\frac{11}{1}$	$\frac{11}{1}$	$\frac{11}{1}$	$\frac{11}{1}$	$\frac{12.5}{1}$	$\frac{12.5}{1}$	$\frac{12.5}{1}$	$\frac{12.5}{1}$	$\frac{11}{1}$	$\frac{11}{1}$	$\frac{11}{1}$	$\frac{11}{1}$	$\frac{11}{1}$
Conditions													
% Excess NaOH	10	10	10	10	25	25	25	10	10	10	10	10	10
Total charge gm.	3280	3280	3280	3280	3580	3580	3580	3280	3280	3280	3280	3280	3280
Feed Time (hrs.)	2	5	2	3	5	3	4	2	2	2	2	1	$\frac{3}{4}$
Hold Time (hrs.)	2	$\frac{1}{2}$	1	1	1	1	1	2	3	1	2	2	3
Reaction Temp., °C.	140—72	165—68	164—65	165	164—66	163—64	163—64	157—62	163—64	174—75	170—88	164—67	173—79
% Conversion to sodium Trichlorophenate	72.2	73.9	89.3	74.5	90.0	85.7	83.3	82.7	92.7	90.2	96.0	89.9	96.8
Maximum Pressure PSIG	340	225	305	360	565	400	280	265	320	420	330	370	385

* 1,2,4,5-tetrachlorobenzene

EXAMPLE 14.

To the reaction vessel is added 1,080 g. (5 mol) of 1,2,4,5-tetrachlorobenzene. A 20% by weight NaOH in methanol solution is prepared by adding 440 g. (11 mol) NaOH pellets to 1,920 g. (60 mol) of commercial grade methanol and heated to 63° C. The reaction vessel is heated to 170° C., at which time the alkali methanol mixture is added to the reaction vessel over a period of 1 hour at a uniform rate, which will ultimately provide a 2.2:1 mol ratio of alkali to tetrachlorobenzene, respectively. At the end of 1 hour, when all the alkali methanol mixture has been added, the closed reaction vessel is maintained at 175° C. for a period of 3 hours. The pressure within the container reaches a maximum of 492 p.s.i.g. approximately one hour after the end of the alkali methanol addition. After cooling, pressure is reduced, and steam is applied to the reaction vessel to distill off the unreacted methanol. When all the methanol has been removed, water is added, and the crude sodium trichlorophenate may be purified if desired.

It is to be understood that, although the invention has been described with specific reference to particular embodiments thereof, it is not to be so limited since changes and alterations therein may be made which are within the full intended scope of this invention, as defined by the appended claims.

WHAT WE CLAIM IS:—

1. A process of preparing an alkali metal polyhalophenate, which comprises heating a 1,2,4,5-tetrahalobenzene in a closed vessel to a temperature in the range of 140° to 250° C., adding a mixture of an alcohol and an alkali metal hydroxide at a controlled rate, the mol ratio of alcohol to alkali metal hydroxide being from 2:1 to 20:1, and maintaining the reaction temperature in the range of 140° to 250° C. under a superatmospheric pressure which is at least equal to the autogenous pressure of the reaction mixture, the amount of alcohol-alkali mixture being such as to provide a mol ratio of alkali to tetrahalobenzene of from 2:1 to 4:1.

2. A process as claimed in Claim 1, wherein the tetrahalobenzene is 1,2,4,5-tetrachlorobenzene.

3. A process as claimed in Claim 1 or 2, wherein the alkali metal hydroxide is sodium hydroxide.

4. A process as claimed in Claim 1, 2 or 3, wherein the alcohol is methanol.

5. A process as claimed in any preceding Claim, wherein the reaction vessel pressure is maintained in the range of 250 to 700 p.s.i.g.

6. A process as claimed in any preceding claim, in which the alkali metal hydroxide in the mixture is added at a controlled rate in the range of 0.4 to 11 mol per hour.

7. A process as claimed in any preceding claim, in which sodium trichlorophenate is prepared by heating 1,2,4,5-tetrachlorobenzene in the closed reaction vessel to a temperature of 175° C., adding 11 mol per hour of sodium hydroxide contained in a mixture with methanol, the mol ratio of methanol to sodium hydroxide being 5.4:1, and maintaining the reaction temperature at 175° C. for a period of 3 hours, under a pressure of 270 to 490 p.s.i.g., the amount of methanol sodium hydroxide mixture being such as to provide a mol ratio of sodium hydroxide to tetrachlorobenzene of about 2.2:1.

8. A process of preparing an alkali metal polyhalophenate, as described with reference to the foregoing Examples.

9. Alkali metal polyhalophenates, when prepared by a process as claimed in any preceding claim.

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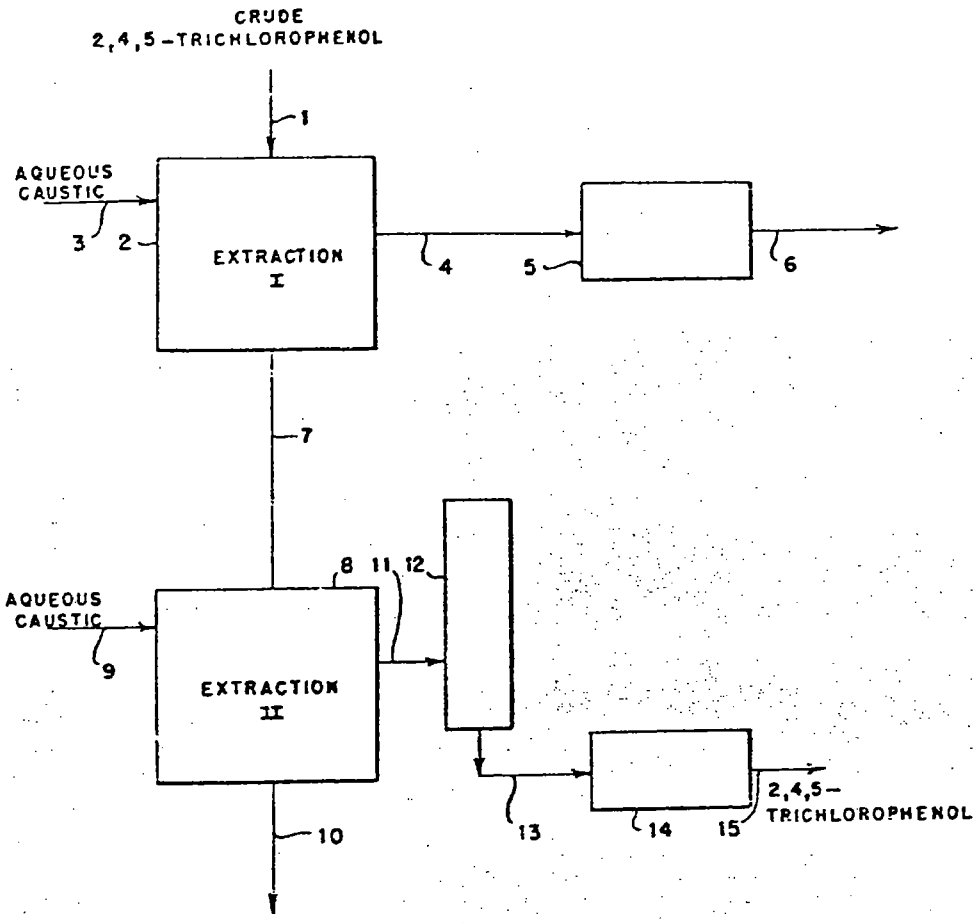
PROCESS FOR THE RECOVERY OF 2,4,5-TRICHLOROPHENOL

Filed May 7, 1953



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United States Patent Office 2,755,307 Patented July 17, 1956

2,755,307

PROCESS FOR THE RECOVERY OF 2,4,5-TRICHLOROPHENOL

Bernard H. Nicolaisen, Kenmore, N. Y., assignor to Olin Mathieson Chemical Corporation, a corporation of Virginia

Application May 7, 1953, Serial No. 353,659

1 Claim. (Cl. 260—623)

My invention relates to the production of 2,4,5-trichlorophenol by caustic hydrolysis of 1,2,4,5-tetrachlorobenzene and in particular relates to the purification of the crude 2,4,5-trichlorophenol product so derived.

In the caustic hydrolysis of 1,2,4,5-tetrachlorobenzene numerous contaminating products are formed. Methanol, for example, which may be used as a solvent for the hydrolysis reaction, tends to cause some production of trichloroanisole and dichlorodimethoxybenzene. The presence of the usual small amounts of other tetrachlorobenzene isomers, such as 1,2,3,4-tetrachlorobenzene, as impurities in the symmetrical 1,2,4,5-tetrachlorobenzene, causes the production of undesired position isomers of 2,4,5-trichlorophenol.

At the present time there exists a substantial demand for a high purity 2,4,5-trichlorophenol product which is not satisfied by the crude derived by the caustic hydrolysis of 1,2,4,5-tetrachlorobenzene. The demand is, in particular, for a product having a melting point over 65° C. which in the molten state has a water-white color. The product must also be completely soluble in caustic solution, e. g. 0.1 N NaOH, and should be at least 99% pure.

Caustic-insoluble materials, such as trichloroanisole and dichlorodimethoxybenzene, may be removed to some extent by steam distillation of the alkaline phenate solution but complete removal of these impurities requires excessive amounts of steam. Other impurities, such as the position isomers of 2,4,5-trichlorophenol are more difficult to separate because of their similar chemical and physical properties.

A high purity 2,4,5-trichlorophenol product meeting the above specifications can be recovered from the crude trichlorophenol obtained by caustic hydrolysis of 1,2,4,5-tetrachlorobenzene. I have found, in particular, that crude 2,4,5-trichlorophenol resulting from the acidification of the alkaline hydrolysis mixture can be separated into pure 2,4,5-trichlorophenol free from undesirable contaminants by a step-wise extraction with aqueous caustic.

The process of my invention thus essentially requires extracting crude 2,4,5-trichlorophenol with aqueous caustic solution sufficient in amount to convert all of the 2,3,6-trichlorophenol and other extraneous phenols present and a minor proportion of the 2,4,5-trichlorophenol to the water-soluble corresponding phenates. The operation is carried out at a temperature at which the phenols are in the liquid state. Unneutralized phenols are then separated from the dilute aqueous phenate solution.

The unneutralized phenols, separated from the aqueous phenate phase, are further extracted by the addition of aqueous caustic solution in an amount sufficient to convert substantially less than the total of the phenols present to the corresponding phenates. The extraction is again carried out at a temperature at which the phenols are in the liquid state. The aqueous phenate extract solution is then separated from the remaining undissolved oils. Acidification of this second extract yields the desired purified 2,4,5-trichlorophenol product which is separated and dried.

The remaining undissolved oils comprise trichlorophenols contaminated with alkali-insoluble impurities and are useful as crude trichlorophenol for most purposes not requiring the pure isomer. The phenate solution obtained in the first extraction step, although relatively impure, is also suitable for use after acidification as crude trichlorophenol. Alternatively, both fractions may be worked up for specific trichlorophenols or phenol ethers contained therein or they may be discarded.

My invention will be further illustrated by reference to the accompanying drawing which is a diagrammatic flow plan of the process.

Crude 2,4,5-trichlorophenol, obtained by caustic hydrolysis of 1,2,4,5-tetrachlorobenzene followed by acidification, is introduced by line 1 to a first extraction step 2. The crude 2,4,5-trichlorophenol is extracted with aqueous caustic introduced by line 3 in an amount sufficient to convert all of the 2,3,6-trichlorophenol and a minor proportion of the 2,4,5-trichlorophenol to the water-soluble corresponding phenates.

Extract phenate solution is separated and removed by line 4. If desired, the phenates are acidified by means of a mineral acid in zone 5 and the phenols containing substantially all the 2,4,6-trichlorophenol and a few per cent of the 2,4,5-trichlorophenol of the original charge are removed by line 6.

The undissolved phenol residue from the aqueous phenate solution of extraction step 1 is separated and removed by line 7 to the second extraction step 8 and treated with aqueous caustic solution introduced by line 9 in an amount sufficient to convert less than the total quantity of the phenols contained in the residue to the corresponding phenates. The undissolved phenol residue after caustic treatment is removed by line 10.

The phenate extract solution is separated and removed by line 11. If desired, the phenate extract is steam distilled in zone 12 to improve the color of the 2,4,5-trichlorophenol. Steam distilled phenol extract is removed by line 13 and acidified by means of a mineral acid in zone 14 and 2,4,5-trichlorophenol is removed by line 15.

It is advantageous to use an aqueous caustic solution extracting agent containing not more than about 10% by weight of caustic since the employment of more concentrated caustic solutions results in dissolving a significant proportion of unneutralized phenols by the resulting aqueous phenate solution. Water should be added, therefore, to the aqueous extracting solution prior to or during each extraction, if required, to adjust the phenate concentration to not more than about 15% by weight to insure the separation of the unneutralized phenols as a separate phase which may be removed from contact with the aqueous phase.

The caustic used in the extraction process will ordinarily be sodium hydroxide but other alkali metal hydroxides, particularly potassium hydroxide, may also be used. The amount of caustic employed in the first extraction step preferably is sufficient to dissolve all of the 2,3,6-trichlorophenol and other extraneous phenols present and at least about 1 or 2% of the 2,4,5-trichlorophenol. The proportion of caustic used in the first extraction is thus dependent on the purity of the original crude 2,4,5-trichlorophenol. This in turn depends on the purity of the 1,2,4,5-tetrachlorobenzene employed to produce the crude 2,4,5-trichlorophenol. Less pure 2,4,5-trichlorophenol requires a greater amount of caustic in the first extraction step than when the crude trichlorophenol contains a smaller proportion of impurities. With very impure mixtures, the caustic may amount to sufficient to extract as much as one-third to one-half of the phenols present. The amount of caustic used to extract the residue from the first extraction step will range from about 25% to

about 95% of that required to extract the phenols present as water-soluble phenates.

Steam distillation before acidification of the crude 2,4,5-trichlorophenate solution resulting from the hydrolysis is extremely beneficial in that it removes some of the caustic insoluble impurities which otherwise are concentrated in the residual materials, making phase separation after each extraction progressively more difficult. Steam distillation thus reduces the proportion of remaining crude trichlorophenol to be reworked or discarded and further permits taking a larger heart cut of the crude product by caustic extraction in the second step and the recovery of a larger proportion of 2,4,5-trichlorophenol of the desired degree of purity. Steam distillation of the 2,4,5-trichlorophenol obtained by acidification of the second extraction is also advantageous in improving the color of the purified product.

While the extraction process of my invention is carried out at temperatures at which the trichlorophenol is liquid, the acidification of the extracts and recovery of phenols therefrom may be carried out at the same or lower temperatures. By acidifying the extracts at relatively low temperatures, the phenols may be precipitated as solids and removed by filtration. Alternatively, at elevated temperatures the trichlorophenol products may be obtained as liquids. The purity of the crude trichlorophenol and of the final products determines the limiting temperatures below which acidification of the extracts must be carried out in order to obtain the products as solids. However, all the operations are preferably carried out between about 20° and 80° C.

Example

A crude 2,4,5-trichlorophenol product (M. P. 60° to 62° C.) is obtained by acidifying the crude alkaline solution resulting from the caustic hydrolysis of 1,2,4,5-tetrachlorobenzene and contains about 97% of 2,4,5-trichlorophenol, 1% of 2,3,6-trichlorophenol and about 2% of trichloroanisole and other impurities. The crude phenol is then extracted at about 70° C. with an amount of 5% aqueous sodium hydroxide calculated to convert about 5% of the phenols present to the corresponding sodium phenates. The extract solution after separation from undissolved phenols yields an impure product containing upon acidification substantially all of the 2,3,6-trichlorophenol and a few per cent of the 2,4,5-trichlorophenol of the original charge.

The separated trichlorophenol residue from the first extraction is then treated at about 70° C. with an amount of 5% aqueous sodium hydroxide calculated to convert about 90% of the original charge, calculated as 2,4,5-trichlorophenol to sodium 2,4,5-trichlorophenate.

After agitating and separating at about 70° C., the undissolved portion is removed and is combined with the crude trichlorophenols obtained by acidifying the first extract. Steam distilling the second extract solution before acidification aids materially in removing undissolved materials and results in an improvement in color of the 2,4,5-trichlorophenol obtained by subsequent acidification of the extract. The second extract solution, with or without the steaming operation, is then acidified by the use of mineral acid, for example sulfuric or hydrochloric acid, at 60° C. The liquid 2,4,5-trichlorophenol formed is separated from the aqueous salt solution, steam distilled, dried, and crystallized. The crystallized product has a melting point in excess of 65° C., is water-white in color, and is in excess of 99% purity.

I claim:

A process for the recovery of 2,4,5-trichlorophenol from crude mixtures thereof obtained by caustic hydrolysis of 1,2,4,5-tetrachlorobenzene, which comprises extracting the crude 2,4,5-trichlorophenol at a temperature at which the mixture is in the liquid state with aqueous caustic solution in an amount calculated to convert the contaminating chlorophenols and a minor proportion of the 2,4,5-trichlorophenol present to the corresponding phenates, the resulting solution having a phenate concentration of not more than about 15 per cent by weight, separating the undissolved residue from the resulting aqueous phenate solution, extracting the separated residue at temperature at which the residue is liquid with aqueous caustic solution in an amount calculated to convert less than the total quantity of the phenols contained in the residue to the corresponding phenates, separating the resulting phenate extract solution from the remaining undissolved residue, and acidifying the extract solution to recover 2,4,5-trichlorophenol.

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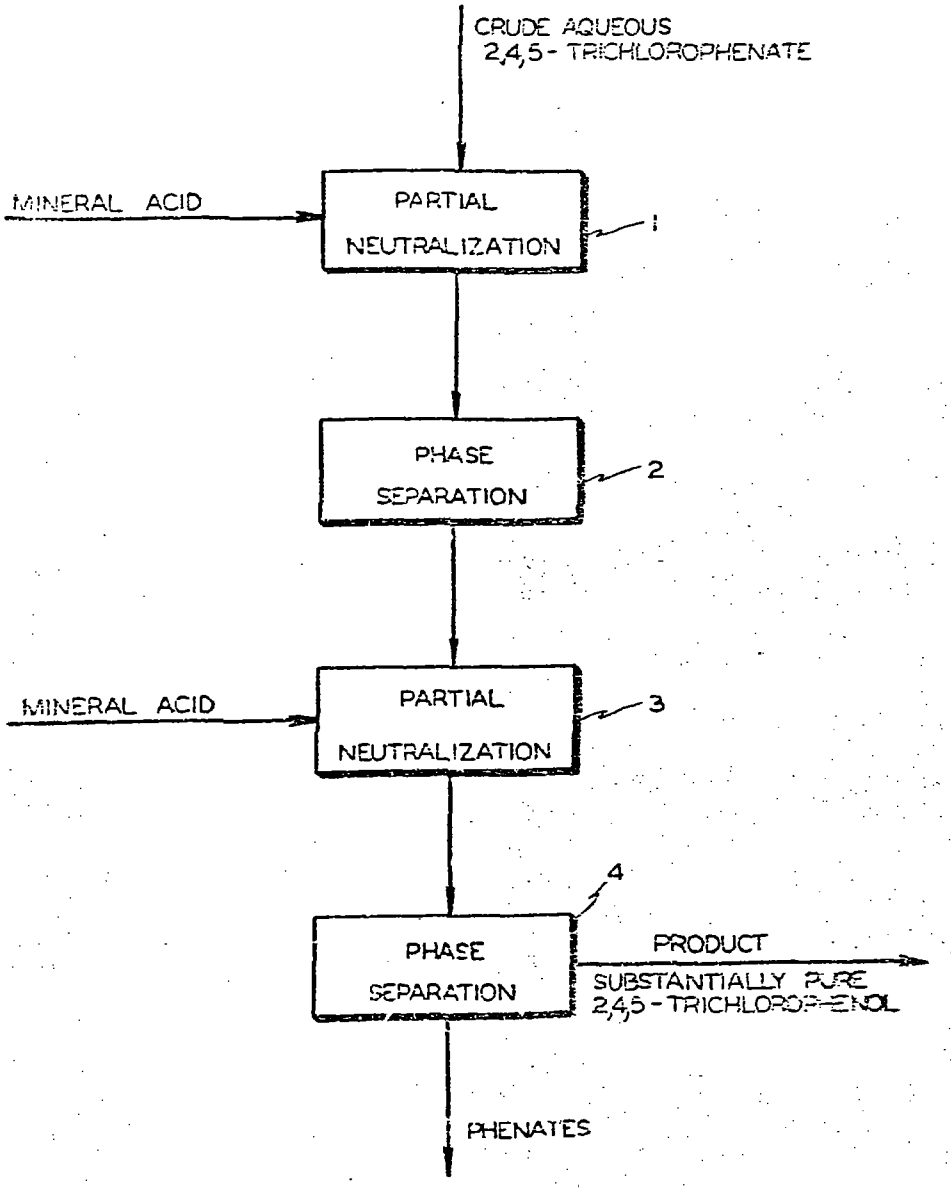
PROCESS FOR THE RECOVERY OF PURE 2,4,5-TRICHLOROPHENOL FROM PRODUCTS OF THE ALKALINE HYDROLYSIS OF 1,2,4,5-TETRACHLOROBENZENE

Filed Feb. 2, 1953



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United States Patent Office

Patented May 22, 1956

2,748,174

PROCESS FOR THE RECOVERY OF PURE 2,4,5-TRICHLOROPHENOL FROM PRODUCTS OF THE ALKALINE HYDROLYSIS OF 1,2,4,5-TETRACHLOROBENZENE

Theodore M. Jenney and Bernard H. Nicolaisen, Kenmore, N. Y., assignors to Olin Mathieson Chemical Corporation, a corporation of Virginia

Application February 2, 1953, Serial No. 334,746

2 Claims. (Cl. 260—623)

Our invention relates to the production of 2,4,5-trichlorophenol by caustic hydrolysis of 1,2,4,5-tetrachlorobenzene and in particular relates to the purification of the crude 2,4,5-trichlorophenol product so derived.

In the caustic hydrolysis of 1,2,4,5-tetrachlorobenzene numerous contaminating products are formed. Methanol, for example, which may be used as a solvent for the hydrolysis reaction, tends to cause some production of trichloroanisole and dichlorodimethoxybenzene. The presence of the usual small amounts of other tetrachlorobenzene isomers, such as 1,2,3,4-tetrachlorobenzene, as impurities in the symmetrical 1,2,4,5-tetrachlorobenzene, causes the production of undesired position isomers of 2,4,5-trichlorophenol.

At the present time there exists a substantial demand for a high purity 2,4,5-trichlorophenol product which is not satisfied by the crude derived by the caustic hydrolysis of 1,2,4,5-tetrachlorobenzene. The demand is, in particular, for a product having a melting point over 65° C. which in the molten state has a color from white to near white. The product must also be completely soluble in caustic solution, e. g. 0.1 N NaOH, and should be at least 99% pure.

Caustic insolubles, such as trichloroanisole and dichlorodimethoxybenzene, may be removed to some extent by steam distillation although their complete removal requires inordinately large amounts of steam. Other impurities, however, such as the position isomers of 2,4,5-trichlorophenol, are more difficult to separate because of their similar chemical and physical properties.

We have discovered that a high purity 2,4,5-trichlorophenol product meeting the above specifications may be recovered from the crude product obtained by the caustic hydrolysis of 1,2,4,5-tetrachlorobenzene. We have found in particular that the solution of crude sodium 2,4,5-trichlorophenate which is recovered from the caustic hydrolysis of 1,2,4,5-tetrachlorobenzene may be separated from the undesirable contaminants noted above by a step-wise neutralization process.

The process of our invention thus essentially requires neutralizing crude 2,4,5-trichlorophenate solution by addition of mineral acid thereto in an amount sufficient to neutralize excess alkalinity of the solution and a minor proportion of the phenates present. The neutralized phenates are released as the free phenols which separate from the dilute aqueous mixture as a separate phase, i. e. when the total phenate-phenol concentration is not more than about 10% by weight. Thus, we contemplate the addition of water, when required, to adjust the phenate-phenol concentration to not more than 10% by weight, either prior to the first neutralization step or immediately thereafter, whereby the resulting phenols are phased out and then may be separated from the aqueous phase which contains the remaining unneutralized phenates.

The aqueous phenate phase separated from the phenol phase is further neutralized by the addition of mineral acid but in an amount sufficient only for recovery as the free phenols of substantially less than the total of the phenates remaining in solution. The phenols phase out upon the second neutralization step without further adjustment of phenate concentration, and are separated from the aqueous phenate phase and recovered as the desired pure 2,4,5-trichlorophenol product.

The invention will be further described in conjunction with the accompanying drawing which comprises a flow sheet illustrating the essential features of the applicants' process.

In the drawing an aqueous solution of crude 2,4,5-trichlorophenate obtained by the caustic hydrolysis of 1,2,4,5-tetrachlorobenzene is introduced to zone 1 of the flow sheet where it is contacted and partially neutralized with mineral acid. The phenols produced by the partial neutralization are separated in zone 2 by a phase separation based upon the insolubility of phenols in aqueous solutions having a phenol-phenate concentration of not more than about 10% by weight. The aqueous phenate solution is then subjected to a second partial neutralization in zone 3 by an additional quantity of mineral acid. The aqueous phenol-phenate solution is then subjected to a second phase separation of phenol in zone 4. The aqueous layer from this separation contains residual phenate which can be recovered as crude phenol and recycled. The phenol layer from the separation of zone 4 is the product, substantially pure 2,4,5-trichlorophenol.

The phenols precipitated in the first neutralization step, although they may be relatively impure, are suitable for use as crude trichlorophenol. The phenates remaining in solution after the second neutralization step may be recovered as the free phenols by complete neutralization and are also useful as crude trichlorophenol.

The amount of acid employed in the first neutralization steps ranges from an amount sufficient to neutralize the excess alkalinity and to spring free as little as about 1 or 2% of the phenates present up to an amount sufficient to spring free as much as a third or a half of the phenates present. The amount of acid added to neutralize the aqueous phase separated from the first neutralization step may range from about 25% to about 90 or 95% of that required to spring the phenates present as the corresponding phenols. The particular choice of proportion of acid added is largely dependent upon the purity of the original crude 2,4,5-trichlorophenate solution. In turn, the purity of this solution depends largely upon the purity of the 1,2,4,5-tetrachlorobenzene employed to produce the crude 2,4,5-trichlorophenate solution. More impure 2,4,5-trichlorophenate solutions require a greater amount of acid in the first neutralization step and a lesser amount in the second neutralization step. Generally, any mineral acid, such as sulfuric or hydrochloric acid, is suitable.

We have found that a pretreatment of the 2,4,5-trichlorophenate solution, such as by steam distillation to remove some of the caustic insoluble impurities, is extremely beneficial in that it lowers the required amount of acid for the first step of neutralization and permits a greater amount of acid to be employed in the second neutralization step, thus permitting highly increased yields of the recovered high purity products. Steam distillation of the product of the second neutralization is also advantageous as the color of the pure 2,4,5-trichlorophenol product is thus improved.

Our process is conveniently carried out at any temperature at which the phenate solution is in the liquid state, preferably between about 20° and about 80° C. The most important aspect of temperature is whether the phenols are to be phased out as solids or liquids; for the temperature at which the process is carried out must of course be selected having in mind whether a liquid-solid or a liquid-liquid separation is contemplated.

Example I

Crude 2,4,5-trichlorophenol obtained by acidifying the crude phenate product of the caustic hydrolysis of 1,2,4,5-tetrachlorobenzene and having the following analysis:

M. P., °C.	60–62
H_2O, wt. percent	0.00
Ash, wt. percent	0.05
Neutral equivalent	207
	(Theoretical 198.5)
2,4,5-trichlorophenol, wt. percent	97.0 (infra-red)
2,3,6-trichlorophenol, wt. percent	1.0 (infra-red)
2,4,5-trichloroanisole, wt. percent	1.0 (infra-red)
Unidentified (*not tars*), wt. percent	1.0 (*approx.*)

was reacted with caustic to a pH of 10 and steam distilled to remove trichloroanisole and some unidentified material, later proven to be dichlorodimethoxybenzene, from the phenate solution. To the resulting aqueous phenate solution was added one-third the amount of aqueous hydrochloric acid required to neutralize the slight excess of alkali and all the phenates present. Sufficient water was added to cause phase separation of the free phenols from the aqueous phenate solution, which was then decanted. The phenol layer was washed free of phenates with water and the washings added to the aqueous phenate layer. After steam distillation to separate color bodies the separated phenol contained 99% 2,4,5-trichlorophenol by infra-red analysis, was completely soluble in 0.1 NaOH solution, melted at 64–65° C. and had a neutral equivalent of 205–7.

An equal amount of hydrochloric acid was added to the residual phenate solution. The free phenol which was separated therefrom contained 100% 2,4,5-trichlorophenol by infra-red analysis, was completely soluble in 0.1 NaOH solution, melted at 65–65.5° C., had a neutral equivalent of 201, and was water white in the molten state.

A third cut was obtained by completely neutralizing the remaining phenates, resulting in precipitation of phenols which analyzed 98% 2,4,5-trichlorophenol and 1.5% 2,3,6-trichlorophenol by infra-red analysis.

Example II

In this example crude phenate solution, prepared as in Example I, was acidified step-wise following the procedure of Example I employing first 10% of the acid theoretically required to neutralize the slight excess alkalinity and all the phenates present as the free phenols, then 80% and then 10%. The steam distillation step was omitted and sufficient water was added before the first acidification to lower the phenate concentration to about 10% by weight. The first cut of phenols recovered was high in alkali insoluble organics containing only 67% 2,4,5-trichlorophenol by infra-red analysis. The center cut was 99.5% 2,4,5- and 0.5% 2,3,6-trichlorophenol by infra-red analysis and melted at 65.5–66° C. The third cut analyzed 98% 2,4,5-trichlorophenol.

In the following two examples all parts are by weight, unless otherwise noted.

Example III

100 parts of crude 2,4,5-trichlorophenol, having the same analysis as in Example I, are reacted with 20 parts sodium hydroxide in 950 parts water and 55 parts of washings from a previous batch to produce about 10% by weight phenate solution. 10% of the phenates are then phased out by addition of 10% of HCl (37% conc.) stoichiometrically required for complete neutralization. The phenols are separated by filtration and washed with 50 parts water, recovering 55 parts washings which are included in the preparation of the 10% phenate solution for a subsequent batch. The impure 2,4,5-trichlorophenol recovered from the washing operation is suitable for sale as crude trichlorophenol.

The filtrate of aqueous phenate solution is then treated with HCl (37% conc.) to phase out 80% of the phenates originally present as free phenols. The phenols are separated from the remaining aqueous layer by filtration and are washed with 50 parts water, recovering 60 parts washing which are added to the aqueous filtrate. The washed phenols are steam distilled and then dried to yield substantially pure 2,4,5-trichlorophenol.

The remaining filtrate, including 60 parts washings, noted above, is then treated with HCl (37% conc.) to spring free the remaining phenates as the phenols. The phenols which phase out are separated by filtration and are recovered for sale as crude trichlorophenols. About half the last group of phenols do not phase out and remain dissolved in the filtrate of the third neutralization step. They also may be recovered for crude sales.

Example IV

250 parts of crude 2,4,5-trichlorophenol of the same analysis as that employed in Example I are reacted with 50 parts sodium hydroxide in 250 parts water. 24.8 parts HCl (37% conc.) are added to spring free a portion of the phenates as the phenols. 2000 parts water are then added to phase out the phenols which are separated from the aqueous phenate phase by filtration. The phenols are washed and 16 parts recovered as crude trichlorophenol. The washings, combined with the aqueous filtrate, are treated with 100 parts HCl (37% conc.) to phase out 212.9 parts of 2,4,5-trichlorophenol which is washed and steam distilled to recover 165.6 parts pure 2,4,5-trichlorophenol. The washings, combined with the aqueous filtrate, are further treated with 27.2 parts HCl (37% conc.) to recover 3.2 parts of crude trichlorophenol.

We claim:

1. A process for the production of 2,4,5-trichlorophenol from aqueous mixtures of crude 2,4,5-trichlorophenate obtained by caustic hydrolysis of 1,2,4,5-tetrachlorobenzene, which comprises adding mineral acid to the crude 2,4,5-trichlorophenate mixture in amount sufficient to neutralize excess alkalinity and a minor proportion of the phenates present, which form corresponding phenols, separating the phenols as separate phase from dilute aqueous mixture having a phenol-phenate content of not more than about 10% by weight, adding mineral acid to the separated aqueous phase in an amount sufficient to convert less than the total quantity of remaining phenates to corresponding phenols, and separating 2,4,5-trichlorophenol from the aqueous phase.

2. A process for the recovery of 2,4,5-trichlorophenol from crude mixtures thereof obtained by caustic hydrolysis of 1,2,4,5-tetrachlorobenzene, which comprises adding aqueous caustic solution to crude 2,4,5-trichlorophenol to convert all phenols present to the corresponding phenates, adding mineral acid to the crude 2,4,5-trichlorophenate mixture in amount sufficient to neutralize excess alkalinity and a minor proportion of the phenates present, which form corresponding phenols, separating the phenols as a separate phase from dilute aqueous mixture having a phenol-phenate content of not more than about 10% by weight, adding mineral acid to the separated aqueous phase in an amount sufficient to convert less than the total quantity of remaining phenates to the corresponding phenols, and separating 2,4,5-trichlorophenol from the aqueous phase.

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Patented May 30, 1950

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UNITED STATES PATENT OFFICE

2,509,245

PREPARATION OF 2,4,5-TRICHLOROPHENOL

Edward Joseph Nikawitz, Passaic, and William S. Gump, Upper Montclair, N. J., assignors to The Givaudan Corporation, a corporation of New Jersey

No Drawing. Application March 20, 1947, Serial No. 736,118

5 Claims. (Cl. 260—623)

1

This invention relates to a process for preparing 2,4,5-trichloro phenol, and more especially to a process wherein 1,2,4,5-tetrachloro benzene is subjected to alkaline hydrolysis in the presence of ethylene- or propylene glycol (propanediol-1,2).

2,4,5-trichloro phenol has been prepared from 1,2,4,5-tetrachloro benzene by hydrolyzing the latter with alkali in the presence of methyl alcohol, the process being conducted under considerable pressure, of the order of 600–800 pounds per square inch. Special pressure equipment is required for conducting such a process. Moreover, appreciable amounts of the methyl ether of 2,4,5-trichloro phenol form when methyl alcohol is employed; and the formation of the ether is undesirable as it decreases the yield of the desired free phenol.

Our present invention overcomes the foregoing disadvantages and provides a process for making 2,4,5-trichloro phenol from 1,2 4,5-tetrachloro benzene which can be conducted with cheaper and simpler equipment than is required by the prior art process, and which does not result in the formation of any appreciable amount of ether.

In general, our process may be conducted by dissolving an alkali metal hydroxide, such as sodium hydroxide, potassium hydroxide and lithium hydroxide, in ethylene glycol or propylene glycol, or a mixture thereof, at elevated temperatures while stirring the contents. The tetrachloro benzene is then added and the mixture is heated for a few hours, normally 3–4 hours being sufficient. The end point of the reaction can be determined easily by taking a sample of the reaction mixture and diluting it with water. If the sample is water soluble or practically entirely soluble in the water, the reaction may be considered to have been completed. The desired phenol may be isolated in accordance with known procedures. For example, the reaction mixture may be cooled after the test as above shows substantial completion of the reaction, and then acidified with a mineral acid such as hydrochloric acid. The precipitated alkali metal chloride is filtered off. The filtrate is poured into water, causing the 2,4,5-trichloro phenol to precipitate. The phenol is extracted with benzene and the benzene extract is distilled to remove the benzene and yield the phenol. The aqueous layer remaining after the benzene extraction is fractionally distilled to remove the glycol employed.

The proportions of the ingredients used may

2

be varied. The alkali metal hydroxide is used in amounts equivalent to at least 2 mols of hydroxide per mol of tetrachloro benzene. 2–3 mols of hydroxide per mol of tetrachloro benzene gives excellent results. Higher amounts of hydroxide may be employed, but are unnecessary.

With regard to the amount of glycol which should be employed in our process, we find that excellent results are obtained when about 750 grams of the glycol per 216 grams (1 mol) of the tetrachloro benzene are used. Larger amounts of glycol may be used, but in such cases no advantageous results follow. Amounts less than 450 grams of glycol per 216 grams of tetrachloro benzene are not recommended, as yield and quality of the desired phenol are adversely affected.

The temperature range at which the hydrolysis may be effected is between about 160° C. and 200° C., the preferred range being between about 170° C. and 180° C. Higher temperatures are obtainable when propylene glycol is employed than is the case when ethylene glycol is employed.

A special advantage of this process is that it can be conducted at atmospheric pressure, under reflux. However, if desired, the contents may be heated in a closed system, whereby a slight pressure is built up, amounting however to not more than 15 to 20 pounds per square inch, and not necessitating the use of any special pressure equipment in the plant.

The invention is illustrated by the following examples without however limiting the same to them.

Example I

60 grams of sodium hydroxide flakes (95% NaOH) were dissolved in 500 grams of ethylene glycol in a 2 liter three-necked flask provided with stirrer and an air condenser. The contents were heated to 150° C.–160° C., this step requiring about 30 minutes. 144 grams of 1,2,4 5-tetrachloro benzene were rapidly added to the solution, and the mixture was heated to 170° C.–180° C. (inside temperature), and maintained at that temperature range for 4 hours. 10 grams of tetrachloro benzene sublimed in the air condenser and were recovered. A sample of the reaction mixture gave a clear solution when dissolved in 10 times its weight of water.

The reaction mixture was allowed to cool; dry hydrogen chloride was passed into it until it became acid to litmus. The slight excess of hydrogen chloride was neutralized by the addition of a small amount of sodium bicarbonate. After cooling again to about 20° C., the salt was filtered

by suction and the salt cake was washed with 50 cc. of isopropyl alcohol. 600 cc. of water were added to the filtrate resulting in a bottom layer of precipitated trichloro phenol and a top layer of dilute ethylene glycol. The entire mixture was extracted with 400 cc. of benzene, then with 100 cc. of benzene and finally with 80 cc. of benzene.

The combined benzene extracts were shaken with 200 cc. of water and the water layer was separated and added to the dilute ethylene glycol. The washed combined benzene extracts were dried by means of anhydrous sodium sulfate, filtered, and distilled. After removal of the benzene, the residue was distilled at a pressure of 4 mm. of mercury. 106 grams of 2,4,5-trichloro phenol, boiling at 101° C.–105° C., and having a congealing point of 63.3° C. (uncorrected), were obtained.

The ethylene glycol can be recovered by distillation of the aforementioned dilute ethylene glycol. The water and isopropyl alcohol were removed in a fractionating still at a pressure of 90 mm. of mercury, the temperature being carried up to 50° C. The ethylene glycol was then distilled under high vacuum (3 mm.), 232 grams of the glycol boiling at 80° C. being recovered. In order to remove practically all of the ethylene glycol from the small amount of salt remaining in the distilling flask, the temperature was raised so that some glycol, boiling from 80° C. to 120° C., was obtained.

Example II

72 grams of 1,2,4,5-tetrachloro benzene were stirred and heated to 190–200° C. with a solution of 30 grams of sodium hydroxide in 250 grams of propylene glycol, the heat treatment being conducted for 6 hours. 24 grams of concentrated sulfuric acid (93% H_2SO_4) were added to the reaction contents after they were cooled to room temperature (about 25° C.). The entire contents were poured into 1000 cc. of water. The solid material was then filtered and washed with 500 cc. of water and finally dissolved in 200 cc. of benzene. The benzene solution was dried with anhydrous sodium sulfate and then filtered.

After removal of the benzene by distillation, the residue was distilled under a high vacuum (5 mm.), 45 grams of 2,4,5-trichloro phenol being obtained thereby.

The foregoing illustrates the practice of this invention, which however, is not to be limited thereby but is to be construed as broadly as permissible in view of the prior art and limited solely by the appended claims.

We claim:

1. The process for preparing 2,4,5-trichlorophenol, which comprises heating at 160°–200° C. in the following proportions: 1 gram molecular weight of 1,2,4,5-tetrachloro benzene and at least 2 gram molecular weights of an alkali metal hydroxide in the presence of at least 450 grams of at least one material from the group consisting of ethylene glycol and propylene glycol, the reaction being conducted under a pressure within the range of that of the atmosphere up to 20 pounds per square inch and for a time sufficient to substantially complete the conversion into 2,4,5-trichlorophenol.

2. The process for preparing 2,4,5-trichlorophenol, which comprises heating at 160°–200° C. in the following proportions: 1 gram molecular weight of 1,2,4,5-tetrachloro benzene and at least 2 gram molecular weights of an alkali metal hydroxide in the presence of at least 450 grams of ethylene glycol, the reaction being conducted under a pressure within the range of that of the atmosphere up to 20 pounds per square inch and for a time sufficient to substantially complete the conversion into 2,4,5-trichlorophenol.

3. The process for preparing 2,4,5-trichlorophenol, which comprises heating at 160°–200° C. in the following proportions: 1 gram molecular weight of 1,2,4,5-tetrachloro benzene and at least 2 gram molecular weights of sodium hydroxide in the presence of at least 450 grams of ethylene glycol, the reaction being conducted under a pressure within the range of that of the atmosphere up to 20 pounds per square inch and for a time sufficient to substantially complete the conversion into 2,4,5-trichlorophenol.

4. The process for preparing 2,4,5-trichlorophenol, which comprises heating at 170°–180° C. in the following proportions: 1 gram molecular weight of 1,2,4,5-tetrachloro benzene and 2–3 gram molecular weights of sodium hydroxide in the presence of 750 grams of ethylene glycol, the reaction being conducted under atmospheric pressure and for a time sufficient to substantially complete the conversion into 2,4,5-trichlorophenol.

5. The process for preparing 2,4,5-trichlorophenol, which comprises heating at 170°–180° C. in the following proportions: 1 gram molecular weight of 1,2,4,5-tetrachloro benzene and 2–3 gram molecular weights of sodium hydroxide in the presence of 750 grams of propylene glycol, the reaction being conducted under atmospheric pressure and for a time sufficient to substantially complete the conversion into 2,4,5-trichlorophenol.

EDWARD JOSEPH NIKAWITZ.
WILLIAM S. GUMP.

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United States Patent [19]
Virgilio et al.

[11] 4,216,342
[45] Aug. 5, 1980

[54] PROCESS FOR THE PURIFICATION OF CRUDE 2,4,5-TRICHLOROPHENOL

[75] Inventors: Joseph A. Virgilio, Wayne; Joachim E. Freudewald, Morristown, both of N.J.

[73] Assignee: Givaudan Corporation, Clifton, N.J.

[21] Appl. No.: 25,419

[22] Filed: Mar. 30, 1979

[51] Int. Cl.² C07C 39/24
[52] U.S. Cl. 568/755; 568/776
[58] Field of Search 568/755, 725, 776, 727

[56] References Cited

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Primary Examiner—Werren B. Lone
Attorney, Agent, or Firm—Robert F. Tavares; Thomas Cifelli, Jr.

[57] ABSTRACT

A novel process for the purification of 2,4,5-trichlorophenol which comprises selectively reacting the major impurities with formaldehyde.

11 Claims, No Drawings

PROCESS FOR THE PURIFICATION OF CRUDE 2,4,5-TRICHLOROPHENOL

BACKGROUND OF THE INVENTION

The conventional industrial method for preparing 2,4,5-trichlorophenol involves the reaction of 1,2,4,5-tetrachlorobenzene with methyl alcoholic or aqueous methyl alcoholic sodium hydroxide. The crude product which is available commercially is about 94% 2,4,5-trichlorophenol and about six percent impurities which are primarily dichlorophenols and dichloromethoxyphenols.

The germacide known as Hexachlorophene ® (bis-[3,5,6-trichloro-2-hydroxyphenyl]methane), is prepared by condensing 2,4,5-trichlorophenol with formaldehyde. In order to get a germicide of high purity, it is desirable to start with a 2,4,5-trichlorophenol of high purity. Since the dichlorophenols and dichloromethoxyphenols present in the commercial grade 2,4,5-trichlorophenol will also react with formaldehyde, it is desirable to remove them prior to the condensation.

SUMMARY OF THE INVENTION

It is the surprising and unexpected finding of this invention that major impurities in the crude product (ca. 94% 2,4,5-trichlorophenol and ca. 5.5% dichlorophenols+dichloromethoxyphenols) can be reacted with formaldehyde under conditions wherein the undesired 5.5% of the impurities react to form condensation products, but the 2,4,5-trichlorophenol does not react to form Hexachlorophene. The unreacted 2,4,5-trichlorophenol can then be separated from the condensation products to provide 99.5% pure 2,4,5-trichlorophenol in high yield.

The critical parameters in this process appear to be the concentration of sulfuric acid, the reaction temperature and the time the reaction is allowed to run.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The method disclosed herein depends upon the ability to judiciously choose reaction conditions wherein the undesirable impurities will form condensation products with the formaldehyde while the 2,4,5-trichlorophenol will not.

The form of the formaldehyde is not critical. Formaldehyde added as a 37% aqueous solution or formaldehyde added as paraformaldehyde are both suitable.

The nature or amount of excess of the formaldehyde used does not appear to be critical. Although stoichiometry demands only one mole of formaldehyde for every two moles of phenolic impurity to be condensed, it is preferred to add an excess of several fold since the reagent is economical and an excess does not have a detrimental effect on the purification process.

An amount of formaldehyde greater than 1 mole per mole of impurity to be removed would be suitable with an amount of 2 to 5 moles/mole preferred. About 3 moles per mole is especially preferred.

The concentration of the sulfuric acid appears to be the most critical factor. When the sulfuric acid concentration is 50% or less, the yields of recovered 2,4,5-trichlorophenol were lower and the improvement in the purity was only marginal. When the concentration of sulfuric acid is 80% or greater, the 2,4,5-trichlorophenol reacts rapidly with the formaldehyde and the result is a lower recovery of 2,4,5-trichlorophenol and only a marginal, if any, improvement as to the purity of the recovered material.

By contrast, at sulfuric acid concentrations between 55% and 75% there is a surprising selectivity demonstrated with the formaldehyde reaction primarily with the dichlorophenol and methoxydichlorophenol impurities and not with the 2,4,5-trichlorophenol. It is preferred to work at the center of this range of concentrations, i.e. at concentrations of 60% to 70%.

The temperature range is less critical than the acid concentration, but should be carefully controlled to insure maximum recovery of high quality 2,4,5-trichlorophenol. Temperatures below 70° C. result in a sluggish reaction between the impurities to be removed and the formaldehyde resulting in a poorer grade of recovered 2,4,5-trichlorophenol.

At temperatures exceeding 90° C. the reaction appears to be less selective and lower yields of recovered 2,4,5-trichlorophenol are obtained. Temperatures in the range of 70° C. to 90° C. are, therefore, preferred. It is especially preferred to work in the middle of this range at temperatures of from 75° C. to 85° C.

The reaction should, of course, be run until all of the impurities to be removed have condensed with the formaldehyde. Under the preferred conditions, this normally occurs from five to eight hours. It is preferred however, to follow the reaction by a suitable analytical tool such as gas liquid chromatography.

The purified 2,4,5-trichlorophenol can be separated from the heavier condensation products by methods known in the art, i.e. by extraction and/or distillation.

A number of suitable extraction solvents will dissolve the trichlorophenol, but not the less soluble bis-phenols. Suitable for this purpose are the alkane solvents such as pentane, hexane, heptane and the like.

It is preferred to separate the lower boiling trichlorophenol from the higher boiling condensation products by a distillation, preferably a steam distillation or vacuum steam distillation.

ILLUSTRATION OF THE PREFERRED EMBODIMENTS

A number of examples are provided herein to illustrate the preferred embodiments of this invention. They are included for the purpose of illustration only and should not be construed as limiting. They are intended to embrace any equivalents or obvious extensions which are known or should be known to a person skilled in the art.

The purity of the 2,4,5-trichlorophenol was determined by vapor phase chromatography using a ¼ in. ×6 ft. stainless steel column packed with 4% FFAP on 100/120 mesh chromsorb W, acid washed, DMCS. A flame ionization detector was used.

The commercial technical grade 2,4,5-trichlorophenol that was purified in these examples was purchased from vendors who are in the business of manufacturing and selling this material and was analysed by gas liquid chromatography as follows:

2,4,5-Trichlorophenol	94.0 ± 0.2%
2,4/2,5-Dichlorophenol	1.0 ± 0.8%
2,3,6/2,4,6-Trichlorophenol	0.3 ± 0.3%
3,4-Dichlorophenol	0.1 ± 0.1%
4,5-Dichloro-2-methoxyphenol 2,5-Dichloro-4-methoxyphenol	4.6 ± 0.7%

-continued

2,4-Dichloro-5-methoxyphenol

The term technical grade TCP refers to a commercially available product similar to that described above and which is about 94% 2,4,5-trichlorophenol. This term (technical grade TCP) when used hereinafter refers to such a commercially available product.

EXAMPLE I

Sulfuric acid (903 grams of 93% H_2SO_4) was diluted by slowly adding it to cold water (347 g) which was cooled and stirred during the addition. Technical grade TCP was added and the reaction mixture heated to and subsequently maintained at 80° C.

Aqueous formaldehyde (14.0 g of a 37% solution) was added slowly over a period of four hours. The reaction mixture was maintained at 80° C. for an additional two hours.

The reaction mixture was diluted by adding about 600 ml water and the product isolated via a steam distillation.

There was obtained 206.5 g of 2,4,5-trichlorophenol which was 99.5% pure. This represents an 87.7% recovery of the 2,4,5-trichlorophenol in the starting material.

The purified product analysed as follows:

2,4,5-Trichlorophenol	99.5
2,4/2,5-Dichlorophenol	—
2,3,6/2,4,6-Trichlorophenol	0.3
3,4-Dichlorophenol	—
4,5-Dichloro-2-methoxyphenol 2,5-Dichloro-4-methoxyphenol 2,4-Dichloro-5-methoxyphenol	0.2

EXAMPLE II

Example I was repeated, substituting 5 g of paraformaldehyde for the 14 g of 37% aqueous formaldehyde. The paraformaldehyde was added portionwise over a 30 minute period.

Pure 2,4,5-trichlorophenol (200.9 g, 85.5% yield, 99.6% pure) was recovered.

EXAMPLE III

Example I was repeated excepting that 21 g of aqueous formaldehyde was used.

Pure 2,4,5-trichlorophenol (200.9 g, 85.5% yield, 99.7% pure) was recovered.

EXAMPLE IV

The process of Example II was repeated using a hot heptane extraction in place of the steam distillation.

There was 190.6 g of 2,4,5-trichlorophenol recovered (91.1% yield, 98.3% pure).

EXAMPLE V

Example I was repeated excepting that a temperature of 100° C. was used. There was 167.1 g of 2,4,5-trichlorophenol recovered (71.0% yield, 99.6% pure). This is considerably less than obtained in Example I illustrating the fact that temperatures in excess of 90° C. result in lower recovery of the desired product.

EXAMPLE VI

Example II was repeated excepting that a sulfuric acid concentration of 50% was used. Product recovered was only 96.2% pure. This illustrates the poor results obtained at low acid concentrations.

EXAMPLE VII

Example I was repeated and followed by gas liquid chromatography to illustrate the shorter reaction times result in a product of lower purity.

After 1 hr 94.7% pure 2,4,5-trichlorophenol recoverable.

After 2 hrs 95.1% pure 2,4,5-trichlorophenol recoverable.

After 4 hrs 98.7% pure 2,4,5-trichlorophenol recoverable.

After 6 hrs. 99.5% pure 2,4,5-trichlorophenol recoverable.

EXAMPLE VIII

Example I was repeated and the 2,4,5-trichlorophenol was recovered via a vacuum steam distillation.

There was recovered 208.0 g (88.5% yield, 99.3% pure).

EXAMPLE IX

Example I was repeated excepting that the concentration of the sulfuric acid used was 80%. The 2,4,5-trichlorophenol reacted with the formaldehyde to form a bis-phenol. This example illustrates the failure of the purification process if the concentration of acid gets too high.

We claim:

1. Process for the purification of technical grade TCP which comprises treating the technical grade TCP with formaldehyde in the presence of 55% to 75% sulfuric acid at a temperature between 70° C. and 90° C. and separating purified TCP therefrom.

2. A process according to claim 1 wherein the purified TCP is isolated by a distillation or an extraction.

3. A process according to claim 2 wherein the purified TCP is isolated by a steam distillation or a vacuum steam distillation.

4. A process according to claim 1 wherein 60–70% sulfuric acid is used.

5. A process according to claim 4 wherein the temperature is between 75° C. and 85° C.

6. A process according to claim 5 wherein the product is isolated by a distillation or an extraction.

7. A process according to claim 6 wherein the product is isolated by a distillation.

8. A process according to claim 1 wherein there is used:

(a) two to five molar equivalents of formaldehyde

(b) 60% to 70% sulfuric acid;

(c) a reaction temperature of 75° C. to 85° C.;

(d) a steam distillation or vacuum steam distillation for the isolation of the purified 2,4,5-trichlorophenol.

9. The process of claim 8 wherein the reaction time is 5 to 8 hours.

10. The process of claim 9 wherein aqueous formaldehyde is used.

11. The process of claim 9 wherein paraformaldehyde is used.

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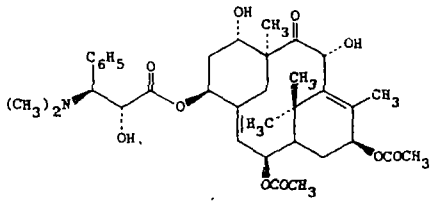
F. Manske, Ed. (Academic Press, New York, 1968) pp 597-626.

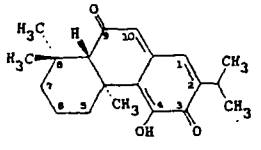


taxine A

Granular amorph powder, mp 121-124°. $[\alpha]_D^{17}$ +95.7° (c = 4.59 in ethanol). Sol in ether, chloroform, alcohol; practically insol in water, petr ether. Undoubtedly responsible for the poisonous properties of the yew. Fatalities among domestic animals due to yew poisoning are not uncommon today. : Human fatal symptoms are those of gastrointestinal irritation, cardiac and respiratory failure.

Taxine A, $C_{35}H_{47}NO_{10}$, mp 204-206°. $[\alpha]_D$ −140° ($CHCl_3$).

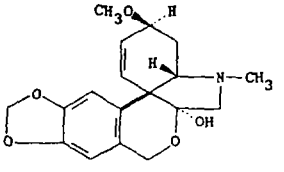
8955. Taxodione. *4b,5,6,7,8,8a-Hexahydro-4-hydroxy-4b,8,8-trimethyl-2-(1-methylethyl)-3,9-phenanthrenedione; 11-hydroxy-13-isopropylpodocarpa-7,9(11),13-triene-6,12-dione.* $C_{20}H_{26}O_3$; mol wt 314.43. C 76.40%, H 8.34%, O 15.26%. Isoln of naturally occurring (+)-form from *Taxodium distichum* Rich, *Taxodiaceae:* Kupchan *et al., J. Am. Chem. Soc.* **90,** 5923 (1968). Structure: *eidem, J. Org. Chem.* **34,** 3912 (1969). Total synthesis of the racemate: Mori, Matsui, *Tetrahedron* **26,** 3467 (1970); T. Matsumoto *et al., Bull. Chem. Soc. Japan* **44,** 2766 (1971); **50,** 1575 (1977); D. L. Snitman, R. J. Himmelsbach, *Tetrahedron Letters* **1979,** 2477; R. V. Stevens, G. S. Bisacchi, *J. Org. Chem.* **47,** 2396 (1982). Total synthesis of the (+)-form: T. Matsumoto *et al., Bull. Chem. Soc. Japan* **50,** 266 (1977). Antitumor activity studies: Hanson *et al., Science* **168,** 378 (1970).



Golden plates from methanol. mp 115-116°. $[\alpha]_D^{28}$ +56° (c = 1 in $CHCl_3$). uv max (methanol): 320, 332, 400 nm (ε 25,000, 26,000, 2000).

THERAP CAT: Antineoplastic.

8956. Tazettine. Sekisanine; sekisanoline; ungernine. $C_{18}H_{21}NO_5$; mol wt 331.26. C 65.24%, H 6.39%, N 4.23%, O 24.14%. From *Narcissus tazetta* L., *Lycoris radiata* Herb., *Ungernia sewerzowi* (Rgl.) Fedtsch., and other *Amaryllidaceae:* Späth, Kahovec, *Ber.* **67,** 1501 (1934). Structure and stereochemistry: Ikeda *et al., J. Chem. Soc.* **1956,** 4749. Abs config: Highet, Highet, *Tetrahedron Letters* **1966,** 4099. Synthesis: Hendrickson *et al., J. Am. Chem. Soc.* **92,** 5538 (1970); Tsuda *et al., Tetrahedron Letters* **1972,** 3153. Biosynthesis: Fales, Wildman, *J. Am. Chem. Soc.* **86,** 294 (1964). Identity with sekisanine and sekisanoline: Ikeda *et al., loc. cit.* Stereospecific total synthesis: Hendrickson *et al., J. Am. Chem. Soc.* **96,** 7781 (1974); S. Danishefsky *et al., ibid.* **102,** 2838 (1980); **104,** 7591 (1982).

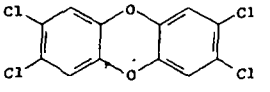


Crystals, mp 210-211° (evac tube); racemate reported as mp 237-238° (Tsuda) and mp 175-176° (Danishefsky). $[\alpha]_D^{25}$ +150.3° (82 mg in 2 ml chloroform). Sol in methanol, ethanol, choroform. Sparingly sol in ether.

Hydrochloride, crystals, mp 206°, water soluble.

Methiodide, crystals, dec 220° (evacuated tube).

8957. TCDD. *2,3,7,8-Tetrachlorodibenzo[b,e][1,4]dioxin; 2,3,7,8-tetrachlorodibenzo-p-dioxin;* 2,3,6,7-tetrachlorodibenzodioxin; dioxin; TCDBD. $C_{12}H_4Cl_4O_2$; mol wt 321.96. C 44.77%, H 1.25%, Cl 44.04%, O 9.94%. Highly toxic and teratogenic contaminant of 2,4,5-trichlorophenol and 2,4,5-T, *q.q.v.*, can be formed during the manufacture of trichlorophenol. Prepn by chlorination of dibenzo-*p*-dioxin: W. Sandermann, *Ber.* **90,** 690 (1957); M. Tomita *et al., Yakugaku Zasshi* **79,** 186 (1959), *C.A.* **53,** 13152d (1959); by condensation of potassium 2,4,5-trichlorophenate: *O. Aniline* in *Chlorodioxins—Origin and Fate,* E. H. Blair, Ed., *Advances in Chemistry Series* **120** (A.C.S., Washington, D.C., 1973) pp 126-135. Crystal structure: F. P. Boer *et al., Acta Crystallogr.* **28B,** 1023 (1972). Toxicity and metabolism studies: R. J. Kociba *et al., Toxicol. Appl. Pharmacol.* **35,** 553 (1976); J. Q. Rose *et al., ibid.* **36,** 209 (1976); A. Poland, A. Kende, *Fed. Proc.* **35,** 2404 (1976). Environmental degradation: D. G. Crosby, A. S. Wong, *Science* **195,** 1337 (1976). Review of carcinogenicity studies: *IARC Monographs* **15,** 41-102 (1977). Comprehensive reviews of formation, chemistry, and toxic and environmental effects: *Chlorodioxins—Origin and Fate,* E. H. Blair, Ed., *loc. cit.* 141 pp; *Environ. Health Perspect.* **5,** 313 pp (1973); R. D. Kimbrough, *Crit. Rev. Toxicol.* **2,** 445-498 (1974); A. Poland, J. C. Knutson, *Ann. Rev. Pharmacol. Toxicol.* **22,** 517-554 (1982). *See also: Dioxin—Toxicological and Chemical Aspects,* F. Cattabeni *et al.,* Eds. (Wiley, New York, 1978) 222 pp; special issue, *Chem. & Eng. News* **61** (June 6, 1983).



Needles, mp 295° (Tomita); crystals from anisole, mp 320-325° (Sandermann). LD_{50} orally in male, female rats (mg/kg): 0.022, 0.045, B. A. Schwetz *et al.* in *Chlorodioxin—Origin and Fate, loc. cit.* pp 55-69.

Note: An industrial accident during the manufacture of 2,4,5-trichlorophenol in Seveso, Italy on July 10, 1976 caused the release of an estimated two to ten pounds of TCDD into the environment. Concentrations as high as 51.3 ppm TCDD were found in some samples: R. Rawls, D. A. O'Sullivan, *Chem. & Eng. News* **54,** 27 (Aug. 23, 1976); A. Hay, *Nature* **262,** 636 (1976).

TCDD, as a contaminant created in the manufacture of *Agent Orange,* a widely used defoliant in Vietnam during the 1960's, has also been implicated as the causative agent of various symptoms described by veterans exposed to the defoliant, *see* C. Holden, *Science* **205,** 770 (1979).

Caution: Extremely potent, low molecular weight toxin. Toxic effects in animals include anorexia, severe weight loss, hepatotoxicity, hepatoporphyria, vascular lesions, chloracne, gastric ulcers, teratogenicity and delayed death. Industrial workers exposed to TCDD have developed chloracne, porphyrinuria and porphyria cutanea tarda. *See* Poland, Kende, *loc. cit.*, C. D. Carter *et al., Science* **188,** 738 (1975). This substance has been listed as a carcinogen by the EPA: *Second Annual Report on Carcinogens* (NTP 81-43, Dec. 1981) pp 226-227.

8958. Technetium. Tc; at. wt (longest-lived isotope) 98; at. no. 43. Usual valences 4 and 7. Trivalent Tc less common. Radioactive element. Discovery claimed by Noddack, Tacke, and Berg who called it "masurium"; the existence of masurium has never been confirmed by isoln of the element. Element no. 43 is the first artificially produced element. Named from the Greek word for "artificial"; separated from a molybdenum plate that had been bombarded for a few months with a strong beam of deuterons in the Berkeley cyclotron: Perrier, Segré, *Nature* **140,** 193 (1937); *eidem, J. Chem. Phys.* **5,** 712 (1937); Cacciapuoti, Segré, *Phys. Rev.* **52,** 1252 (1937). The most commonly available isotope, ^{99}Tc,

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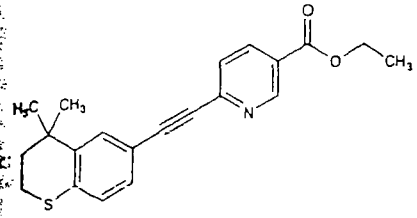
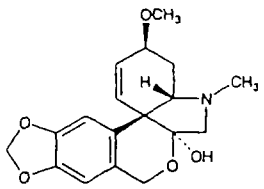


...te solid.

THERAP CAT: Antiacne; antipsoriatic.

9250. Tazettine. Sekisanine; sekisanoline; ungernine. ...NO_5; mol wt 331.37. C 65.24%, H 6.39%, N 4.23%, ...4%. From *Narcissus tazetta* L., *Lycoris radiata* Herb., ...*sewerzowi* (Rgl.) Fedtsch., and other *Amaryllida-* ...Späth, Kahovec, *Ber.* 67, 1501 (1934). Structure and ...chemistry: Ikeda *et al., J. Chem. Soc.* **1956**, 4749; ...ofig: Highet, Highet, *Tetrahedron Letters* **1966**, ...Synthesis: Hendrickson *et al., J. Am. Chem. Soc.* **92**, ...(1970); Tsuda *et al., Tetrahedron Letters* **1972**, 3153. ...thesis: Fales, Wildman, *J. Am. Chem. Soc.* **86**, 294 ...): Identity with sekisanine and sekisanoline: Ikeda *et* ...*cit.* Stereospecific total synthesis: Hendrickson *et* ...*Am. Chem. Soc.* **96**, 7781 (1974); S. Danishefsky *et al.*, ...**102**, 2838 (1980); **104**, 7591 (1982).

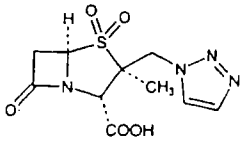


...stals, mp 210-211° (evac tube); racemate reported as ...7,238° (Tsuda) and mp 175-176° (Danishefsky). $[\alpha]_D^{25}$ ...(82 mg in 2 ml chloroform). Sol in methanol, ...choroform. Sparingly sol in ether.

...trochloride, crystals, mp 206°, water soluble.

...iodide, crystals, dec 220° (evacuated tube).

9251. Tazobactam. *[2S-(2α,3β,5α)]-3-Methyl-7-oxo-3-(1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]heptanecarboxylic acid 4,4-dioxide;* 2β-[(1,2,3-triazol-1-yl)-methyl]-2α-methylpenam-3α-carboxylic acid 1,1-dioxide; ...30H; CL-298741. $C_{10}H_{12}N_4O_5S$; mol wt 300.30. C ...H 4.03%, N 18.66%, O 26.64%, S 10.68%. β-Lac-...inhibitor. Prepn: R. G. Micetich *et al.*, Eur. pat. ...7,446; *eidem*, U.S. pat. 4,562,073 (1984, 1985 both ...); R. G. Micetich *et al., J. Med. Chem.* **30**, 1469 ...Degradation in solution: T. Marunaka *et al., Chem. Bull.* **36**, 4478 (1988); in solid state: E. Matsushima *ibid.* 4593. β-Lactamase inhibiting activity in com-...with clavulanic acid and sulbactam, *q.q.v.*, vs aer-...: R. Jacobs *et al., Antimicrob. Ag. Chemother.* **29**, ...86); vs anaerobes: P. C. Appelbaum *et al., ibid.* **30**, ...HPLC determn in biological materials: T. Marunaka ...*Chromatog.* **431**, 87 (1988). Clinical trial in combi-...with piperacillin, *q.v.*: I. M. Gould *et al., Drugs Exp. Clin.* **17**, 187 (1991).

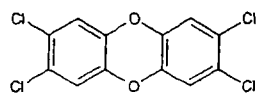


...um salt, $C_{10}H_{11}N_4NaO_5S$. *YTR-830, CL-307579.* ...bous solid, mp > 170° (dec).

...bination of sodium salt with piperacillin sodium. ...*line, Tazocin, Zosyn.*

THERAP CAT: In combination with β-lactam antibiotics as antibacterial.

9252. TCDD. *2,3,7,8-Tetrachlorodibenzo[b,e][1,4]dioxin; 2,3,7,8-tetrachlorodibenzo-p-dioxin;* 2,3,6,7-tetrachlorodibenzodioxin; dioxin; TCDBD. $C_{12}H_4Cl_4O_2$; mol wt 321.97. C 44.77%, H 1.25%, Cl 44.04%, O 9.94%. Highly toxic contaminant; produced as a by-product during the manuf of chlorinated phenols (2,4,5-trichlorophenol, *q.v.*) and phenoxyherbicides (2,4-D and 2,4,5-T, *q.q.v.*), chlorine bleaching of paper pulp and combustion of chlorine-containing waste. Prepn: W. Sandermann, *Ber.* 90, 690 (1957); M. Tomita *et al., Yakugaku Zasshi* 79, 186 (1959), *C.A.* 53, 13152d (1959). Crystal structure: F. P. Boer *et al., Acta Crystallogr.* **28B**, 1023 (1972). Toxicity and metabolism: B. A. Schwetz *et al.*, in *Chlorodioxins-Origin and Fate*, E. H. Blair, Ed., *Advances in Chemistry Series* **120** (A.C.S., Washington, D.C., 1973) pp 55-69; A. Poland, A. Kende, *Fed. Proc.* **35**, 2404 (1976). Environmental degradation: D. G. Crosby, A. S. Wong, *Science* **195**, 1337 (1976). Comprehensive review of formation, chemistry, and toxic and environmental effects: *Chlorodioxins—Origin and Fate, loc. cit.* 141 pp; *Dioxin—Toxicological and Chemical Aspects*, F. Cattabeni *et al.*, Eds. (Wiley, New York, 1978) 222 pp; special issue, *Chem. & Eng. News* **61** (June 6, 1983). Review of toxicology and human exposure: *Toxicological Profile for 2,3,7,8-Tetradichlorodibenzo-p-dioxin* (PB89-214522, 1989) 135 pp; of receptor binding and mechanism of toxicity: J. P. Whitlock, Jr., *Ann. Rev. Pharmacol. Toxicol.* **30**, 251-277 (1990); of epidemiological data: L. Tollefson, *Regul. Toxicol. Pharmacol.* **13**, 150-169 (1991); of carcinogenicity: J. Huff *et al., Ann. Rev. Pharmacol. Toxicol.* **34**, 343-372 (1994).



Needles, mp 295° (Tomita); crystals from anisole, mp 320-325° (Sandermann). LD_{50} in male, female rats (mg/kg): 0.022, 0.045 orally (Schwetz).

Note: An industrial accident during the manufacture of 2,4,5-trichlorophenol in Seveso, Italy on July 10, 1976 caused the release of an estimated two to ten pounds of TCDD into the environment. Concentrations as high as 51.3 ppm TCDD were found in some samples: R. Rawls, D. A. O'Sullivan, *Chem. & Eng. News* **54**, 27 (Aug. 23, 1976); A. Hay, *Nature* **262**, 636 (1976).

TCDD, as a contaminant created in the manufacture of *Agent Orange*, a widely used defoliant in Vietnam during the 1960's, has also been implicated as the causative agent of various symptoms described by veterans exposed to the defoliant, *see* C. Holden, *Science* **205**, 770 (1979).

Caution: Toxic effects in animals include the wasting syndrome, gastric ulcers, immunotoxicity, hepatotoxicity, hepatoporphyria, vascular lesions, chloracne, teratogenicity, fetotoxicity, impaired reproductive performance, endometriosis and delayed death. Industrial workers exposed to TCDD have developed chloracne, porphyrinuria and porphyria cutanea tarda. *See* Poland, Kende, *loc. cit.*; C. D. Carter *et al., Science* **188**, 738 (1975). This substance may reasonably be anticipated to be a carcinogen: *Seventh Annual Report on Carcinogens* (PB95-109781, 1994) p 369.

9253. Tebuconazole. *(±)-α-[2-(4-Chlorophenyl)ethyl]-α-(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol; (RS)*-1-(4-chlorophenyl)-4,4-dimethyl-3-(1*H*-1,2,4-triazol-1-ylmethyl)-pentan-3-ol; ethyltrianol; fenetrazole; terbuconazole; terbutrazole; BAY HWG 1608; HWG-1608; Corail; Elite; Folicur; Horizon; Lynx; Raxil; Silvacur. $C_{16}H_{22}ClN_3O$; mol wt 307.82. C 62.43%, H 7.20%, Cl 11.52%, N 13.65%, O 5.20%. Ergosterol biosynthesis inhibitor. Prepn: G. Holmwood *et al.*, Eur. pat. Appl. 40,345; *eidem*, U.S. pat. 4,723,-984 (1981, 1988 both to Bayer). Synthesis of enantiomers: J. Kaulen, *Agnew. Chem. Int. Ed. Engl.* **28**, 462 (1989). Photodegradation: H. Wamhoff *et al., Z. Naturforsch.* **49b**, 280 (1994). GC determn in plant material, soil and water: W. Maasfeld, *Pflanzenschutz-Nachr. Bayer (Eng. Ed.)* **40**, 29 (1987). Review of chemistry and biochemistry: D. Berg *et*

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U.S. PHARMACOPEIA

The Standard of Quality SM

PLAINTIFF'S EXHIBIT 2 CLERK - 2/10/03

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Rockville, MD 20852
Tel: (800) 227-8772 or (301) 881-0666
Fax: (301) 816-8148
Web: www.usp.org
E-mail: custsvc@usp.org

Vital Statistics

Year Founded: 1820

Who We Are

USP IS AN INDEPENDENT, NON-GOVERNMENT, not-for-profit organization that promotes the public health by establishing state-of-the art standards and developing programs to ensure the quality of medicines and related healthcare technologies and practices.

A unique process of public involvement is central to USP's public health work and stewardship. Equally significant are the vital contributions of volunteers representing pharmacy, medicine, and other healthcare professions, as well as science, academia, the U.S. government, the pharmaceutical industry, and other consumer organizations.

Major Markets

USP STANDARDS ARE KNOWN WORLDWIDE as an assurance of high quality.

Services Offered

USP–NF: The United States Pharmacopeia–National Formulary (USP–NF) is the FDA-recognized source for standards of identity, strength, quality, and purity for drug substances, dosage forms, excipients, and dietary supplements; tests and assays; and more. The latest annual edition, USP 26–NF 21, becomes official on January 1, 2003. USP–NF is available in print, online, intranet, and CD formats.

Reference Standards: USP Reference Standards are highly characterized specimens of drug substances, excipients, major impurities, degradation products, and performance calibrators. They are provided for use in compendial methodology. USP Reference Standards are established through an extensive process of collaborative laboratory testing among USP, FDA, and the pharmaceutical industry.

Pharmacopeial Forum: USP's Pharmacopeial Forum (PF) and PF Online complement USP–NF. PF and PF Online feature proposed revisions to USP–NF, as well as revisions that become official and binding before the next USP–NF edition is published. PF and PF Online also request public review and comment on proposed revisions.

Pharmacopeial Education: USP's Pharmacopeial Education program helps pharmaceutical professionals better understand and apply official USP–NF standards and test methods required for quality control and product release testing. Courses also help companies meet GMP and ISO training requirements.

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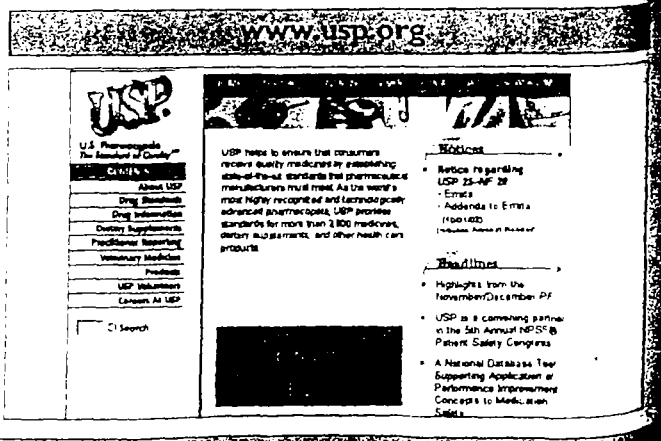
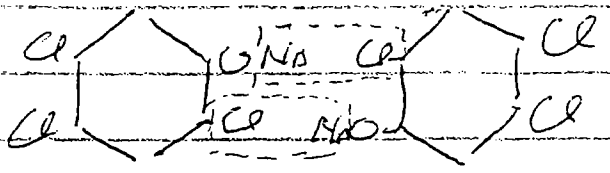
Medmarx Patient Safety Solutions: USP's Medmarx is a national medication error reporting database and system for data analysis designed to improve patient safety and reduce costs. More than 500 hospitals and health care organizations have enrolled and collectively have submitted over 300,000 anonymous medication error records, making it the largest database of its kind.

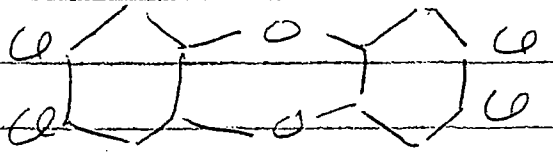


PLAINTIFF'S EXHIBIT 21 CLEARY-2/10/03

Notes

One doesn't need any chemistry to visualize how TCDD is formed when TCP, as its Sodium salt, is subjected to high temperature, >150°C





TCDD

In the course of producing TCP from TCB, TCDD is formed to the extent of about 15-25 ppm in the TCP.

TCPAA (2,4,5-T) the herbicide used in "Agent Orange" was introduced into general use in the 50's, heavily used for controling brush along Roadways. It was made (from crude TCP such as purchased by Metro-Atlantic) by the millions of pounds, by Monsanto, Dow, Thompson Chem (St. Louis) and Diamond Alkali, among others.

The only "pure" TCP being

produced was by Hooker Chem. Co. of Niagara Falls who sold it exclusively to Givaudan for the production of Hexachlorophene. Hooker's waste went into "Love Canal"

All of the 2,4,5-T acquired for "Agent Orange" was made directly from the same solution form of crude TCP shipped to Centredale.

I have included herein several pages copied from Merck Index, Vol. XII which will help to elucidate the relationships among TCB, TCP, 2,4,5-T and TCDD.

TCB = 1,2,4,5-Tetrachlorobenzene
TCP = 2,4,5-Trichlorophenol
2,4,5-T = 2,4,5-Trichlorophenoxy-acetic Acid
TCDD = Dioxin*

*There are numerous other "Dioxins", this one being, purportedly, far more toxic than the others

Action/Use
ACTION: Volatile insecticide in controlled release strip formulation. Acts by fumigant action on trapped insects. Inner reservoir automatically replenishes the insecticide to maintain effective concentration in traps.
USE: For insect monitoring and mass trapping programs for control of boll weevil, codling moth, gypsy moth, spruce budworm, forest tent caterpillar, Mediterranean fruit fly, Oriental fruit fly, southwestern corn borer, and sweetpotato weevil. Used in conjunction with insect attractants to kill trapped insects. Increases trap and monitoring efficiency by reducing the number of escapees before and during counts; especially effective in non-sticky traps.
Safety Guidelines
SIGNAL WORD: CAUTION.
TOXICITY CLASS: III.
HANDLING AND STORAGE CAUTIONS: Do not open pouch until ready to use. Keep out of reach of children. Avoid contact with eyes, skin, and clothing. Always wash hands with soap and water after handling.
Emergency Guidelines
FIRE EXTINGUISHING MEDIA: CO_2, powder, foam. Use self-contained breathing apparatus.
ANTIDOTE: Atropine sulfate and 2-PAM.
FIRST AID: Get immediate medical aid. Eyes, wash with water for at least 15 minutes. Skin, wash with soap and water; remove contaminated clothing. Ingestion, induce vomiting. Inhalation, remove from exposure. Give oxygen if breathing labored.
EMERGENCY TELEPHONE: 717-764-1191 (Hercon Environmental Corp.).

Hercules 7531 — see Herban*.
Hercules 9573 — see Azak*.
Hercules 14503 — see Torak*.
Hercules AC 528 — see Dioxathion.
Hercules AC 5727 — see UC 10854.
Heritage* — see Azoxystrobin.
Herkol* — see Dichlorvos.

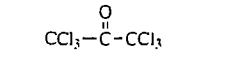
HETP

Chemistry
COMPOSITION: Ethyl polyphosphates containing 12-20% tetraethyl pyrophosphate. Also known as hexa-ethyl tetraphosphate.
Action/Use
ACTION: Insecticide.
USE: TEPP is the insecticidal component of HETP, and is the material now in production.
Safety Guidelines
HANDLING AND STORAGE CAUTIONS: HETP acts as a contact poison and hydrolyzes rapidly in aqueous solution. Therefore, sprays should be applied immediately after mixing. Absorbed rapidly through the skin of warm-blooded animals and inhalation of the vapors also may be dangerous. Possesses no phytotoxicity at normal concentrations.
See TEPP.

Hexablanc* Insecticide (BHC) — Discontinued by Rhone-Poulenc.

Hexachloroacetone

Identification
COMMON NAME: Hexachloroacetone (ISO); HCA (WSSA).
CODE NUMBERS: CAS 116-16-5; SHA 043701.
Chemistry
COMPOSITION: 1,1,1,3,3,3-hexachloro-2-propanone (CAS 8 and 9CI).



Hexachloroacetone

Action/Use
ACTION: Nonselective herbicide.
Safety Guidelines
SIGNAL WORD: CAUTION.
TOXICITY CLASS: III.
TOXICITY: (Rat): Oral LD_{50} 3550 mg/kg.

Hexachlorobenzene

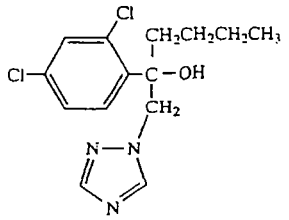
Identification
COMMON NAME: Hexachlorobenzene (ISO, BSI).
TRIVIAL NAME: HCB.
CODE NUMBERS: CAS 118-74-1; SHA 061001.
FORMULATORS' TRADE NAMES: No Bunt*.
DISCONTINUED NAMES: Anticarie*, Ceku C.B.* (Cequisa); Granero* (Atanor S.A.); Res-Q* (+ maneb + captan) (PBI/Gordon).
Chemistry
COMPOSITION: Hexachlorobenzene (IUPAC and CAS).
Action/Use
ACTION: Seed protectant.
Safety Guidelines
SIGNAL WORD: CAUTION.
TOXICITY CLASS: IV.
TOXICITY: (Rat): Oral LD_{50} 40,000 mg/kg. May cause slight irritation to skin.
Emergency Guidelines
FIRST AID: Get immediate medical aid. Ingestion, induce vomiting with warm salt water or syrup of Ipecac. Note: Some physicians may discourage use of saline emesis.

Hexachlorophene

Identification
COMMON NAME: Hexachlorophene (INN, USP, USAN); hexachlorophane (BAN).
EXP. CODE NUMBERS: G-11.
OTHER CODE NUMBERS: CAS 70-30-4; SHA 044901.
FORMULATORS' TRADE NAMES: Seribak*.
DISCONTINUED NAMES: Hexalint*, Hexaphene* L.V., Hexide*, Isobac*, Nabac* (Webb Wright Corp.).
Chemistry
COMPOSITION: 2,2'-methylenebis(3,4,6-trichlorophenol) (IUPAC).
Action/Use
ACTION: Broad spectrum contact soil, foliar fungicide.
Environmental Guidelines
HAZARDS: Bird: 575 mg/kg (bobwhite quail); 1450 mg/kg (mallard, female).
Safety Guidelines
SIGNAL WORD: CAUTION.
TOXICITY CLASS: III.
TOXICITY: (Rat): Oral LD_{50} 560 mg/kg.
HANDLING AND STORAGE CAUTIONS: May be fatal if swallowed. Do not get in eyes or on skin. Do not breathe spray mist.
Emergency Guidelines
FIRST AID: Get immediate medical aid. Eyes, flush with water. Skin, wash with soap and water. Ingestion, induce vomiting with warm salt water or syrup of Ipecac. Note: Some physicians may discourage use of saline emesis.

Hexaconazole

BP: Rallis India Ltd. (Contaf*)
ZENECA Agrochemicals (Anvil*, Planete Aster*)
Identification
COMMON NAME: Hexaconazole (ISO draft, ANSI, BSI).
CODE NUMBERS: CAS 79983-71-4.
FORMULATORS' TRADE NAMES: Canvil* (VAPCO).
Chemistry
COMPOSITION: (RS)-2-(2,4-dichlorophenyl)-1-(IH-1,2,4-triazol-1-yl)-hexan-2-ol (IUPAC).
PROPERTIES: White crystalline solid with no odor. Melting point 111°C. Soluble in a range of organic solvents.



Hexaconazole

Action/Use
ACTION: Fungicide.
USE: Controls powdery mildews, scabs and rusts of vines, pome fruits, vegetables, and major diseases of small grain cereals.
FORMULATIONS: Oil miscible liquid, soluble grain, suspension concentrate.
PREMIXES: Various Planete* premixes (+ carbendazim or chlorothalonil or fenpropidin) (ZENECA Agrochemicals).
Environmental Guidelines
SOLUBILITY: Low solubility in water.
Safety Guidelines
SIGNAL WORD: CAUTION.
TOXICITY CLASS: IV.
TOXICITY: (Rat): Oral LD_{50} 6071 mg/kg (female).
PROTECTIVE CLOTHING: Protective gloves and eye protection when handling concentrate.
HANDLING AND STORAGE CAUTIONS: Refer to individual formulations.

Hexadienyl Isobutyrate

BP: Agri-Pharm de Mexico, S.A. de C.V.

HESPERIDIN
- ACTA PHARMACAL
- ● ASHLAND CHEMICAL COMPANY
- DNP INTERNATIONAL CO., INC.
- FREEMAN INDUSTRIES, L.L.C.
- KADEN BIOCHEMICALS GMBH
- KINGCHEM INC.
- MAYPRO INDUSTRIES, INC.
- Pharmline, Inc.
- STAUBER PERFORMANCE INGREDIENTS, INC.
- F. H. Taussig, Inc.
- P.L. Thomas & Co., Inc.

HESPERIDIN COMPLEX
- ARROW CHEMICAL INC.
- ● ASHLAND CHEMICAL COMPANY
- Belmont Chemicals Inc.
- ● BOTANICALS INTERNATIONAL, INC., DIV. OF ZUELLIG BOTANICALS, INC.
- CPB INTERNATIONAL, INC.
- FREEMAN INDUSTRIES, L.L.C.
- GENERICHEM CORP.
- H. INTERDONATI, INC.
- RIA International
- SELTZER CHEMICALS, INC.
- STAUBER PERFORMANCE INGREDIENTS, INC.

HESPERIDIN METHYL CHALCONE
- FREEMAN INDUSTRIES, L.L.C.

HEXABROMOCYCLODODECANE
- AMERIBROM INC.
- ★ BERJE INC.

1,2,5,6,9,10-HEXABROMOCYCLODODECANE
- ALBEMARLE CORP. (FORMERLY ETHYL CHEMICALS GROUP)
- Great Lakes Chemical Corp.

HEXACHLOROACETONE *See Hexachloro-2-Propanone*

HEXACHLORO CYCLOPENTADIENE
- VELSICOL CHEMICAL CORP.

HEXACHLOROCYCLOTRIPHOSPHAZENE
- ESPRIT CHEMICAL CO.

HEXACHLOROETHANE
- FABRICHEM, INC.
- HUMMEL CROTON INC.
- Neuchem Inc.
- Service Chemical, Inc.
- Skyline International

HEXACHLOROPHENE
- International Commodities Export Corp.
- ● SPECTRUM BULK CHEMICALS, DIVISION OF SPECTRUM QUALITY PRODUCTS, INC.

HEXACHLOROPHENE, DIOXIN-FREE
- Inchema, Inc.

HEXACHLORO-2-PROPANONE (Hexachloroacetone)
- WACKER CHEMICALS (USA), INC.
- WACKER-CHEMIE GMBH

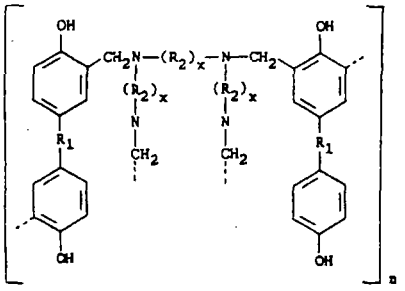
1H,1H,9H-HEXADECAFLUORO-1-NONANOL
- OAKWOOD PRODUCTS

n-HEXADECANE
- ● SPECTRUM BULK CHEMICALS, DIVISION OF SPECTRUM QUALITY PRODUCTS, INC.

HEXADECANEDIOIC ACID
- ● SPECTRUM BULK CHEMICALS, DIVISION OF SPECTRUM QUALITY PRODUCTS, INC.

THERAP CAT: Poloxamer 182LF as pharmaceutic aid; 188 as cathartic.

7433. Polyamine-Methylene Resin. Resinat; Exorbin. Phenol condensation product with polyamines. An ion-exchange resin specially purified for medicinal use.



Light amber, granular, free-flowing powder. Insol in water, alcohol, ether, aq solns of acids and alkalies. Under the conditions of the old N.N.R. assay for acid-consuming capacity, not less than 50 ml 0.1 *N* hydrochloric acid is consumed by 0.2 g of the resin.

THERAP CAT: Antacid.

7434. Polybasite. $8Ag_2S.Sb_2S_3$—silver antimony sulfide.

7435. Polybenzarsol. *(4-Hydroxyphenyl)arsonic acid polymer with formaldehyde;* Benzodol. A polymeric mixture obtained by adding formaldehyde (40%) (0.116 mole) over a 3-hr period to *p*-hydroxybenzenearsonic acid (0.209 mole) in 180 g of 90% H_2SO_4 at 0-5° and keeping it cold for 21 hrs. Dilution of the mixture with H_2O precipitates the product: Faith, *J. Am. Chem. Soc.* **72**, 837 (1950). Description: Jones *et al., Antibiot. & Chemother.* **8**, 400 (1958).

White powder. Somewhat sol in water; sol in alcoholic NaOH. LD_{50} i.p. in mice: 235 mg/kg. No deaths after 4 g/kg i.g. in mice.

THERAP CAT: Antiprotozoal.

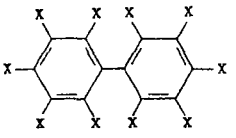
7436. Polybrominated Biphenyls. PBB's; brominated biphenyls; polybromobiphenyls. Mixtures with structures similar to polychlorinated biphenyls, *q.v.*, where each X = H or Br. Once widely used commercially. Prepn: H. Hahn *et al.*, Ger. pat. **1,161,547** (1964 to Chem. Fabrik Kalb); G. A. Burk, U.S. pat. **3,733,366** (1973 to Dow); L. C. Mitchell, D. R. Breckenridge, U.S. pats. **3,763,248** and **3,833,674** (1973, 1974 both to Ethyl Corp.). Persistence in soils: L. W. Jacobs *et al., J. Agr. Food Chem.* **24**, 1198 (1976). Photodegradation: L. O. Ruzo *et al., ibid.* 1062. Review of environmental hazards: K. Kay, *Environ. Res.* **13**, 74-93 (1977); F. J. DiCarlo *et al., Environ. Health Perspect.* **23**, 351-365 (1978).

Firemaster BP-6, major component is *2,2',4,4',5,5'-hexabromobiphenyl.* Softens at 72°, dec above 300°. Low vapor press; degraded by uv light. Very sol in benzene, toluene; insol in water.

Note: The 1973 "Michigan Incident" in which BP-6 was accidentally added to animal feed, and resulted in widespread destruction of contaminated farm animals, led to the removal of BP-6 from the market: L. J. Carter, *Science* 192, 240 (1976).

USE: Flame retardant.

7437. Polychlorinated Biphenyls. PCBs; chlorinated biphenyls; chlorobiphenyls; Aroclor; Clophen; Fenclor; Kanechlor; Phenoclor; Pyralene; Santotherm. Once widely used industrial chemicals whose high stability contributed to both their commercial usefulness and their long-term deleterious environmental and health effects. Early synthesis: H. Schmidt, G. Schulz, *Ann.* 207, 338 (1881). Commercially available since 1930: C. Penning, *Ind. Eng. Chem.* **22**, 1180 (1930). Commercial PCBs are mixtures. The Aroclors are characterized by four digit numbers. The first two digits indicate that the mixture contains biphenyls (12), triphenyls (54) or both (25, 44); the last two digits give the weight percent of chlorine in the mixture (e.g. Aroclor 1242 contains biphenyls with approx 42% chlorine). Reviews of environmental impact and toxicity: L. Fishbein, *Ann. Rev. Pharmacol.* **14**, 139-156 (1974); R. D. Kimbrough, *CRC Crit. Rev. Toxicol.* **2**, 445-498 (1974); *National Conference on Polychlorinated Biphenyls,* Nov. 19-21, 1975 (EPA-560/6-75-004, 1976) 487 pp. Accumulation of airborne PCBs in foliage: E. H. Buckley, *Science* **216**, 520 (1982). *Reviews:* H. L. Hubbard in *Kirk-Othmer Encyclopedia of Chemical Technology* vol. 5 (Interscience, New York, 2nd ed., 1964) pp 289-297; O. Hutzinger *et al., The Chemistry of PCB's* (CRC Press, Cleveland, Ohio, 1974) 269 pp; J. W. Lloyd *et al., J. Occup. Med.* **18**, 109-113 (1976). Review of carcinogenicity studies: *IARC Monographs* **18**, 43-103 (1978).



X = H or Cl

Aroclor 1242, clear, mobile liquid; av. number Cl/molecule: 3.10. d_4^{25} 1.381, $d_4^{15.5}$ 1.392. Distillation range 325-366°. Flash point (open cup) 348-356°F. n_D^{20} 1.627-1.629. Dielectric constant (1000 cycles) 5.6 (25°), 4.9 (100°).

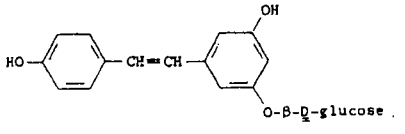
Aroclor 1254, light yellow, viscous liquid; av. number Cl/molecule: 4.96. d_4^{65} 1.495; $d_4^{15.5}$ 1.505. Distillation range 365-390°. No open cup flash point to boiling. n_D^{20} 1.629-1.641. Dielectric constant (1000 cycles) 5.0 (25°), 4.3 (100°). LD_{50} orally in weanling rats: 1295 mg/kg, Kimbrough, *loc. cit.*

Aroclor 1260, light yellow, soft, sticky resin; av. number Cl/molecule: 6.30. d_4^{90} 1.555; $d_4^{15.5}$ 1.566. Distillation range 385-420. No open cup flash point to boiling. n_D^{20} 1.647-1.649. Dielectric constant (1000 cycles) 4.3 (25°); 3.7 (100°). LD_{50} orally in weanling rats: 1315 mg/kg, Kimbrough, *loc. cit.*

Caution: Toxic effects in humans include chloracne, pigmentation of skin and nails, excessive eye discharge, swelling of eyelids, distinctive hair follicles, gastrointestinal disturbances. In Japan, accidental contamination of rice bran oil with Kanneclor 400 led to an outbreak of what became known as "Yusho disease", *see* M. Kuratsune *et al., in* EPA-560/6-75-004, *loc. cit.*, p 14. Toxic symptoms in animals include hepatocellular carcinoma, hypertrophy of the liver, adenofibrosis, weight and hair loss, mouth and eyelid edema, acneform lesions, decreased hemoglobin + hematocrit, gastric mucosal ulceration and reduced ability to reproduce. These substances have been listed as carcinogens by the EPA: *Second Annual Report on Carcinogens* (NTP 81-43, Dec. 1981) pp 206-209.

USE: In electrical capacitors, electrical transformers, vacuum pumps, gas-transmission turbines. Formerly used in U.S. as hydraulic fluids, plasticizers, adhesives, fire retardants, wax extenders, dedusting agents, pesticide extenders, inks, lubricants, cutting oils, in heat transfer systems, carbonless reproducing paper.

7438. Polydatin. *3-Hydroxy-5-[2-(4-hydroxyphenyl)ethenyl]phenyl-β-D-glucopyranoside; 3-hydroxy-5-(p-hydroxystyryl)phenyl glucoside;* 3,4',5-trihydroxystilbene-3-β-D-glucoside; resveratrol-3-β-mono-D-glucoside; piceid. $C_{20}H_{22}O_8$; mol wt 390.40. C 61.53%, H 5.68%, O 32.79%. Isoln from fresh root of *Polygonum cuspidatum* Sieb. & Zucc., *Polygonaceae,* and structure: Nonomura *et al., Yakugaku Zasshi* **83**, 988 (1963).



Trihydrate, crystals, mp 225-226°. $[\alpha]_D^{17}$ −74.9° (c = 1.709 in ethanol).

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9450. 1,1,2-Trichloroethane. *Vinyl trichloride.* $C_2H_3Cl_3$; mol wt 133.42. C 18.00%, H 2.27%, Cl 79.73%. CH_2Cl-$CHCl_2$. Prepd by catalytic chlorination of ethane or ethylene: Joseph, U.S. pat. **2,752,401** and Pye, U.S. pat. **2,752,402** (both 1956 to Dow); Reynolds, U.S. pat. **2,783,286** (1957 to Olin Mathieson).

Nonflammable liquid; pleasant odor; d_4^{20} 1.4416; solidif −35°; bp 113-114°; n_D^{20} 1.4711. Insol in water; misc with alcohol, ether, and many other organic liquids. LD_{50} orally in rats: 0.58 ml/kg, H. F. Smyth *et al., Am. Ind. Hyg. Assoc. J.* **30**, 470 (1969).

USE: Solvent for fats, waxes, natural resins, alkaloids. *Caution:* Irritating to eyes, mucous membranes, and, in high concns, narcotic.

9451. 2,2,2-Trichloroethanol. Trichloroethyl alcohol. $C_2H_3Cl_3O$; mol wt 149.42. C 16.08%, H 2.02%, Cl 71.19%, O 10.71%. CCl_3CH_2OH. Prepd by reduction of the corresponding ester, acid chloride, or acid with lithium aluminum hydride: Sroog *et al., J. Am. Chem. Soc.* **71**, 1710 (1949). Manufacture by reduction of chloral hydrate with an amine borane: Chamberlain, Schechter, U.S. pat. **2,898,379** (1959 to Callery Chem.).

Hygroscopic liquid, ethereal odor. At low temps it crystallizes in rhombic tablets. mp at 18°; bp 151-153°; d_{20}^{20} 1.55. Sol in about 12 parts water; miscible with alcohol or ether. pH of aq soln is 5-6, but on prolonged contact with water some free acid is formed. *Keep well closed and protected from light.* LD_{50} orally in rats: 600 mg/kg, *Handbook of Toxicology* vol. **1**, W. S. Spector, Ed. (Saunders, Philadelphia, 1955) pp 302-303.

THERAP CAT: Hypnotic, anesthetic.

9452. Trichloroethylene. *Trichloroethene;* ethinyl trichloride; Tri-Clene; Trielene; Trilene; Trichloran; Trichloren; Algylen; Trimar; Triline; Tri; Trethylene; Westrosol; Chlorylen; Gemalgene; Germalgene. C_2HCl_3; mol wt 131.40. C 18.28%, H 0.77%, Cl 80.95%. CCl_2=$CHCl$. Usually prepd from *sym*-tetrachloroethane by elimination of HCl (by boiling with lime): Ger. pat. **171,900**. By passing tetrachloroethane vapor over $CaCl_2$ catalyst at 300°: Ger. pat. **263,457**; without catalyst at 450-470°: Brit. pat. **575,530** (1946 to du Pont). Review of mfg processes: S. A. Miller, *Chem. Process Eng.* **47**, 268 (1966); Faith, Keyes & Clark's *Industrial Chemicals,* F. A. Lowenheim, M. K. Moran, Eds. (Wiley-Interscience, New York, 4th ed., 1975) pp 844-848. Toxicity and metabolism: E. Browning, *Toxicity and Metabolism of Industrial Solvents* (Elsevier, New York, 1965) pp 189-212.

Nonflammable, mobile liquid. Characteristic odor resembling that of chloroform. d_4^4 1.4904; d_4^{15} 1.4695; d_4^{20} 1.4649. Vapor density: 4.53 (air = 1.00). Solidifies at −84.8°. bp_{760} 86.7°; bp_{400} 67.0°; bp_{200} 48.0°; bp_{100} 31.4°; bp_{60} 20.0°; bp_{20} −1.0°; bp_{10} −12.4°; bp_5 −22.8°; $bp_{1.0}$ −43.8°; n_D^{17} 1.47914; n_D^{25} 1.45560. Practically insol in water; misc with ether, alcohol, chloroform. Dissolves most fixed and volatile oils. Slowly dec (with formn of HCl) by light in the presence of moisture. Trichloroethylene for medicinal purposes may contain some thymol or ammonium carbonate (not more than 20 mg/100 ml) as a stabilizer. Industrial grades of trichloroethylene may contain other stabilizers such as triethanolamine stearate and cresol. LD_{50} orally in rats: 4.92 ml/kg; LC (4 hrs) in rats: 8000 ppm, Smyth *et al., Am. Ind. Hyg. Assoc. J.* **30**, 470 (1969).

Caution: Use with adequate ventilation. Preserve trichloroethylene in sealed, light-resistant ampuls or in frangible, light-resistant glass tubes. Avoid prolonged exposure of the product to excessive heat. It must be dispensed in the unopened glass container in which it was placed by the manufacturer.

*Human Toxicity: Moderate exposures can cause symp*toms similar to alcohol inebriation. Higher concns can have narcotic effect. Deaths occurring after heavy exposure have been attributed to ventricular fibrillation. Liver injury is not definitely established in occupational exposures. Found to induce hepatocellular carcinomas in National Cancer Institute tests on mice: *Chem. & Eng. News* **54**, 4 (Apr. 5, 1976).

USE: Solvent for fats, waxes, resins, oils, rubber, paints, and varnishes. Solvent for cellulose esters and ethers. Used for solvent extraction in many industries. In degreasing, in dry cleaning. In the manuf of organic chemicals, pharmaceuticals, such as chloroacetic acid.

THERAP CAT: Analgesic (inhalation).

THERAP CAT (VET): Inhalant anesthetic.

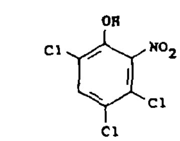
9453. Trichlorofluoromethane. Trichloromonofluoromethane; fluorotrichloromethane; Freon 11; Frigen 11; Arcton 9. CCl_3F; mol wt 137.38. C 8.74%, Cl 77.43%, F 13.83%. Prepn: Henne, *Organic Reactions* **2**, 64 (1944). Manuf: Faith, Keyes & Clark's *Industrial Chemicals,* F. A. Lowenheim, M. K. Moran, Eds. (Wiley-Interscience, New York, 4th ed., 1975) pp 325-330.

Liquid at temps below 23.7°. Faint ethereal odor. Nonflammable. $d_4^{17.2}$ 1.494; d_{gas}^{25} 5.04 (air = 1). mp −111°. bp_{760} 23.7°; bp_{400} +6.8°; bp_{200} −9.1°; bp_{100} −23.0°; bp_{60} −32.3°; bp_{40} −39.0°; bp_{20} −49.7°; bp_{10} −59.0°; bp_5 −67.6°; $bp_{1.0}$ −84.3°. Crit temp 198°; crit press. 43.2 atm (635 lb/sq inch, abs). $n_D^{18.5}$ 1.3865. Dipole moment 0.45. Practically insol in water. Sol in alcohol, ether, other, organic solvents. Less *toxic than carbon dioxide, but decomposes into harmful* materials by flames or high heat.

USE: In refrigeration machinery requiring a refrigerant effective at negative pressures. As aerosol propellant. *Caution:* May be narcotic in high concentrations.

Note: Consult latest Government regulations on use as aerosol propellant.

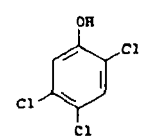
9454. 3,4,6-Trichloro-2-nitrophenol. 2-Nitro-3,4,6-trichlorophenol; 2,4,5-trichloro-6-nitrophenol; Dowlap. $C_6H_2Cl_3NO_3$; mol wt 242.44. C 29.72%, H 0.83%, Cl 43.87%, N 5.78%, O 19.80%. Prepd by dissolving 2,4,5-trichlorophenol in glacial acetic acid and treating with concd nitric acid: Kohn, Fink, *Monatsh.* **58**, 73 (1931); Harrison *et al., J. Chem. Soc.* **1943**, 235.



Pale yellow crystals from petr ether, mp 92-93°.

USE: To combat the sea lamprey, an eel-like fish which attacks trout, especially in the Great Lakes region.

9455. 2,4,5-Trichlorophenol. Collunosol; Dowicide 2. $C_6H_3Cl_3O$; mol wt 197.46. C 36.49%, H 1.53%, O 8.10%, Cl 53.87%. Prepd by treating 1,2,4,5-tetrachlorobenzene with methanolic NaOH in autoclave at 160° for several hrs: Harrison *et al., J. Chem. Soc.* **1943**, 235; Agfa, Ger. pat. **411,052** (1925); *Chem. Zentr.* **1925, I**, 2411.



Needles from alcohol or ligroin. Strong phenolic odor. mp 67°. Sublimes. bp_{746} 248°. bp_{760} 253°. Weak monobasic acid. K at 25° = 4.3 × 10^{-8}. Soly (g/100 g of solvent at 25°): acetone 615; benzene 163; carbon tetrachloride 51; ether 525; denatured alcohol formula 30, 525; methanol 615; liquid petrolatum (at 50°) 56; soybean oil 79; toluene 122; water <0.2. LD_{50} orally in rats: 0.82 g/kg, Deichmann, *Fed. Proc.* 2, 76 (1943).

Sodium salt sesquihydrate, *Dowicide B.* Flakes [prepd according to U.S. pat. **1,991,329** (1935 to Dow)]. Solubility (g/100 g solvent at 25°); acetone *163;* denatured alcohol formula 30, 186; ethylene glycol 33; methanol 241; water 113. pH of satd aq soln 11.0-13.0.

Complex with triisobutyl phosphate, $C_{18}H_{30}ClO_5P$, *Trichlorex.* Prepn: Bouillenne-Wallrand *et al.,* Fr. pat. **M149** (1961 to Pechiney). Liquid. $bp_{0.01}$ 94-103°.

USE: Fungicide, bactericide.

9456. 2,4,6-Trichlorophenol. Dowicide 2S; Omal. $C_6H_3Cl_3O$; mol wt 197.46. C 36.49%, O 8.10%, H 1.53%, Cl

 Consult the cross index before using this section.

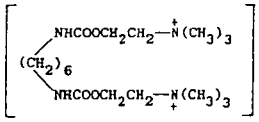
√ – This would equal more than half a pound for a 150 lb man.

USE: As reagent for pyrophosphoric acid, for the estimation of phosphate.

4571. Hexaborane(10). Hexaboron decahydride; borohexane. B_6H_{10}; mol wt 75.00. B 86.56%, H 13.44%. Prepd by the reaction of magnesium boride with hydrochloric or phosphoric acid: Stock, Kuss, *Ber.* 56B, 789 (1923).

Liquid. mp −62.3°; bp 108°; vapor pressure (0°): 7.5 mm: Burg, Kratzer, *Inorg. Chem.* 1, 725 (1962). d^0 0.69. Slowly dec at room temp. Hydrolyzes in water after long heating.

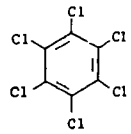
4572. Hexacarbacholine Bromide. *2,2'-[1,6-Hexanediylbis(iminocarbonyloxy)]bis[N,N,N-trimethylethanaminium] dibromide;* choline bromide hexamethylenedicarbamate; hexamethylenedicarbamic acid choline bromide diester; hexamethylene-1,6-bis(carbamoylcholine bromide); *N,N'*-hexamethylenebis[(2-carbamoyloxyethyl)trimethylammonium bromide]; BC 16; Imbretil. $C_{18}H_{40}Br_2N_4O_4$; mol wt 536.38. C 40.31%, H 7.52%, Br 29.80%, N 10.45%, O 11.93%. Preparation: Schmied *et al.*, Austrian pat. 185,371 (1956); Ger. pat. 1,021,842 (1958 to Oesterreichische Stickstoffwerke).



Crystals from ethanol, mp 174-176°.

THERAP CAT: Skeletal muscle relaxant.

4573. Hexachlorobenzene. Perchlorobenzene; Anticarie; Bunt-cure; Bunt-no-more; Julin's carbon chloride. C_6Cl_6; mol wt 284.80. C 25.30%, Cl 74.70%. Not to be confused with benzene hexachloride, *see* Lindane. Prepn: Becke, Sperber, U.S. pat. 2,792,434 (1957 to BASF). Teratogenicity studies: K. D. Courtney *et al., Toxicol. Appl. Pharmacol.* 35, 239 (1976). Carcinogenicity studies: J. R. P. Cabral *et al., Nature* 269, 510 (1977).



Needles. d^{23} 2.044. mp 231°. bp 323-326°. Vapor press at 20°: 1.09 × 10^{-5} mm Hg. Sublimable. Insol in water; sparingly sol in cold alcohol; sol in benzene, chloroform, ether. LD_{50} orally in rats: 10,000 mg/kg, *RTECS* Vol. I, R. J. Lewis, R. L. Tatken, Eds. (1979) p 216.

USE: In organic syntheses. Fungicide. *Caution:* Cutaneous porphyria may result from prolonged periods of ingestion, R. Ockner, R. Schmid, *Nature* 189, 499 (1961).

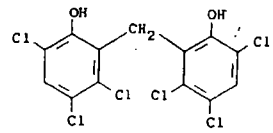
4574. Hexachloroethane. Carbon hexachloride; perchloroethane. C_2Cl_6; mol wt 236.74. C 10.15%, Cl 89.85%. CCl_3CCl_3. Prepn: *Beilstein* 1, 87 (1918) and suppls.

Crystals; camphoraceous odor. d 2.09. Readily sublimes without melting. bp 186.8° (triple point). Heat of sublimation 12.2 kcal/mol. Sol in alcohol, benzene, chloroform, ether, oils. Insol in water. MLD i.v. in dogs: 325 mg/kg, Barsoum, Saad, *Quart. J. Pharm. Pharmacol.* 7, 205 (1934).

USE: Solvent; in explosives; as camphor substitute in celluloid; rubber vulcanizing accelerator. *Caution:* May be moderately irritating to skin, mucous membranes.

THERAP CAT (VET): Anthelmintic (flukicide).

4575. Hexachlorophene. *2,2'-Methylenebis[3,4,6-trichlorophenol];* 2,2'-dihydroxy-3,3',5,5',6,6'-hexachlorodiphenylmethane; bis(3,5,6-trichloro-2-hydroxyphenyl)methane; G-11; AT-7; Bilevon; Dermadex; Exofene; Gamophen; Hexosan; pHisohex; Surgi-Cen; Surofene. $C_{13}H_6Cl_6O_2$; mol wt 406.92. C 38.37%, H 1.49%, Cl 52.28%, O 7.86%. Prepd by the condensation of 2 mols of 2,4,5-trichlorophenol with 1 mol formaldehyde in the presence of concd sulfuric acid: Gump, U.S. pat. 2,250,480 (1941 to Burton T. Bush). Improved procedures: U.S. pat. 2,435,593 (1948) and 2,812,365 (1957 to Givaudan).



Crystals from benzene, mp 164-165°. Practically insol in water; sol in alcohol, acetone, ether, chloroform, propylene glycol; polyethylene glycols; olive oil; cottonseed oil; dil aq solns of the alkalies. Forms salts with alkalies and alkaline earths. Phenol coefficient ~125 (monopotassium salt). Incompatible with Tweens from bacteriological point of view.

Monophosphate, *Hepadist.*

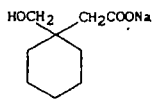
Toxicity: Excessive dosage to animals results in symptoms of neurotoxicity. Reversible vacuolar changes mainly affecting the myelin of the brain and spinal cord have been reported. Because of potential neurotoxicity in humans, the FDA has regulated use. *See* Lockhart, *Pediatrics* 50, 229 (1972).

USE: Chiefly in the manuf of germicidal soaps.

THERAP CAT: Anti-infective, topical; detergent.

THERAP CAT (VET): Anthelmintic (flukicide).

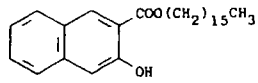
4576. Hexacyclonate Sodium. *1-(Hydroxymethyl)cyclohexaneacetic acid sodium salt;* sodium 3,3-pentamethylene-4-hydroxybutyrate; sodium β,β-pentamethylene-γ-hydroxybutyrate; β,β-pentamethylene-γ-hydroxybutyric acid sodium salt; Gevilon; Neuryl. $C_9H_{15}NaO_3$; mol wt 194.21. C 55.66%, H 7.78%, Na 11.84%, O 24.71%. Prepn: Van Wessem, Sakal; Shavel *et al.*, U.S. pats. 2,960,441; 3,007,940 (1960; 1961 to Warner-Lambert).



Monohydrate, platelets from *n*-butanol + benzene, mp 106-108°. The anhydr salt is hygroscopic. Readily sol in water, methanol, ethanol; sparingly sol in ether, acetone.

THERAP CAT: Central stimulant.

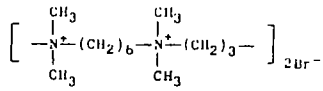
4577. Hexadecyl 3-Hydroxy-2-naphthoate. *3-Hydroxy-2-naphthalenecarboxylic acid hexadecyl ester.* $C_{27}H_{40}O_3$; mol wt 412.59. C 78.59%, H 9.77%, O 11.63%. Prepd by the action of 3-hydroxy-2-naphthoyl chloride on cetyl alc: Oshima, Hayashi, *J. Soc. Chem. Ind. Japan* 44, 821 (1941).



Greenish-white, flaky crystals, mp 72-73°. Soluble in benzene, glacial acetic acid, petr ether. Sparingly sol in cold alcohol. Insol in water.

USE: As waterproofing agent for rayon.

4578. Hexadimethrine Bromide. *N,N,N',N'-Tetramethyl-1,6-hexanediamine polymer with 1,3-dibromopropane;* polymer of *N,N,N',N'*-tetramethylhexamethylenediamine and trimethylene bromide; poly(*N,N,N',N'*-tetramethyl-*N*-trimethylenehexamethylenediammonium dibromide); Polybrene. $(C_{13}H_{30}Br_2N_2)_x$.



White, hygroscopic, amorphous polymer. Soluble in water up to 10%. pH of 1% saline soln 5-9. Stable in soln and when autoclaved. Polymers with mol wt of 5000-10,000 have LD_{50} i.v. in mice of 25-40 mg/kg. Ref: Kimura *et al., Toxicol. Appl. Pharmacol.* 1, 185 (1959).

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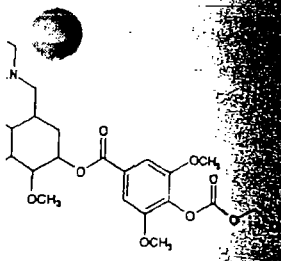
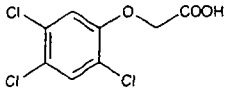


9194. 2,4,5-T. *(2,4,5-Trichlorophenoxy)acetic acid;* Esteron 245; Trioxone; Weedone. $C_8H_5Cl_3O_3$; mol wt 255.48. C 37.61%, H 1.97%, Cl 41.63%, O 18.79%. Post-emergence herbicide. Prepd from 2,4,5-trichlorophenol: Pokorny, *J. Am. Chem. Soc.* 63, 1768 (1941); from benzenehexachloride: Dalton, *ibid.* 74, 3890 (1952). Activity: C. L. Hamner, T. B. Tukey, *Science* 100, 154 (1944). Contains trace levels of TCDD, *q.v.*, as a contaminant: J. Smith, *Science* 203, 1090 (1979); *Chem. & Eng. News* 59, 6 (Jan. 5, 1981). Toxicity: W. A. Rowe, T. A. Hymas, *Am. J. Vet. Res.* 15, 622 (1954). *See also* 2,4-D.



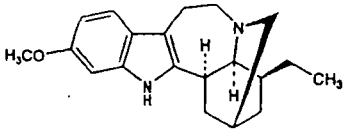
Crystals from benzene, mp 153°. d_{20}^{20} 1.80. Soly in water at 30°: 238 mg/kg. Sol in alcohol. Forms water-soluble sodium and alkanolamine salts. Commercial products are usually in the form of amines or esters, often in mixture with 2,4-D. LD_{50} orally in mice, rats: 389, 500 mg/kg (Rowe, Hymas).

Caution: Potential symptoms of overexposure in animals are ataxia; skin irritation, acne-like rash. *See NIOSH Pocket Guide to Chemical Hazards* (DHHS/NIOSH 90-117, 1990) p 302.

Note: In March 1985 the E.P.A. terminated all registrations for the use of this herbicide on rice fields, orchards, sugarcane, rangeland and other noncrop sites. This follows a 1970 action of the Department of Agriculture halting the use of the pesticide on all food crops except rice: Chem. & Eng. News 63, 6 (Mar. 25, 1985).

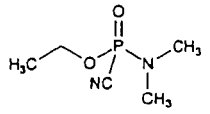
USE: Formerly as herbicide.

9195. Tabernanthine. *13-Methoxyibogamine.* $C_{20}H_{26}N_2O$; mol wt 310.44. C 77.38%, H 8.44%, N 9.02%, O 5.15%. Indole alkaloid isolated from root of *Tabernanthe iboga* Baill., *Apocynaceae:* Delourme-Houdé, *Ann. Pharm. Fr.* 4, 30 (1946); Dickel *et al., J. Am. Chem. Soc.* 80, 123 (1958). Also in *Tabernaemontana* and *Stemmadenia* spp.; usually found in ibogaine mother liquors: Walls *et al., Tetrahedron* 2, 173 (1958). Isoln from genus *Conopharingia, Apocynaceae:* Renner, Prins, U.S. pat. 3,008,954 (1961 to Ciba). Structure: Bartlett *et al., J. Am. Chem. Soc.* 80, 126 (1958). Mass spectrum: Biemann, Friedmann-Spiteller, *ibid.* 83, 4805 (1961). Derivs: Taylor, U.S. pat. 2,877,229 (1959 to Ciba). Interaction with benzodiazepine receptors: M. Trouvin *et al., Eur. J. Pharmacol.* 140, 303 (1987).



Needles or shiny leaflets from ethanol, mp 213.5-215°. Sublimes at 160° (0.005 mm pressure). $[\alpha]_D^{20}$ −40° (acetone). pK' 6.04 in 80% methylcellosolve. uv max (ethanol): 228, 295, 299 nm (log ε 4.53, 3.64, 3.77). Sol in alcohol, benzene, ether, chloroform. Practically insol in water. Hydrochloride, $C_{20}H_{26}N_2O.HCl$, crystals from water, dec 270-277°. $[\alpha]_D^{25}$ −66° (methanol, Dickel, *loc. cit.*); mp 210°, $[\alpha]_D$ −76.5° (methanol, Delourme-Houdé). Sol in water. More sol in chloroform than ibogaine hydrochloride.

9196. Tabun. *Dimethylphosphoramidocyanidic acid, ethyl ester;* ethyl *N*-dimethylphosphoramidocyanidate; dimethylamidoethoxyphosphoryl cyanide; GA. $C_5H_{11}N_2O_2P$; mol wt 162.13. C 37.04%, H 6.84%, N 17.28%, O 19.74%, P 19.10%. Military nerve gas; prepd from dimethylamidophosphoryl dichloride and sodium cyanide in the presence of ethanol: Holmstedt, *Acta Physiol. Scand.* 25, Suppl. 90, 1 (1951). The synthesis of dimethylamidophosphoryl dichloride is also described by Michaelis, *Ann.* 326, 129 (1903). Alternate synthetic route: B. C. Saunders, *Some Aspects of the Chemistry and Toxic Action of Organic Compounds Containing Phosphorus and Fluorine* (Cambridge, 1957) p 91. Toxicity study: B. Holmstedt, *Pharmacol. Rev.* 11, 567 (1959). Brief review: Schrader, *Die Entwicklung neuer insektizider Phosphorsaüre-Ester* (Verlag Chemie, Weinheim, 1963) p 3.

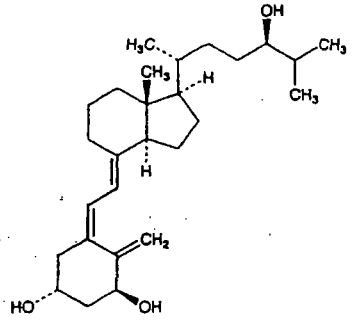


Liquid. Fruity odor reminiscent of bitter almonds. d 1.077. mp −50°. bp_{760} 240°; bp_{10} 120°; bp_9 100-108°. n_D^{20} 1.4250. IR absorption: *Acta Chem. Scand.* 5, 1179 (1951). Readily sol in organic solvents. Miscible with water, but quickly hydrolyzed. Bleaching powder (chlorinated lime) destroys Tabun, but gives rise to cyanogen chloride. *Extremely poisonous!* LD_{50} i.p. in mice: 0.6 mg/kg (Holmstedt). The lethal dose for man may be as low as 0.01 mg/kg, *Chem. & Eng. News* 31, 4676 (1953).

Caution: Potent cholinesterase inhibitor. Toxic not only by inhalation but by absorption through skin and eyes. Inhalation produces constriction of pupils of the eye, difficulty in breathing followed by bronchial constriction, convulsions, death.

USE: Chemical warfare agent.

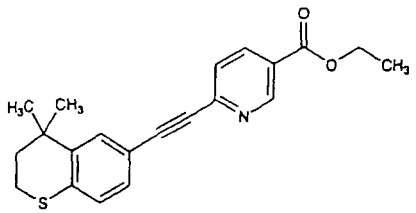
9197. Tacalcitol. *(1α,3β-5Z,7E,24R)-9,10-Secocholesta-5,7,10(19)-triene-1,3,24-triol;* 1α,24(*R*)-dihydroxycholecalciferol; 1α,24*R*-dihydroxyvitamin D_3; TV-02; Bonalfa. $C_{27}H_{44}O_3$; mol wt 416.64. C 77.84%, H 10.64%, O 11.52%. Bioactive, synthetic vitamin D_3 analog; exhibits antiproliferative effect on keratinocytes. Prepn: T. Takeshita *et al.*, Ger. pat. 2,526,981; *eidem*, U.S. pat. 4,022,891 (1976, 1977 both to Teijin); M. Morisaki *et al., J. Chem. Soc, Perkin Trans. I* 1975, 1421; K. Ochi *et al., ibid.* 1979, 165. Pharmacology: T. Matsunage *et al., J. Dermatol.* 17, 135 (1990). Clinical evaluation in psoriasis: M. J. P. Gerritsen *et al., Brit. J. Dermatol.* 131, 57 (1994). *Review:* M. Nishimura *et al., Eur. J. Dermatol.* 3, 255-261 (1993).



White solid. uv max (ethanol): 265 nm.

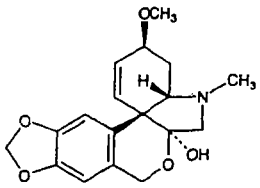
THERAP CAT: Antipsoriatic.

9198. Tachysterol. *(3β,6E,22E)-9,10-Secoergosta-5(10),6,8,22-tetraen-3-ol.* $C_{28}H_{44}O$; mol wt 396.66. C 84.79%, H 11.18%, O 4.03%. From ergosterol or lumisterol by ultraviolet irradiation: Windaus *et al., Ann.* 492, 226 (1932); *Ann.* 499, 188 (1932); Dimroth, *Ber.* 70, 1631 (1937). From calciferol by adsorption on acid clay: Thibaudet, *Compt. Rend.* 220, 751 (1945). From precalciferol: Velluz, Goffinet, U.S. pat. 2,847,426 (1958 to UCLAF). Structure: Grundmann, *Z. Physiol. Chem.* 252, 151 (1938); Thibaudet, *loc. cit.* Stereochemistry of the tachysterol system: Inhoffen, *Ber.* 88, 1424 (1955); Verloop, *Rec. Trav. Chim.* 76, 689 (1957); Delaroff *et al., Bull. Soc. Chim. France* 1963, 1739.



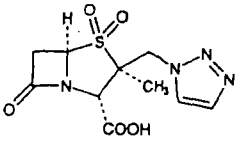
White solid.
THERAP CAT: Antiacne; antipsoriatic.

9250. Tazettine. Sekisanine; sekisanoline; ungernine. $C_{18}H_{21}NO_5$; mol wt 331.37. C 65.24%, H 6.39%, N 4.23%, O 24.14%. From *Narcissus tazetta* L., *Lycoris radiata* Herb., *Ungernia sewerzowi* (Rgl.) Fedtsch., and other *Amaryllidaceae*: Späth, Kahovec, *Ber.* **67**, 1501 (1934). Structure and stereochemistry: Ikeda *et al., J. Chem. Soc.* **1956**, 4749. Abs config: Highet, Highet, *Tetrahedron Letters* **1966**, 4099. Synthesis: Hendrickson *et al., J. Am. Chem. Soc.* **92**, 5538 (1970); Tsuda *et al., Tetrahedron Letters* **1972**, 3153. Biosynthesis: Fales, Wildman, *J. Am. Chem. Soc.* **86**, 294 (1964). Identity with sekisanine and sekisanoline: Ikeda *et al.*; *loc. cit.* Stereospecific total synthesis: Hendrickson *et al., J. Am. Chem. Soc.* **96**, 7781 (1974); S. Danishefsky *et al., ibid.* **102**, 2838 (1980); **104**, 7591 (1982).



Crystals, mp 210-211° (evac tube); racemate reported as mp 237-238° (Tsuda) and mp 175-176° (Danishefsky). $[\alpha]_D^{25}$ +150.3° (82 mg in 2 ml chloroform). Sol in methanol, ethanol, choroform. Sparingly sol in ether.
Hydrochloride, crystals, mp 206°, water soluble.
Methiodide, crystals, dec 220° (evacuated tube).

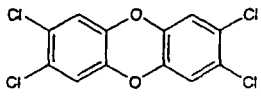
9251. Tazobactam. *[2S-(2α,3β,5α)]-3-Methyl-7-oxo-3-[1H-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid 4,4-dioxide;* 2β-[(1,2,3-triazol-1-yl)-methyl]-2α-methylpenam-3α-carboxylic acid 1,1-dioxide; YTR-830H; CL-298741. $C_{10}H_{12}N_4O_5S$; mol wt 300.30. C 40.00%, H 4.03%, N 18.66%, O 26.64%, S 10.68%. β-Lactamase inhibitor. Prepn: R. G. Micetich *et al.*, Eur. pat. Appl. 97,446; *eidem*, U.S. pat. 4,562,073 (1984, 1985 both to Taiho); R. G. Micetich *et al., J. Med. Chem.* **30**, 1469 (1987). Degradation in solution: T. Marunaka *et al., Chem. Pharm. Bull.* **36**, 4478 (1988); in solid state: E. Matsushima *et al., ibid.* 4593. β-Lactamase inhibiting activity in comparison with clavulanic acid and sulbactam, *q.q.v.*, vs aerobes: M. R. Jacobs *et al., Antimicrob. Ag. Chemother.* **29**, 780 (1986); vs anaerobes: P. C. Appelbaum *et al., ibid.* **30**, 789. HPLC determn in biological materials: T. Marunaka *et al., J. Chromatog.* **431**, 87 (1988). Clinical trial in combination with piperacillin, *q.v.*: I. M. Gould *et al., Drugs Exp. Clin. Res.* **17**, 187 (1991).



Sodium salt, $C_{10}H_{11}N_4NaO_5S$. *YTR-830, CL-307579.* Amorphous solid, mp > 170° (dec).
Combination of sodium salt with piperacillin sodium, *Tazocilline, Tazocin, Zosyn.*

THERAP CAT: In combination with β-lactam antibiotics as antibacterial.

9252. TCDD. *2,3,7,8-Tetrachlorodibenzo[b,e][1,4]dioxin; 2,3,7,8-tetrachlorodibenzo-p-dioxin;* 2,3,6,7-tetrachlorodibenzodioxin; dioxin; TCDBD. $C_{12}H_4Cl_4O_2$; mol wt 321.97. C 44.77%, H 1.25%, Cl 44.04%, O 9.94%. Highly toxic contaminant; produced as a by-product during the manuf of chlorinated phenols (2,4,5-trichlorophenol, *q.v.*) and phenoxyherbicides (2,4-D and 2,4,5-T, *q.q.v.*), chlorine bleaching of paper pulp and combustion of chlorine-containing waste. Prepn: W. Sandermann, *Ber.* **90**, 690 (1957); M. Tomita *et al., Yakugaku Zasshi* **79**, 186 (1959), *C.A.* **53**, 13152d (1959). Crystal structure: F. P. Boer *et al., Acta Crystallogr.* **28B**, 1023 (1972). Toxicity and metabolism: B. A. Schwetz *et al.*, in *Chlorodioxins-Origin and Fate.* E. H. Blair, Ed., *Advances in Chemistry Series* **120** (A.C.S., Washington, D.C., 1973) pp 55-69; A. Poland, A. Kende, *Fed. Proc.* **35**, 2404 (1976). Environmental degradation: D. G. Crosby, A. S. Wong, *Science* **195**, 1337 (1976). Comprehensive review of formation, chemistry, and toxic and environmental effects: *Chlorodioxins—Origin and Fate, ioc. cit.* 141 pp; *Dioxin—Toxicological and Chemical Aspects,* F. Cattabeni *et al.*, Eds. (Wiley, New York, 1978) 222 pp; special issue, *Chem. & Eng. News* **61** (June 6, 1983). Review of toxicology and human exposure: *Toxicological Profile for 2,3,7,8-Tetradichlorodibenzo-p-dioxin* (PB89-214522, 1989) 135 pp; of receptor binding and mechanism of toxicity: J. P. Whitlock, Jr., *Ann. Rev. Pharmacol. Toxicol.* **30**, 251-277 (1990); of epidemiological data: L. Tollefson, *Regul. Toxicol. Pharmacol.* **13**, 150-169 (1991); of carcinogenicity: J. Huff *et al., Ann. Rev. Pharmacol. Toxicol.* **34**, 343-372 (1994).



Needles, mp 295° (Tomita); crystals from anisole, mp 320-325° (Sandermann). LD_{50} in male, female rats (mg/kg): 0.022, 0.045 orally (Schwetz).

Note: An industrial accident during the manufacture of 2,4,5-trichlorophenol in Seveso, Italy on July 10, 1976 caused the release of an estimated two to ten pounds of TCDD into the environment. Concentrations as high as 51.3 ppm TCDD were found in some samples: R. Rawls, D. A. O'Sullivan, *Chem. & Eng. News* **54**, 27 (Aug. 23, 1976); A. Hay, *Nature* **262**, 636 (1976).

TCDD, as a contaminant created in the manufacture of *Agent Orange*, a widely used defoliant in Vietnam during the 1960's, has also been implicated as the causative agent of various symptoms described by veterans exposed to the defoliant, *see* C. Holden, *Science* **205**, 770 (1979).

Caution: Toxic effects in animals include the wasting syndrome, gastric ulcers, immunotoxicity, hepatotoxicity, hepatoporphyria, vascular lesions, chloracne, teratogenicity, fetotoxicity, impaired reproductive performance, endometriosis and delayed death. Industrial workers exposed to TCDD have developed chloracne, porphyrinuria and porphyria cutanea tarda. *See* Poland, Kende, *loc. cit.*; C. D. Carter *et al., Science* **188**, 738 (1975). This substance may reasonably be anticipated to be a carcinogen: *Seventh Annual Report on Carcinogens* (PB95-109781, 1994) p 369.

9253. Tebuconazole. *(±)-α-[2-(4-Chlorophenyl)ethyl]-α-(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol; (RS)*-1-(4-chlorophenyl)-4,4-dimethyl-3-(1*H*-1,2,4-triazol-1-ylmethyl)-pentan-3-ol; ethyltrianol; fenetrazole; terbuconazole; terbutrazole; BAY HWG 1608; HWG-1608; Corail; Elite; Folicur; Horizon; Lynx; Raxil; Silvacur. $C_{16}H_{22}ClN_3O$; mol wt 307.82. C 62.43%, H 7.20%, Cl 11.52%, N 13.65%, O 5.20%. Ergosterol biosynthesis inhibitor. Prepn: G. Holmwood *et al.*, Eur. pat. Appl. 40,345; *eidem*, U.S. pat. 4,723,984 (1981, 1988 both to Bayer). Synthesis of enantiomers: J. Kaulen, *Agnew. Chem. Int. Ed. Engl.* **28**, 462 (1989). Photodegradation: H. Wamhoff *et al., Z. Naturforsch.* **49b**, 280 (1994). GC determn in plant material, soil and water: W. Maasfeld, *Pflanzenschutz-Nachr. Bayer (Eng. Ed.)* **40**, 29 (1987). Review of chemistry and biochemistry: D. Berg *et*

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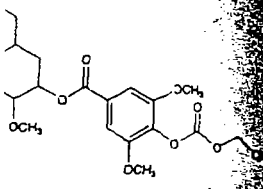

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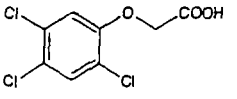

Crystals from benzene, mp 153°. d_{20}^{20} 1.80. Soly in water at 30°: 238 mg/kg. Sol in alcohol. Forms water-soluble sodium and alkanolamine salts. Commercial products are usually in the form of amines or esters, often in mixture with 2,4-D. LD_{50} orally in mice, rats: *389, 500 mg/kg* (Rowe, Hymas).

Caution: Potential symptoms of overexposure in animals are ataxia; skin irritation, acne-like rash. *See NIOSH Pocket Guide to Chemical Hazards* (DHHS/NIOSH 90-117, 1990) p 302.

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USE: Formerly as herbicide.

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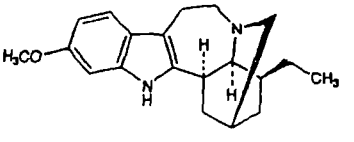
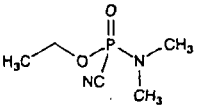


Needles or shiny leaflets from ethanol, mp 213.5-215°. Sublimes at 160° (0.005 mm pressure). $[\alpha]_D^{20}$ −40° (acetone). pK 6.04 in 80% methylcellosolve. uv max (ethanol): 228, 271-299 nm (log ε 4.53, 3.64, 3.77). Sol in alcohol, benzene, ether, chloroform. Practically insol in water.

Hydrochloride, $C_{20}H_{26}N_2O.HCl$, crystals from water, dec 275-277°. $[\alpha]_D^{25}$ −66° (methanol, Dickel, *loc. cit.*); mp 210°, $[\alpha]_D$ −76.5° (methanol, Delourme-Houdé). Sol in water. More sol in chloroform than ibogaine hydrochloride.

9196. Tabun. *Dimethylphosphoramidocyanidic acid, ethyl ester;* ethyl *N*-dimethylphosphoramidocyanidate; dimethylamidoethoxyphosphoryl cyanide; GA. $C_5H_{11}N_2O_2P$; mol wt 162.13. C 37.04%, H 6.84%, N 17.28%, O 19.74%, P 19.10%. Military nerve gas; prepd from dimethylamidophosphoryl dichloride and sodium cyanide in the presence of ethanol: Holmstedt, *Acta Physiol. Scand.* 25, Suppl. 90, 26 (1951). The synthesis of dimethylamidophosphoryl dichloride is also described by Michaelis, *Ann.* 326, 129 (1903). Alternate synthetic route: B. C. Saunders, *Some Aspects of the Chemistry and Toxic Action of Organic Compounds Containing Phosphorus and Fluorine* (Cambridge, 1957) p 91. Toxicity study: B. Holmstedt, *Pharmacol. Rev.* 11, 567 (1959). Brief review: Schrader, *Die Entwicklung neuer insektizider Phosphorsaüre-Ester* (Verlag Chemie, Weinheim, 1963) p 3.

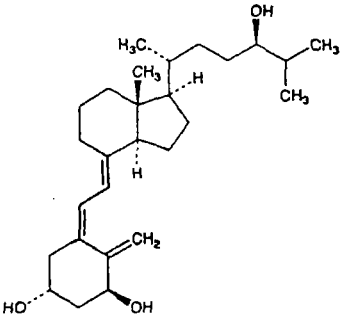


Liquid. Fruity odor reminiscent of bitter almonds. d 1.077. mp −50°. bp_{760} 240°; bp_{10} 120°; bp_9 100-108°. n_D^{20} 1.4250. IR absorption: *Acta Chem. Scand.* 5, 1179 (1951). Readily sol in organic solvents. Miscible with water, but quickly hydrolyzed. Bleaching powder (chlorinated lime) destroys Tabun, but gives rise to cyanogen chloride. *Extremely poisonous!* LD_{50} i.p. in mice: 0.6 mg/kg (Holmstedt). The lethal dose for man may be as low as 0.01 mg/kg, *Chem. & Eng. News* 31, 4676 (1953).

Caution: Potent cholinesterase inhibitor. Toxic not only by inhalation but by absorption through skin and eyes. Inhalation produces constriction of pupils of the eye, difficulty in breathing followed by bronchial constriction, convulsions, death.

USE: Chemical warfare agent.

9197. Tacalcitol. *(1α,3β-5Z,7E,24R)-9,10-Secocholesta-5,7,10(19)-triene-1,3,24-triol;* 1α,24(*R*)-dihydroxycholecalciferol; 1α,24*R*-dihydroxyvitamin D_3; TV-02; Bonalfa. $C_{27}H_{44}O_3$; mol wt 416.64. C 77.84%, H 10.64%, O 11.52%. Bioactive, synthetic vitamin D_3 analog; exhibits antiproliferative effect on keratinocytes. Prepn: T. Takeshita *et al.*, Ger. pat. 2,526,981; *eidem*, U.S. pat. 4,022,891 (1976, 1977 both to Teijin); M. Morisaki *et al., J. Chem. Soc, Perkin Trans. I* 1975, 1421; K. Ochi *et al., ibid.* 1979, 165. Pharmacology: T. Matsunage *et al., J. Dermatol.* 17, 135 (1990). Clinical evaluation in psoriasis: M. J. P. Gerritsen *et al., Brit J. Dermatol.* 131, 57 (1994). *Review:* M. Nishimura *et al., Eur. J. Dermatol.* 3, 255-261 (1993).



White solid. uv max (ethanol): 265 nm.

THERAP CAT: *Antipsoriatic.*

9198. Tachysterol. *(3β,6E,22E)-9,10-Secoergosta-5(10),6,8,22-tetraen-3-ol.* $C_{28}H_{44}O$; mol wt 396.66. C 84.79%, H 11.18%, O 4.03%. From ergosterol or lumisterol by ultraviolet irradiation: Windaus *et al., Ann.* 492, 226 (1932); *Ann.* 499, 188 (1932); Dimroth, *Ber.* 70, 1631 (1937). From calciferol by adsorption on acid clay: Thibaudet, *Compt. Rend.* 220, 751 (1945). From precalciferol: Velluz, Goffinet, U.S. pat. 2,847,426 (1958 to UCLAF). Structure: Grundmann, *Z. Physiol. Chem.* 252, 151 (1938); Thibaudet, *loc. cit.* Stereochemistry of the tachysterol system: Inhoffen, *Ber.* 88, 1424 (1955); Verloop, *Rec. Trav. Chim.* 76, 689 (1957); Delaroff *et al., Bull. Soc. Chim. France* 1963, 1739.

9450. 1,1,2-Trichloroethane. Vinyl trichloride. $C_2H_3Cl_3$; mol wt 133.42. C 18.00%, H 2.27%, Cl 79.73%. CH_2Cl-$CHCl_2$. Prepd by catalytic chlorination of ethane or ethylene: Joseph, U.S. pat. **2,752,401** and Pye, U.S. pat. **2,752,402** (both 1956 to Dow); Reynolds, U.S. pat. **2,783,286** (1957 to Olin Mathieson).

Nonflammable liquid; pleasant odor; d_4^{20} 1.4416; solidif −35°; bp 113-114°; n_D^{20} 1.4711. Insol in water; misc with alcohol, ether, and many other organic liquids. LD_{50} orally in rats: 0.58 ml/kg, H. F. Smyth *et al., Am. Ind. Hyg. Assoc. J.* **30**, 470 (1969).

USE: Solvent for fats, waxes, natural resins, alkaloids. *Caution:* Irritating to eyes, mucous membranes, and, in high concns, narcotic.

9451. 2,2,2-Trichloroethanol. Trichloroethyl alcohol. $C_2H_3Cl_3O$; mol wt 149.42. C 16.08%, H 2.02%, Cl 71.19%, O 10.71%. CCl_3CH_2OH. Prepd by reduction of the corresponding ester, acid chloride, or acid with lithium aluminum hydride: Sroog *et al., J. Am. Chem. Soc.* **71**, 1710 (1949). Manufacture by reduction of chloral hydrate with an amine borane: Chamberlain, Schechter, U.S. pat. **2,898,379** (1959 to Callery Chem.).

Hygroscopic liquid, ethereal odor. At low temps it crystallizes in rhombic tablets. mp at 18°; bp 151-153°; d_{20}^{20} 1.55. Sol in about 12 parts water; miscible with alcohol or ether. pH of aq soln is 5-6, but on prolonged contact with water some free acid is formed. *Keep well closed and protected from light.* LD_{50} orally in rats: 600 mg/kg, *Handbook of Toxicology* **vol. 1**, W. S. Spector, Ed. (Saunders, Philadelphia, 1955) pp 302-303.

THERAP CAT: Hypnotic, anesthetic.

9452. Trichloroethylene. *Trichloroethene;* ethinyl trichloride; Tri-Clene; Trielene; Trilene; Trichloran; Trichloren; Algylen; Trimar; Triline; Tri; Trethylene; Westrosol; Chlorylen; Gemalgene; Germalgene. C_2HCl_3; mol wt 131.40. C 18.28%, H 0.77%, Cl 80.95%. CCl_2=CHCl. Usually prepd from *sym*-tetrachloroethane by elimination of HCl (by boiling with lime): **Ger. pat. 171,900.** By passing tetrachloroethane vapor over $CaCl_2$ catalyst at 300°: Ger. pat. **263,457**; without catalyst at 450-470°: **Brit. pat. 575,530** (1946 to du Pont). Review of mfg processes: S. A. Miller, *Chem. Process Eng.* **47**, 268 (1966); Faith, Keyes & Clark's *Industrial Chemicals*, F. A. Lowenheim, M. K. Moran, Eds. (Wiley-Interscience, New York, 4th ed., 1975) pp 844-848. Toxicity and metabolism: E. Browning, *Toxicity and Metabolism of Industrial Solvents* (Elsevier, New York, 1965) pp 189-212.

Nonflammable, mobile liquid. Characteristic odor resembling that of chloroform. d_4^4 1.4904; d_4^{15} 1.4695; d_4^{20} 1.4649. Vapor density: 4.53 (air = 1.00). Solidifies at −84.8°. bp_{760} 86.7°; bp_{400} 67.0°; bp_{200} 48.0°; bp_{100} 31.4°; bp_{40} 20.0°; bp_{20} −1.0°; bp_{10} −12.4°; bp_5 −22.8°; $bp_{1.0}$ −43.8°; n_D^{17} 1.47914; n_D^{25} 1.45560. Practically insol in water; misc with ether, alcohol, chloroform. Dissolves most fixed and volatile oils. Slowly dec (with formn of HCl) by light in the presence of moisture. Trichloroethylene for medicinal purposes may contain some thymol or ammonium carbonate (not more than 20 mg/100 ml) as a stabilizer. Industrial grades of trichloroethylene may contain other stabilizers such as triethanolamine stearate and cresol. LD_{50} orally in rats: 4.92 ml/kg; LC (4 hrs) in rats: 8000 ppm, Smyth *et al., Am. Ind. Hyg. Assoc. J.* **30**, 470 (1969).

Caution: Use with adequate ventilation. Preserve trichloroethylene in sealed, light-resistant ampuls or in frangible, light-resistant glass tubes. Avoid prolonged exposure of the product to excessive heat. It must be dispensed in the unopened glass container in which it was placed by the manufacturer.

Human Toxicity: Moderate exposures can cause symptoms similar to alcohol inebriation. Higher concns can have narcotic effect. Deaths occurring after heavy exposure have been attributed to ventricular fibrillation. Liver injury is not definitely established in occupational exposures. Found to induce hepatocellular carcinomas in National Cancer Institute tests on mice: *Chem. & Eng. News* **54**, 4 (Apr. 5, 1976).

USE: Solvent for fats, waxes, resins, oils, rubber, paints, and varnishes. Solvent for cellulose esters and ethers. Used for solvent extraction in many industries. In degreasing, in dry cleaning. In the manuf of organic chemicals, pharmaceuticals, such as chloroacetic acid.

THERAP CAT: Analgesic (inhalation).

THERAP CAT (VET): Inhalant anesthetic.

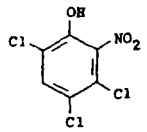
9453. Trichlorofluoromethane. Trichloromonofluoromethane; fluorotrichloromethane; Freon 11; Frigen 11; Arcton 9. CCl_3F; mol wt 137.38. C 8.74%, Cl 77.43%, F 13.83%. Prepn: Henne, *Organic Reactions* **2**, 64 (1944). Manuf: Faith, Keyes & Clark's *Industrial Chemicals*, F. A. Lowenheim, M. K. Moran, Eds. (Wiley-Interscience, New York, 4th ed., 1975) pp 325-330.

Liquid at temps below 23.7°. Faint ethereal odor. Nonflammable. $d_4^{17.2}$ 1.494; d_{gas}^{25} 5.04 (air = 1). mp −111°. bp_{760} 23.7°; bp_{400} +6.8°; bp_{200} −9.1°; bp_{100} −23.0°; bp_{60} −32.3°; bp_{40} −39.0°; bp_{20} −49.7°; bp_{10} −59.0°; bp_5 −67.6°; $bp_{1.0}$ −84.3°. Crit temp 198°; crit press. 43.2 atm (635 lb/sq inch, abs). $n_D^{18.5}$ 1.3865. Dipole moment 0.45. Practically insol in water. Sol in alcohol, ether, other, organic solvents. Less toxic than carbon dioxide, but decomposes into harmful materials by flames or high heat.

USE: In refrigeration machinery requiring a refrigerant effective at negative pressures. As aerosol propellant. *Caution:* May be narcotic in high concentrations.

Note: Consult latest Government regulations on use as aerosol propellant.

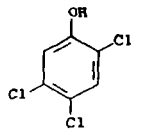
9454. 3,4,6-Trichloro-2-nitrophenol. 2-Nitro-3,4,6-trichlorophenol; 2,4,5-trichloro-6-nitrophenol; Dowlap. $C_6H_3Cl_3NO_3$; mol wt 242.44. C 29.72%, H 0.83%, Cl 43.87%, N 5.78%, O 19.80%. Prepd by dissolving 2,4,5-trichlorophenol in glacial acetic acid and treating with concd nitric acid: Kohn, Fink, *Monatsh.* **58**, 73 (1931); Harrison *et al., J. Chem. Soc.* **1943**, 235.



Pale yellow crystals from petr ether, mp 92-93°.

USE: To combat the sea lamprey, an eel-like fish which attacks trout, especially in the Great Lakes region.

9455. 2,4,5-Trichlorophenol. Collunosol; Dowicide 2. $C_6H_3Cl_3O$; mol wt 197.46. C 36.49%, H 1.53%, O 8.10%, Cl 53.87%. Prepd by treating 1,2,4,5-tetrachlorobenzene with methanolic NaOH in autoclave at 160° for several hrs: Harrison *et al., J. Chem. Soc.* **1943**, 235; Agfa, Ger. pat. **411,052** (1925); *Chem. Zentr.* **1925, I**, 2411.



Needles from alcohol or ligroin. Strong phenolic odor. mp 67°. Sublimes. bp_{746} 248°. bp_{760} 253°. Weak monobasic acid. K at 25° = 4.3 × 10^{-8}. Soly (g/100 g of solvent at 25°): acetone 615; benzene 163; carbon tetrachloride 51; ether 525; denatured alcohol formula 30, 525; methanol 615; liquid petrolatum (at 50°) 56; soybean oil 79; toluene 122; water <0.2. LD_{50} orally in rats: 0.82 g/kg, Deichmann, *Fed. Proc.* **2**, 76 (1943).

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Complex with triisobutyl phosphate, $C_{18}H_{30}ClO_3P$, *Trichlorex.* Prepn: Bouillenne-Wallrand *et al.*, Fr. pat. **M149** (1961 to Pechiney). Liquid. $bp_{0.01}$ 94-103°.

USE: Fungicide, bactericide.

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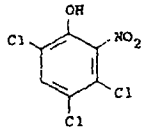

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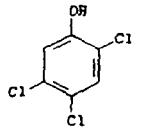

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