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UNITED STATES PATENT OFFICE

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PROCESS OF MANUFACTURING CHLORAL

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2 Claims. (Cl. 260—601)

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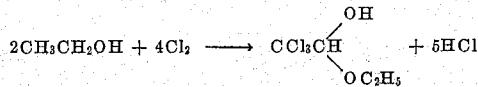
My present invention relates to the manufacture of chloral by the chlorination of ethyl alcohol.

It is a principal object of my invention materially to increase the yield of chloral by such process. In addition to its higher yield, my improved process permits greater capacity to be had from the same or equivalent equipment heretofore used.

In addition to its many older uses, chloral is now one of the starting materials in the manufacture of DDT (1,1,1-trichloro-2,2-bis (p-chlorophenyl) ethane).

The method now in general use, which is essentially the textbook method for making chloral, consists principally in introducing chlorine into ethyl alcohol until the specific gravity of the mixture reaches a value between 1.50 and 1.60 at 20° C. after which the reaction products are mixed with sulphuric acid and distilled or the chloral layer in the vessel is separated, as by decanting and used directly in the manufacture of DDT for its chloral content. If the mixture is distilled with sulphuric acid the distillate may be used directly or it may be purified by further fractional distillation or by other known methods.

The mechanism in the liquid phase chlorination of alcohol is not very clear, various explanations having been advanced. But as final result a mixture containing mostly chloral alcoholate is formed, so that the reaction can be summarized as follows:



In practice an excess of chlorine is used which, however, does not convert the alcohol content of the chloral alcoholate to chloral but rather to ethyl chloride and other undesirable products from the point of view of chloral manufacture. Thus the maximum theoretical yield obtainable is one mole of chloral for two moles of alcohol or 10.5 lbs. chloral per gallon of ethyl alcohol. Of course, in actual practice, owing to undesirable side reactions and physical and mechanical losses, this theoretical yield is never obtained, actual yields based on alcohol being 9 lbs. of chloral per gallon of alcohol which is 85% of the above theory, assuming two moles of alcohol to be required for one mole of chloral.

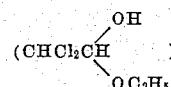
The older literature specifies the use of absolute alcohol for the production of chloral although many producers use ordinary 95% alcohol. However, it is generally accepted in the art that the presence of water in excess of that required to form 95% alcohol by volume produces lower yields of chloral and is to be avoided.

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Contrary to this accepted theory and practice I have found that as described herein the addition of water to the reaction in proper amounts is highly beneficial. Further, I have found that for the highest yields at least the major portion of the water should be added after the reaction has proceeded to a certain point, although a substantial increase in yield as compared to the classic method will be had even if all the water be added initially. In brief, the presence of a sufficient amount of water changes the mechanism of the reaction transforming it from a reaction conducted in an organic medium into one conducted in an aqueous medium so that in theory only one mole of alcohol is required to produce one mole of chloral.

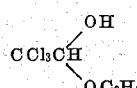
In actual practice the yields obtained are in excess of 70% of this theory, i. e., assuming one mole of alcohol to be theoretically required to produce one mole of chloral. Expressed in other units, a gallon of alcohol will thus yield 15 lbs. of chloral or over 60% more than is obtained by the classic method.

I have found that in the classic method of chlorinating alcohol, the absorption of chlorine proceeds very rapidly until a specific gravity at 25° C. of 1.33 plus or minus .05 is reached. I found this point to correspond to the point of substantially complete formation of dichloroacetaldehyde alcoholate

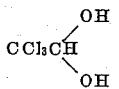


as evidenced first by the amount of chlorine absorbed, second by the amount of hydrochloric acid given off, third by the increase in weight of the chlorinated alcohol and fourth by the actual isolation of dichloroacetaldehyde by distillation with sulfuric acid, all of which quantities I have found to correspond for all practical purposes with those theoretically required for the formation of the said dichloroacetaldehyde alcoholate.

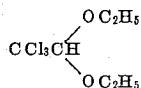
From this point on in the classic method of operation, the absorption of chlorine proceeds very slowly and large excesses of chlorine are necessary for the maximum yield of chloral. It is common to consider the chlorination complete when a specific gravity of 1.50 to 1.60 at 20° C. is reached. The end products consist of a mixture of chloral alcoholate



chloral CCl_3CHO , chloral hydrate



and chloral diethylacetal



which are further treated as already described.

If now at the point in the classic method above described where a gravity of 1.33 plus or minus .05 at 25° C. is reached, the proper amount of water is added, the mechanism of the reaction is changed with the results stated. In accordance with an explanation which I believe to be correct the water which is added at this point in sufficient amounts performs two functions: 1) it acts as a solvent and dielectric thus facilitating further chlorination, 2) it partially hydrolyzes dichloroacetaldehyde alcoholate and subsequently chloral alcoholate which are formed into their respective hydrates and alcohol, which is thus released for further chlorination. This latter proceeds smoothly and rapidly to the formation of a major portion of chloral hydrate which sometimes contains small quantities of chloral alcoholate and chloral diethylacetal. If desired, the chloral may be separated in any convenient known way or the crude chloral mixture may be used directly in the manufacture of DDT, or the reaction mixture may be distilled with sulphuric acid to give chloral in excess of 70% of the theory as above pointed out.

In general the amount of water added should be somewhat greater than that stoichiometrically required for the formation of the chloral hydrate and I have found in practice that this quantity should vary between somewhat in excess of 1 and not in excess of 3 moles per mole of alcohol started with, preference being had for the quantity of 2 moles of water per mole of alcohol. It will be understood that the addition of water in excess of 3 moles per mole of alcohol started with merely dilutes the reacting products and thereby causes a reduction of the yield. Similarly if an amount of water is added which is less than 1 mole per mole of alcohol, the chlorination is found to be incomplete.

My invention will be further explained by the following illustrative example:

206 cc. of 95½% (by volume) alcohol (3.37 moles) is placed in a suitable vessel provided with reflux condenser and means of introducing chlorine gas. The chlorine is introduced as rapidly as it is absorbed as evidenced by the practical absence of chlorine in the exit gases. The evolved hydrochloric acid gas is absorbed in a suitable trap.

The temperature soon approaches the boiling point of the mixture and the rate of addition of chlorine will depend to some extent on the efficiency of the reflux condenser as care should be exercised not to exceed its capacity to return condensable vapors to the chlorinating vessel. Given a rate of 3½ grams of chlorine per minute, in about 2½ hours the chlorination mixture will have increased so as to weigh from 260 to 280 grams. The specific gravity will be between 1.29 and 1.35 at 25° C., the HCl traps by weight or titration will show an increase of about 245 grams of HCl gas (equivalent to two moles per mole of

alcohol). All such data correspond to the point where the alcohol has been chlorinated to yield a maximum of dichloroacetaldehyde alcoholate.

Now 120 cc. of water are added and the introduction of chlorine is continued at the rate of 2.5 gms. per minute for about 8 hours. During this stage the chlorinating vessel should be heated by any suitable means to reach and maintain the boiling temperature of the mixture, which averages about 95° C. Chlorinating below the boiling points slows down the rate of chlorination; chlorination under pressure which raises the boiling points, increases the rate of chlorination. At the end of this period the weight of the chlorination mixture should be between 500 and 550 gms. and its specific gravity should be between 1.50 and 1.57 at 25° C.

For practical purposes the chlorination may now be considered completed and if free chloral is desired the product is treated in the usual manner, that is, the mixture is mixed with an approximately equal volume of concentrated sulphuric acid and distilled to yield about 362 grams of chloral, equivalent to 73% of the theory based on one mole of alcohol to yield one mole of chloral. When the 120 cc. of water was added at the start of the chlorination instead of at the point mentioned in the above example the yield was 60% of this theory. In explanation it may be pointed out that the formation of dichloroacetaldehyde alcoholate is not facilitated, though not prevented entirely by having not in excess of a slight amount of water present.

Various departures from the specific example given will occur to those skilled in the art, without, however, departing from the spirit of my invention. For example, absolute alcohol may be started with, although no substantial advantage has been found to occur from its use.

40 I claim:

1. In the method of making chloral by the liquid phase chlorination of ethyl alcohol in which chlorine is passed into alcohol of not substantially less than 190° proof, the steps which consist in adding water to the reacting mixture formed by the passing of said chlorine into said alcohol at the point where the formation of dichloro-acetaldehyde alcoholate is substantially completed and before any substantial amount of chloral alcoholate is formed, as is evidenced by the specific gravity of the reacting mixture being substantially 1.33 as of 25° C., the amount of water added being substantially two mols per mol of alcohol started with and continuing the chlorination at temperatures not substantially lower than the boiling point of the mixture until the formation of chloral hydrate is substantially complete.

2. The method according to claim 1 in which chloral is recovered by distillation of the reaction products with sulphuric acid.

JACOB ROSIN.

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United States Patent Office

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Patented Aug. 21, 1956

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2,759,978

PRODUCTION OF CHLORAL

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Serial No. 354,382

6 Claims. (Cl. 260—601)

The present invention relates to a novel method for producing chloral.

According to the present invention, chloral may be prepared by reaction of hypochlorous acid and trichloroethylene. Notably, this reaction is performed in the liquid phase, e. g., with the temperature of the reaction being such that the reacting mass is liquid. As will become more apparent, the reaction temperature may be varied widely as long as it permits the presence of a liquid phase in the reaction mixture.

In accordance with this invention, hypochlorous acid and trichloroethylene are brought in contact and permitted to react in a liquid phase. This may be achieved, for example, by mixing trichloroethylene and hypochlorous acid at a temperature between the freezing and boiling points of trichloroethylene when the acid is added to a pool of the trichloroethylene.

In a preferred expedient for accomplishing the desired reaction, aqueous solutions of hypochlorous acid are employed as one of the reagents. Thus, an aqueous solution of hypochlorous acid and trichloroethylene may be introduced into a reaction zone and permitted to react. Generally, however, it is advantageous to add trichloroethylene to a pool of aqueous hypochlorous acid. Alternatively, the aqueous acid solution may be introduced into a pool of trichloroethylene. In the former procedure, the temperature of the pool is between about plus 30° C. and minus 40° C., such that the aqueous acid does not solidify. Within this temperature range, the specific minimum temperature employed is related to the concentration of the acid, with more concentrated acid solutions permitting the lower temperatures by depressing the freezing point of the solution.

It has been found that practice of this embodiment of the invention requires that concentrated solutions of aqueous hypochlorous acid be utilized. Solutions of 1 molar strength and above are necessary, and as used herein, the phrase "concentrated solutions of hypochlorous acid" is meant to define solutions of at least 1 molar strength. Preferably, solutions of about 3 molar or stronger are used. The hypochlorous acid should be maintained at such strengths for at least the major portion of the reaction, e. g., at least 50 per cent conversion of one of the reactants. In this regard, it may be noted that aqueous solutions of chlorine are not suitable for use in performing the reaction with trichloroethylene even though some hypochlorous acid may be present therein by virtue of reaction of elemental chlorine with water. Moreover, elemental chlorine is undesirable and the aqueous solutions of hypochlorous acid should not contain any appreciable quantity of elemental chlorine. An aqueous solution of hypochlorous acid which contains less than 10 parts per million of chlorine by weight of the HOCl is preferred, and for purposes of this invention an acid having such an elemental chlorine content is considered to contain essentially no elemental chlorine.

Elemental chlorine appears to more readily react with trichloroethylene than hypochlorous acid under normal

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reaction conditions and, therefore, should not be present in the reaction medium. Complete absence of elemental chlorine is preferred. However, the reaction may be performed in the presence of some elemental chlorine if the equivalents of the reactants exceed the chlorine equivalent. For example, if one mole of hypochlorous acid and one mole of trichloroethylene are present in the reaction mixture and the amount of elemental chlorine therein is below one mole, chloral may be produced. A decrease in yield, however, may be expected when elemental chlorine is present.

Normally, the hypochlorous acid is treated to insure the absence of appreciable quantities of elemental chlorine, and preferably the total absence thereof. One expedient that is used involves blowing air through the acid which has been cooled, such as by contact with an ice bath. The elemental chlorine content of the acid may be determined for example, by taking a sample of the treated acid, adding a potassium iodide solution, titrating to the disappearance of color with a sodium thiosulfate solution, adding some hydrochloric acid, and completing the titration.

It appears that yield of chloral is related to the concentration of hypochlorous acid, with higher concentrations apparently favoring increased yields of chloral. Usually it is beneficial to employ acid solutions of strengths in excess of about three molar. It further appears that the concentration of the acid in the liquid phase of the reacting mass is related to the yield. At higher acid concentrations, more favorable yields appear possible.

One embodiment of this invention takes advantage of the above-outlined apparent effects on yield by introducing trichloroethylene into a pool of aqueous hypochlorous acid, notably a solution having a strength of at least 3 molar. In this manner, higher concentrations of acid in the reaction mixture may be attained. Adjunct to this expedient is the addition of less than theoretical amounts of trichloroethylene (or an excess of hypochlorous acid), so that the conversion is performed while the mixture contains high concentrations of hypochlorous acid.

The reaction of hypochlorous acid and trichloroethylene is equimolar, one mole of each reagent reacting. Thus, this invention is performed by employing equimolar ratios of the reactants. Under certain circumstances, such as the one described in the preceding paragraph, an excess of hypochlorous acid may be utilized. It will, of course, be realized that any ratio of reactants is suitable as far as preparing chloral is concerned.

Temperatures as low as about minus 40° C. may be employed when trichloroethylene is added to a pool of liquid aqueous hypochlorous acid solution. When such low temperatures are employed, concentrated acid solutions are required to avoid solidification. Typically at about minus 20° C., a 7.7 molar solution of hypochlorous acid is suitable to preclude freezing. Above 0° C., the minimum concentration of acid that may be employed is chosen in accordance with the freezing point curve of the acid solution.

Recovery of chloral from the reaction mixtures is possible in accordance with several techniques. For example, the chloral may be separated by extraction with a suitable solvent, e. g., ethyl ether and thereafter evaporating the solvent leaving the product. The chloral may be recovered by fractional distillation of the reaction mixture after first neutralizing the mixture (notably unreacted hypochlorous acid).

Chloral may be isolated from the aqueous distillate obtained when the reaction mixture is fractionally distilled by adding benzene, n-hexane, or other entrainment to the aqueous solution and performing an azeotropic distillation until the water is removed. The remaining

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bottom mixture may thereafter be distilled to recover the purified chloral. It is also possible to recover chloral by addition of sulfuric acid to the aqueous distillate, and thereafter distilling the mixture.

The following examples illustrate the manner in which this invention may be performed:

Example I

Five moles (657 grams) of essentially pure trichloroethylene were placed in a three-necked, three-liter flask provided with a paddle-type stirrer, adding funnel, thermometer, and gas outlet tube. The gas outlet was connected to a carbon dioxide-acetone cooled trap. The flask was disposed in an ice salt bath and the contents were cooled to 5° C.

To the cooled charge, with the stirrer operating, was added 1,615 milliliters of 3.1 molar aqueous hypochlorous acid solution over a period of 105 minutes via the adding funnel while maintaining the temperature at 5° C. to 10° C. This acid solution was previously treated to remove elemental chlorine by blowing air through it while cooling it in an ice bath. The temperature of the reac-

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Todd column until the refractive index of the distillate was 1.3332, indicative that all chloral had been removed. This required distillation until 524 milliliters of distillate had been collected. The yield of chloral, determined by analysis of the refractive index of the distillate indicated 102.2 grams (0.69 mole) were prepared.

The water insoluble phase (organic phase) was distilled in a 2.5 x 70 centimeter column packed with glass helices at barometric pressure (737 millimeters mercury) to determine the composition thereof. About 0.43 mole trichloroethylene, 2.53 moles pentachloroethane, and 0.06 mole dichloroacetyl chloride were recovered.

Overall, approximately 91 per cent of the olefin was converted. Based on the olefin conversion, the yield of chloral was about 30 per cent.

Example II

A series of experiments were conducted following the general procedure described in Example I to illustrate various modes of performing the reaction.

The following table lists these experiments, the variation in procedure, and the results:

Exp. No.	Method	HOCl Concentration, (Molarity)	Trichloroethylene Conversion, Percent	Yields based on Trichloroethylene Consumed, percent	
				Chloral	Penta-chloro-ethane
44	Similar to Example I except trichloroethylene added to HOCl.	3.4	81	40	44
53	Same as No. 44 except temperature = 15-20° C.	2.8	73	37	52
54	Same as No. 53 with no stirring after addition of trichloroethylene finished.	3.1	69	38	48
57	Duplicate of No. 44 except temperature was minus 5° to minus 8° C.	3.2	60	44	48
58	Same as No. 54 except 1.5 molar HOCl	1.5	50	28	62
59 ¹	Trichloroethylene added to 7.7 molar HOCl at minus 18° to minus 29° C.	7.7	97	73	21

¹ In this experiment, only 0.59 mole of trichloroethylene added per mole of HOCl in the reaction mixture.

tion mixture was held at 5° C. to 10° C. for 50 additional minutes. To neutralize the unreacted hypochlorous acid (analysis of a sample revealed that 94.5 per cent of the acid had reacted), 270 milliliters (0.32 mole) of an aqueous solution of sodium sulfite containing 15 per cent by weight of sodium sulfite was added.

The organic layer was separated and washed twice with 100 milliliters of water. This was washed further with 100 milliliters of an aqueous sodium carbonate solution containing 10 per cent by weight of sodium carbonate, 50 milliliters of water and then 100 milliliters of saturated aqueous sodium chloride solution (at room temperature). All the washings were extracted with 100 milliliters of ethyl ether, the ether extract being combined with the organic layer, and the mixture was dried over anhydrous sodium sulfate.

The aqueous layer was extracted with a 50-milliliter portion of petroleum ether (B. P. 35-70° C.) to remove any trace of pentachloroethane that might be present. Chloral hydrate is relatively insoluble in petroleum ether. A solution containing chloral hydrate and 2,100 milliliters in volume was obtained. It was divided in two equal parts, each portion being treated differently.

One part (1,050 milliliters) was extracted twice with 1,000-milliliter portions of ethyl ether. After treating the ether extract with two 50-milliliter portions of an aqueous solution of sodium carbonate containing 10 per cent by weight of sodium carbonate, the ether was removed from the extract by heat distilling through a column to a maximum residue temperature of 80°-85° C. Analysis indicated that 96 grams (0.65 mole) of chloral was in the residue.

The second part was distilled in a 1.2 x 90 centimeter

While the invention has been described with reference to batchwise operations, the reaction of HOCl with trichloroethylene to prepare chloral may be performed in a continuous manner by establishing a reaction zone containing an appropriate reaction medium and withdrawing continuously or periodically a portion of that medium while adding reactants to the zone at appropriate rates. After recovering the product, the unreacted reagents may be appropriately purified if necessary, and recycled to the zone as a portion of the fresh reagents being added.

Although the invention has been described with reference to certain details of specific embodiments, such details are not intended to be construed as limitations thereon except insofar as they are included in the accompanying claims.

We claim:

- 60 1. The method of reacting hypochlorous acid and trichloroethylene to produce chloral which comprises adding trichloroethylene to a liquid pool containing an aqueous concentrated solution of hypochlorous acid.
- 65 2. The method of preparing chloral which comprises reacting trichloroethylene and an aqueous concentrated solution of hypochlorous acid.
- 70 3. The method of claim 2, wherein the hypochlorous acid solution is essentially free from elemental chlorine.
- 75 4. The method of preparing chloral which comprises reacting trichloroethylene and an aqueous concentrated solution of hypochlorous acid, the molarity of said hypochlorous acid solution being at least about 3.0.
5. The method of reacting hypochlorous acid and trichloroethylene to produce chloral which comprises adding trichloroethylene to a liquid pool containing an aqueous

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concentrated solution of hypochlorous acid, the concentration of said acid solution being at least about 3.0 molarity throughout a major portion of the reaction period.

6. The method of claim 5 wherein the acid solution is essentially free from elemental chlorine.

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Chemical Reviews

Volume 75, Number 3 June 1975

The Chemistry of Chloral†

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I. Introduction

Over a century has passed since the discovery of chloral by Liebig,¹ who named it, and also since the first Dumas² experiments with it. But new horizons in the chemistry of chloral are being opened to this day, despite the great amount of knowledge already attained in this realm. In recent years a catalytic function of chloral has been discovered, as well as its reactivity toward element- (Pb-, Sn-, Si-) organic compounds, ketene and its hetero analogs, and so on.

† EDITOR'S NOTE: This manuscript required extensive language editing before it could be published. The editor tried to follow the author's presentation as closely as possible and apologizes for any changes in meaning that may have crept in as the English was being clarified.

Well known are such key syntheses based on chloral as dichloroacetic acid and its derivatives (for example, syntomicine), vanillin, isatin, DDT, phosphororganic pesticides, etc.

The presence of two functional groups—carbonyl and trichloromethyl—in the chloral molecule and their mutual activating influence extend the synthetic capabilities of chloral as a compound with dual reactivity. It can be transformed into dichlorovinyl and formyl derivatives.

Regrettably, reviews dealing with the chemistry of aldehydes^{3,4} do not give chloral sufficient consideration, and even short reviews^{5,6} do not supply any knowledge about the research for the last 30 years or so. Perhaps this accounts for duplications in research, and for a certain inaccuracy in outlining some of chloral's properties in organic chemistry courses and in reference books.

The object of the present review is to generalize our knowledge of the chemistry of chloral up to 1971 inclusive. With the aim of drawing the reader's attention to the chemistry of chloral, it has been expedient to omit several early physical results, as well as numerous publications about the biological action of chloral.

The reactivity of the trichloromethyl group (reduction, radiolysis, photolysis, the relation to nucleophilic agents, etc.) is not treated separately but is discussed together with that of the carbonyl group in the relevant sections of the review.

II. Methods of Preparation

The result of chlorination of ethanol or other substrates depends on the nature of the chlorinating agent. When ethanol is heated with calcium hypochlorite, one obtains chloral and also chloroform, dichloroacetaldehyde, and the hemiacetal of chloroacetaldehyde.⁷ Ethyl hypochlorite was proposed⁷ as the intermediate chlorinating agent in this reaction and acetaldehyde (with vinylic alcohol) as intermediates. At 20° trichloroacetic acid is obtained instead of chloral.⁷

Liebig¹ was the first to obtain chloral by passing chlorine through absolute ethanol. This method is in principle the most widespread to this day. The best results are achieved by chlorinating directly with chlorine. Many intermediates and by-products can be converted to chloral, a yield up to 70–80% being attainable in the presence of traces of water and by chlorinating until the specific weight reaches 1.57–1.63.^{8,9} A Japanese patent¹⁰ points to the necessity of traces of water, in the absence of which the yield of chloral diminishes more than three

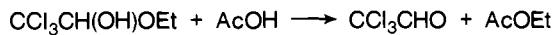
times. The reaction is not enhanced by uv irradiation¹¹ or by vapor-phase chlorination in an electric field;¹² in the last case many by-products are obtained (paraldehyde and dichloroacetaldehyde and their acetals, perchloroethane, di- and trichloroethyl ethers, and so on). Even when the reaction in an electric field (3–8 kV) is carried out with recirculation of the intermediate compounds, the yield is not increased.¹³ Electrochemical oxidation of ethanol at 110–115° in the presence of NaCl¹⁴ or CaCl₂¹⁵ leads to moderate yields of chloral (61% with cyanuric acid as catalyst¹⁵).

Many chemists recorded a gradual course of chlorination in stages through mono- and di- to trichloroacetaldehyde at temperatures of 0–100°. Even prolonged chlorination of ethanol at 35° does not lead to a high yield of chloral,¹⁶ only mono- and dichloroacetaldehydes being obtained. Too high a temperature (120–200°, with catalysis by FeCl₂, FeCl₃) is also undesirable.¹⁷

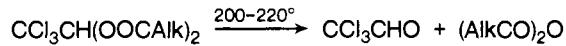
Several catalysts of heterolytic chlorination of ethanol were tested. Lewis acids,^{18–20} iodo, sulfur, and phosphorus chlorides,²¹ or a mixture of borax with SnI₄, H₃PO₄, AlCl₃ (3:1:3:3)²² are effective, but the temperature (80–100° at the end of the process,²³ as a rule) plays a decisive role.

Acetaldehyde is one of the intermediate products of the chlorination of ethanol, so one may consider chlorination of acetaldehyde as a modification of Liebig's method. This process is described in many articles and patents.^{24–40} Noncatalytic chlorination in aqueous solutions makes it possible to obtain chloral with yields up to 83–90%^{28,29,36} (preferably with addition of chloral hydrate to the initial solution). A high yield of chloral is reached in 7 N HCl.³⁴ In the absence of water and catalysts with excess of chlorine,³⁰ the main product is hexachloroparaldehyde. Chlorination of acetaldehyde in the presence of catalysts (Fe, Sb, Al, Zn, Sn, or P halogenides) yielded chloral, mono- and dichloroacetaldehyde,^{33,35–40} and also acetic acid and α-chlorocrotonaldehyde.⁴⁰ Only chloroacetaldehyde was isolated³³ in the absence of the catalyst. Selective catalysis by Cu(II) salts is recorded;³² the yield of chloral is as high as 93% without by-products. With regard to temperature, the conditions are similar to those for the chlorination of ethanol; intermediate mono- or dichloroacetaldehyde can be obtained with high yields if the reaction is completed at temperatures up to 30 and 60°, respectively. Chloral can be also obtained in addition to ethanol and acetaldehyde by chlorination of poly(ethylene glycol),⁴¹ ethylene chlorohydrin,⁴² chloroacetaldehyde,⁴³ and bis(β-chloroethyl) ether^{44,45} (in the last case in the presence of uv irradiation,⁴⁴ or in darkness,⁴⁵ with heating at over 100°; in all cases, at about 80–100°). In each case the presence of water is desirable.

Chloral was also obtained by an interchange of acetic acid with chloral alcoholate⁴⁶

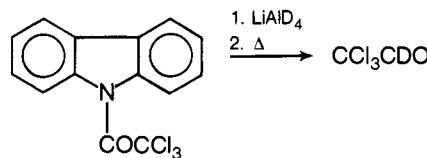


or by the thermolysis of chloral hydrate esters⁴⁷ such as



The interaction between CCl₄ or alkyl halides and aliphatic aldehydes under rigorous conditions (200–500°, 20–200 atm)⁴⁸ also produces chloral.

Only recently chloral-d⁴⁹ and chloral-t⁵⁰ were synthesized. In the first case the product obtained by reducing N-trichloroacetylcarbazole with LiAlD₄ was thermolyzed:

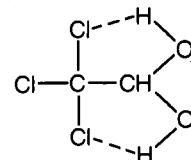


The interaction of chloral hydrate with T₂ at 12 Torr with subsequent dehydration over P₂O₅ produces CCl₃CTO.

III. Hydration. Stability of Chloral Hydrate Solutions

The high reactivity of the chloral carbonyl group toward nucleophiles is confirmed by the ease of formation of a stable hydrate, whose decomposition into the initial compounds is achieved only by distillation over concentrated H₂SO₄ or by azeotropic dehydration in toluene or benzene.^{51,52} This is connected with the destabilizing effect of the CCl₃ group on the carbonyl group.

The question about the bond character of water in chloral hydrate has remained open for a long time. Even now some investigators represent it as a complex, CCl₃CHO · H₂O, although many comprehensive physical researches confirm the *gem*-diol structure, CCl₃CH(OH)₂. The Raman spectrum⁵³ and osmometric measurements⁵⁴ confirm the presence of two hydrogen bonds in the molecule:



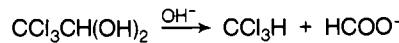
This is one of the reasons for the stability of chloral hydrate.

The length of the C–O bond (1.4–1.48 Å) is also evidence for the absence of a free carbonyl group.⁵⁵ Dipole moments of chloral and its hydrate,^{56,57} nmr spectra,⁵⁸ and other arguments^{59–61} also support the *gem*-diol structure.

In spite of the stability of chloral hydrate, its solutions are not stable. On the one hand, this is connected with the hydration equilibrium; some researchers^{53,62–65} have recorded decomposition with elimination of water, as judged, for instance, by the appearance of a carbonyl band in the ir spectra of chloral hydrate solutions in benzene and CCl₄.⁶²

On the other hand, chloral hydrate decomposes in neutral, acidic, and basic solutions. "Neutral" aqueous solutions are not stable for a long time;⁶⁶ after 15 weeks the pH decreases from 6.72 to 4.75–2.33 (more in light and on cooling). Uv irradiation accelerates this process; the pH decreases from 6.25 to 1.6 in 10 hr. Chloral hydrate has a low pK_a in water (10.04; in comparison the pK_a of methylene glycol is 13.27⁶⁷) but does not produce AgCl with silver ion. Nevertheless, the large decrease in pH of aqueous solutions on standing is the result of CCl₃-group destruction, with HCl formation.^{68,69} The instability of chloral hydrate in alkaline solutions is well known. But most investigators have taken into account only the heterolysis of C–C bonds or have made their studies at such pH and temperature ranges that the other reaction—hydrolysis of the trichloromethyl group without C–C bond rupture—has been repressed almost completely (see section VI.C).

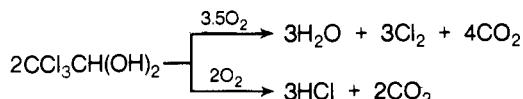
The exothermic reaction



is catalyzed by water, OH^- , and chloralate anion;⁷⁰ the energy of C-C bond dissociation is 62 kcal/mol.⁷¹ For this bimolecular reaction, the pH, temperature, and half-life are:⁷² 12, 22°, 25 min; 9, 20°, 4 days; 9, 60°, 1.5 hr; 8, 20°, 17.5 days; 8, 35°, 2 days.

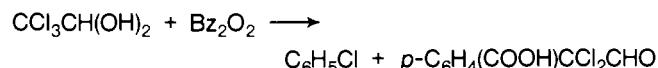
IV. Oxidation and Reduction with Typical Redox Reagents

Anhydrous chloral is oxidized by air in light⁷³⁻⁷⁵ with a temperature coefficient of 1.14⁷⁴ by means of a radical mechanism, forming phosgene, HCl , and CO or CO_2 . It is assumed that the reaction proceeds through either formyl chloride or dichloroketene which is subsequently decomposed. The following results were obtained, depending on the completeness of oxidation:⁶⁹



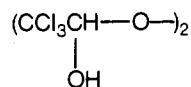
At the same time it was observed⁷³ that chloral in air and in darkness was stable for nearly 3 months.

Radical oxidation of chloral by heating with benzoyl peroxide in accordance with the following scheme

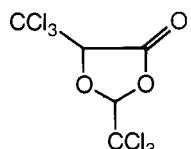


was patented,⁷⁶ but Wieland and Richter⁷⁷ have failed to reproduce that result.

The use of hydrogen peroxide and also of Karo's acid enabled Baeyer and Villiger⁷⁸ to be the first to obtain chloral α,α -dioxyperoxide, a good initiator for homolytic reactions.⁷⁹



By interaction of chloral with 30% H_2O_2 and oleum under mild conditions,⁸⁰ pertrichloroacetic acid is formed with a yield of 93%. Oleum itself oxidizes chloral to "chloralide." The reaction of concentrated H_2SO_4 with



chloral leads to a similar result.⁸¹⁻⁸³ On the other hand, Grabowski^{84,85} obtained from the reaction of oleum with chloral, besides chloralide, also the compounds $\text{C}_8\text{H}_6\text{O}_{11}\text{Cl}_2\text{S}_6$ (which decomposes into H_2SO_4 and chloral alcoholate upon the action of ethanol) and $\text{C}_{10}\text{H}_9\text{O}_{16}\text{Cl}_{15}\text{S}_3$ (which does not change with ethanol). The investigator attributed to them the complex structures $4\text{CCl}_3\text{CHO} \cdot \text{H}_2\text{S}_2\text{O}_7$ and $5\text{CCl}_3\text{CHO} \cdot \text{H}_2\text{S}_2\text{O}_7 \cdot \text{H}_2\text{SO}_4$; the correct structures have not been ascertained as yet.

Oxidation of chloral with aqueous HIO_3 at 100° leads to destruction of the chloral molecule, forming CO_2 , CHCl_3 , ICl_3 and iodine.⁸⁶ Fuming nitric acid oxidizes chloral to trichloroacetic acid,^{87,88} but it is possible to obtain a high (about 95%) yield as well by using 45-85% HNO_3 with gradual heating from 50 to 120°.⁸⁹ Under mild conditions dilute nitric acid reacts with chloral hydrate to give the mononitro ester.^{90,91} The action of nitrogen oxides has also been^{92,93} studied.

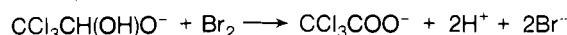
Some researchers took up the halogenation of chloral and its hydrate. Photochemical chlorination leads,

through the intermediate radicals $\text{CCl}_3\text{CO} \cdot$,⁹⁴ to trichloroacetyl chloride whose yield increases with a drop in temperature (55% at -50°, 7.3% at 10°)⁹⁵ owing to the subsequent decomposition to CCl_4 , CO , and HCl , which are the only reaction products at 70-90°.⁹⁴ Gautier⁹⁶ also observed the evolution of phosgene.

In the presence of aluminum chloride, heterolytic halogenation of chloral leads to hexachloroethane,⁹⁷ regardless of the nature of the halogen.

As a consequence of homolytic bromination in light at 70-90°, chloral is decomposed, forming a mixture of the following compounds:^{98,99} CO , HCl , HBr , BrCl , H_2O , CHCl_3 , COBr_2 , CBrCl_3 , with the activation energy amounting to about 6.5 kcal/mol. Vapor-phase bromination at 150° leads to CCl_3COBr , CCl_3Br , CO , and HBr .¹⁰⁰

Chloral hydrate is oxidized with bromine in water slowly according to the scheme:¹⁰¹

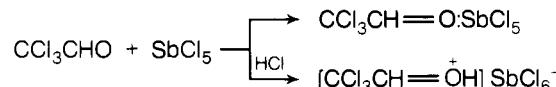


The activation energy is ca. 15.8 kcal/mol.

By heating chloral hydrate with solid potassium chloride,¹⁰² a mixture of CCl_3COOK , COCl_2 , CO_2 , Cl_2 , and CHCl_3 is produced.

Interaction of chloral and chlorosulfonic acid at 50° for a few days produced 1,2,2,2-tetrachloroethyl ether with a yield of 65%, along with chloralide. The same product is also obtained, but in a lower yield, in the reaction of chloral with fluorosulfonic acid. The investigators¹⁰³ assumed that an intermediate adduct was formed ($\text{CCl}_3\text{CHCl}-\text{OSO}_3\text{H}$, in the first case, and CISO_3H , in the second case) thereby accounting for both the identity of the reaction product and its reduced yield in the reaction with fluorosulfonic acid.

Oxidation of chloral hydrate by PCl_5 in acetone¹⁰⁴ leads to the formation of pentachloroethane and tetrachloroethylene. The same products are obtained¹⁰⁵ by heating chloral hydrate with aluminum chloride. With SbCl_5 chloral reacts as a Lewis base, forming an adduct in yield 80%;¹⁰⁶ in the presence of hydrogen chloride 56% of the onium salt is obtained:



Phosphorus pentasulfide under severe conditions (160° or higher)¹⁰⁷ converts chloral to trichloroethylene.

Boron halides can be involved in different reactions: boron trifluoride adds to the chloral carbonyl group as a Lewis acid;¹⁰⁸ with boron trichloride at -80° tris(1,2,2,2-tetrachloroethyl) borate is produced¹⁰⁹ with a yield up to 90%. The researchers noticed that, unlike chloral, bromal does not undergo this transformation, even at 20°.

In conclusion it should be noticed that only some of the oxidizing reagents in question can be used for oxidation of the chloral carbonyl group proper without the destruction of the substrate molecule. Besides the above-mentioned^{87,89,101} there are some other methods;¹¹⁰⁻¹¹⁵ for instance, trichloroacetic acid is obtained with good yields by the action of chloral with hypochlorites at pH 2-7,¹¹⁰ cerium perchlorate solution in HClO_4 ,¹¹² and CrO_3 ,¹¹⁶ and also by air oxidation but only in the presence of aqueous solutions of Cu(II) and Fe(III) salts.¹¹³

Electrolysis of chloral on a Pb anode¹¹⁶ at a current density of 1.25 A/dm² gives trichloroacetic acid with a yield of 72%.

In general, chloral's capacity for heterolytic oxidation, in comparison with that of other aldehydes, is weakened

as a consequence of the reduced electron density of the C-H bond caused by the strong negative inductive influence of the trichloromethyl group.

In view of the dual capacity of chloral for reduction (of the carbonyl and/or the trichloromethyl group), it is possible to choose conditions for such processes selectively. Reduction to mono- and dichloroacetaldehyde results from electrolysis with a copper or, preferably, a lead cathode; on a Pt cathode, chloral is not reduced.¹¹⁷ It is worth noting that trichloroacetic acid in each of the cases under consideration is reduced to monochloroacetic acid;¹¹⁷ CCl_4 is not reduced on a Pt cathode but is transformed into chloroform and dichloroethane¹¹⁸ on electrolysis with a Pb cathode.

Aluminum amalgam reduces chloral to dichloroacetaldehyde.¹¹⁹ More complete reduction to acetaldehyde is possible using hydrogen generated *in situ* (from Zn and HCl).¹²⁰ Heating with powder-like zinc or iron leads to destructive reduction with the formation of methane and dichloroethane.¹²¹

Recently¹²² reductive dehalogenation of chloral by chromium chloride in alcohol has been suggested. The trichloromethyl group is also reduced¹²³ by interaction of chloral with ammonium sulfide, although the structure of the product ($C_{18}H_{24}N_4O_6S_{13}$) was not established.

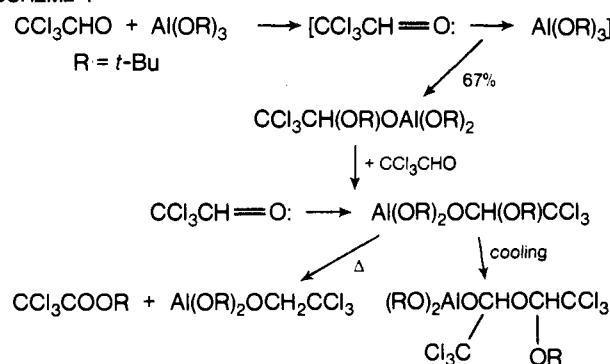
Upon interaction of chloral with hydrogen halides or their salts in an anhydrous medium, only potassium iodide reduces (chloroform and free iodine were isolated¹²⁴) while hydrogen chloride and bromide form solid adducts with chloral (1:1).¹²⁵

A study¹²⁶ of the oxidation-reduction interaction of chloral with Hg(I) and Hg(II) salts has shown that heating with HCOOHg produces the mixture Hg, Hg₂Cl₂, CO, CO₂, HCOOH, and H₂O; Hg(OAc)₂ is reduced by chloral hydrate to Hg(I).

Selective reduction of the carbonyl group to a hydroxyl group results from hydrogenation of chloral on powder-like Ni, Co, Fe, and also through nickel or copper chromite catalysis under vigorous conditions (120–150 atm, 50–150°).¹²⁷ If, however, such components as pyridine, hydrazine, acetonitrile, thiophenol, CuSO₄, HgCl₂, etc., are added to the reaction mixture, reduction of the trichloromethyl group also takes place, forming acetaldehyde and its mono- and dichloro-substituted derivatives.¹²⁷

A complex of calcium hydride with trimethyl borate reduces chloral hydrate in water-methanol¹²⁸ with a yield of trichloroethanol up to 60%. The same product is obtained¹²⁹ after hydrolysis of chloral with siloxene ($\text{Si}_6\text{H}_6\text{O}_3$) reduction product.

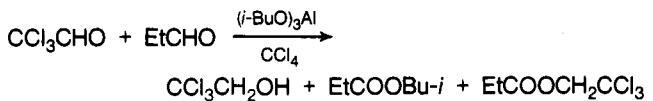
The trichloromethyl group is fully preserved in the reaction of chloral with metallic alcoholates. In the aspect of Tishchenko's reaction, chloral disproportionates into trichloroethanol and trichloroacetic acid. Upon interaction with aluminum ethylate, trichloroethyl trichloroacetate is formed.



tate is produced.¹³⁰ The same result was obtained¹³¹ upon reaction with aluminum β -trichloroethylate. The mechanism in Scheme I is assumed¹³² for the conversion of chloral under the influence of aluminum *tert*-butylate; all intermediate compounds, with the exception of the first one, were isolated and identified.

Meerwein and associates,¹³³ repeating Tishchenko's¹³⁰ experiment in a nitrogen atmosphere, obtained trichloroethanol with a yield of 88.5%. In the reaction of excess chloral with aluminum ethylate (10:1) in benzene, a mixture of ethyl and trichloroethyl trichloroacetate was obtained.¹³⁴ When the process was carried out in ethanol, and in a nitrogen or hydrogen atmosphere, trichloroethanol and acetaldehyde were also found¹³⁵ among the reaction products.

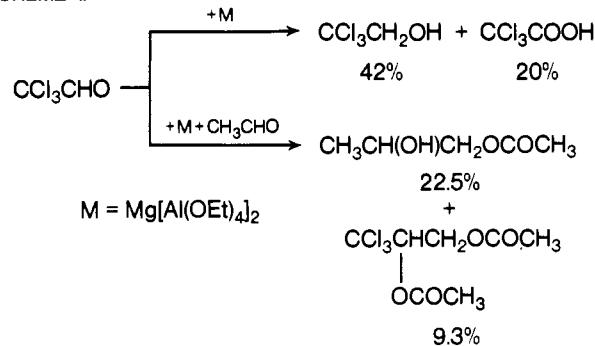
The use of magnesium and aluminum alcoholates in the interaction of chloral with acetaldehyde¹³⁶ and propionaldehyde¹³⁷ results in several products of a mixed Tishchenko reaction, for example



Heating with magnesium ethylate in ethanol solution leads to reduction with destruction, forming chloroform, ethyl formate, and carbon monoxide.¹³⁸

The behavior of chloral in the presence of complex alcohohlates¹³⁹ is shown in Scheme II.

SCHEME II



In conclusion, mention should be made¹⁴⁰ of chloral reduction by 1-benzyl-1,4-dihydronicotinamide in the presence of uv irradiation or peroxides; by that method selective homolytic reduction of the carbonyl to a hydroxyl group proceeds in cyclohexane. If nitromethane is the solvent, the carbonyl and the trichloromethyl groups are reduced simultaneously.

V. Radiolysis

Even in early research^{68,69} the instability of chloral and the appearance of acidity were recorded in its aqueous solutions; in the presence of light, decomposition of chloral with evolution of hydrogen chloride increases. Andrews and Shore¹⁴¹ discovered an acceleration of this process with γ -irradiation and, because of the linear conductivity dependence on dose of radiation, they recommended use of this effect for dosimetry. Even for that purpose, spectrophotometric control was suggested,¹⁴² based on the change of indicator color with pH variation as a function of radiation dosage.

Investigations by Spinks and McIntosh and associates¹⁴³⁻¹⁴⁷ have shown that on γ -irradiation (^{60}Co , ^{90}Sr), chloral decomposition has a free radical character. Decomposition to hydrogen chloride, trichloroethanol, and trichloroacetic acid¹⁴⁵ takes place both in the presence of oxygen and in a nitrogen or hydrogen atmo-

sphere; in the latter cases the hydrogen chloride yield decreases. Its yield depends not only on the radiation dose but also on the concentration of the chloral hydrate in solution.¹⁴⁸

Other kinds of irradiation likewise destroy the chloral molecule, splitting off hydrogen chloride. By a conductometric method, possible mono- and bimolecular heterolytic mechanisms of that reaction on X-irradiation was established.^{149,150} Decomposition of chloral upon the action of electron radiation¹⁴³ proceeds by a chain mechanism whose rate depends on the radiation dose and the initial substrate concentration; the hydrogen chloride yield also depends on the above factors. It has been noted¹⁵¹ that this method is not suitable for dosimetric purposes.

VI. Electrophilic Reactivity

The existence of two reaction centers—carbonyl and trichloromethyl carbon atoms—leads to a dual electrophilic reactivity of chloral. As a rule addition to the carbonyl group is preferred because its carbon atom is less hindered sterically than the other carbon atom. But in some cases both functional groups take part in the reaction.

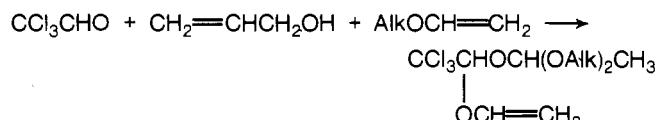
A. Interaction with Aliphatic Alcohols*

Anhydrous chloral adds vigorously monohydric alcohols, forming a hemiacetal (along with hemiacetals, products of exchange interaction may also be formed:³³⁴ $\text{CCl}_3\text{CH}(\text{OH})_2 + \text{RCH}_2\text{OH} \rightarrow \text{RCHO} + \text{CCl}_3\text{CH}(\text{OH})\text{CH}_2\text{R}$ where R = Me, Ph). Chloral hydrate reacts similarly, but for the most part in the presence of a catalyst. That role, as a rule, is played by concentrated H_2SO_4 which above all apparently dehydrates and also additionally polarizes the carbonyl group of chloral. Acetals are formed only with acid catalysis and azeotropic water distillation.¹⁵²⁻¹⁶³

For a kinetic study,¹⁵⁷ the hemiacetal of (R)-(-)-menthol with chloral was obtained in hexane in the presence of acetic acid.

Many patents are devoted to obtaining hemiacetals and acetals from steroidal alcohols for the purpose of producing biologically active compounds and drugs. High yields are achieved by interaction of the reagents in benzene or dioxane at 20° for 17–48 hr. In such a way hemiacetals of testosterone¹⁶⁴⁻¹⁶⁶ and some of its derivatives,¹⁶⁷⁻¹⁷⁰ 21-hemiacetals of cortisone, hydrocortisone, and prednisolone,¹⁷¹ 17-hemiacetal of estradiol, its 3-acetate and -benzoate,¹⁷² hemiacetals of tetracycline,¹⁷³ and 16,17-acetals of pregnane series^{174,175} were obtained. By interaction with cholesterol two isomeric products (mp 121 and 140°) were isolated, which are assumed to have the structure of trichloroacetates,¹⁷⁶ because these compounds are formed through replacement of chloral by trichloroacetic acid; with a rise in temperature, the yield of the high-melting isomer increases. The addition of monohydric unsaturated alcohols with an allylic type of multiple bond to chloral proceeds in the usual way, either with or without acidic catalysis,¹⁷⁷⁻¹⁸¹ forming acetals and hemiacetals.

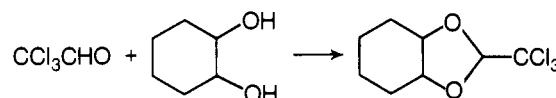
In the presence of vinylic ethers, addition of the intermediate hemiacetals to the ether C=C bond takes place; for example¹⁷⁹



* Interaction with aromatic alcohols is discussed in section VI.E.

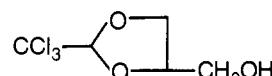
In this connection one may mention the interaction between chloral and camphor oxime. Frankforter and Mayo have isolated an adduct, from ether solution, characterized as the appropriate acetal.¹⁸² Later van Alphen and Drost¹⁸³ obtained under similar conditions a hemiacetal of composition $\text{C}_{10}\text{H}_{16}\text{NOCH}(\text{OH})\text{CCl}_3$ which was obtained before by Van Heyden¹⁸⁴ through interaction between the reagents in petroleum ether.

The products of a more complex structure are formed through interaction of chloral with polyhydric alcohols. In the case of 1,2-glycols, it is possible to obtain cyclic acetals if the process is carried out in the presence of concentrated H_2SO_4 and with azeotropic distillation of water; for instance¹⁸⁵



1,3-Glycols form mono- and bis(hemiacetals) of chloral.¹⁸⁶

With glycerol, depending on the reaction conditions, chloral produces a tris(hemiacetal)¹⁸⁷ or a cyclic acetal¹⁸⁸

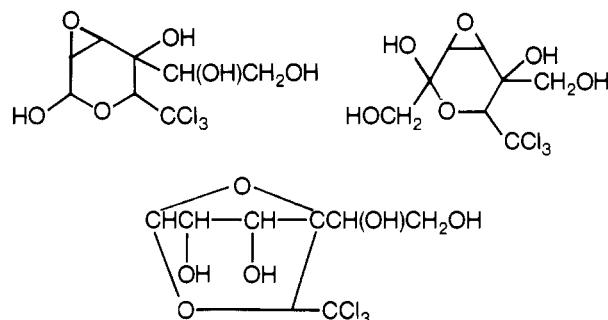


On distillation of chloral hydrate with a fivefold excess of glycerol, the following decomposition products were isolated:¹⁸⁹ formic acid, chloroform, and allyl formate.

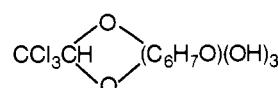
Bis-, tris-, and tetrakis(hemiacetals) are formed with pentaerythritol.^{187,190-192} Tetrakis(hemiacetals) are obtained by fusion of the reagents at 140° for 3 hr.¹⁸⁷ In this respect chloral differs from other aldehydes (and ketones) which form only bis acetals (and ketals)¹⁹⁰ with pentaerythritol.

Hemiacetals containing up to six chloral fragments were obtained with mannitol and sorbitol.^{187,192}

Attention of many researchers has been drawn to the structure of the interaction products between chloral and glucose. The series of early investigations¹⁹³⁻¹⁹⁶ told about obtaining 1:1 adducts named α - and β -glucochloralose. Later Hixon and associates^{197,198} pointed out that the structures of these compounds suggested by the ear-

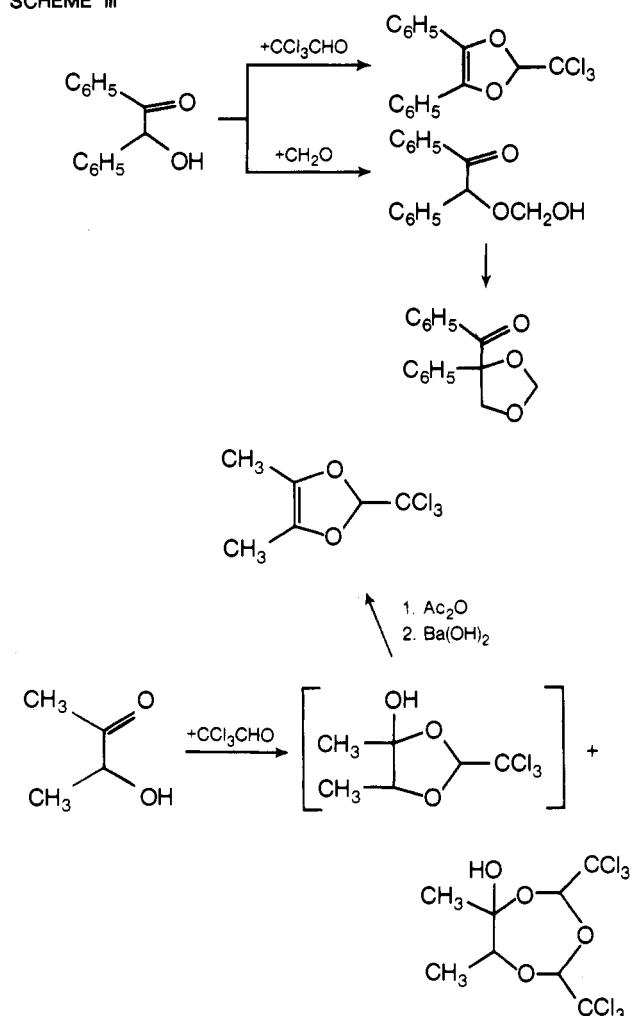


lier investigators were erroneous, and gave them the formula of acetal



Glucochloraloses may be obtained from the reagents in the presence of concentrated H_2SO_4 or with azeotropic distillation of water.^{199,200} Heating at 70° of chloral, glucose, and ZnCl_2 produces a mixture of α - and β -glucochloralose; $[\alpha]^{20}\text{D} + 18.9^\circ$ (EtOH) and -15.2° (Py).²⁰¹ To obtain glucose hemiacetals containing four to six frag-

SCHEME III

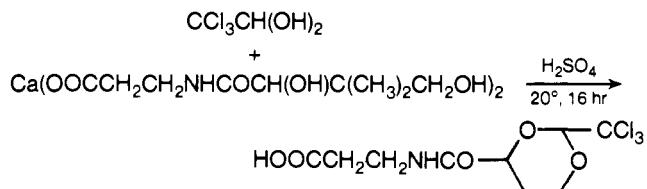


ments of chloral, the mixture of the reagents should be heated for a few hours at 120°.²⁰²

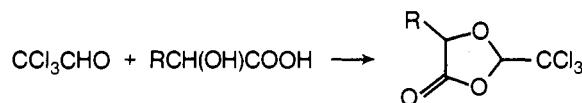
A study was also made of the formation of hemiacetals of chloral with amylose²⁰³ and polyvinyl alcohol.^{204,205}

Worth noting is the peculiar interaction of chloral with α -keto alcohols. Dietrich and Karabinos²⁰⁶ isolated in 85% yield 2-trichloromethyl-4,5-diphenyl-1,3-dioxol by boiling a mixture of chloral with benzoin in benzene. It was the first instance of chloral fixation by an enediol, since the other aldehydes with benzoin or the other α -ketols with chloral do not form products of such a structure. Presented in Scheme III are trends of interactions of chloral with benzoin and acetoin and also, by way of comparison, of formaldehyde with benzoin.²⁰⁶ The reaction of chloral with benzoin is favored in this direction both by high polarization of the chloral carbonyl group and stability of the enediol form of benzoin.

With hydroxy acids, chloral reacts differently. When the hydroxyl group is remote from the carboxyl group, hemiacetals (and occasionally acetals) are formed, as in the case with pantothenic acid²⁰⁷:



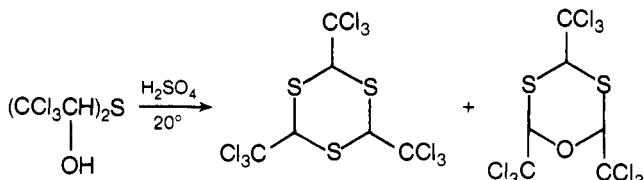
Aliphatic α -hydroxy acids form, with chloral or its hydrate, compounds named "chloralides":



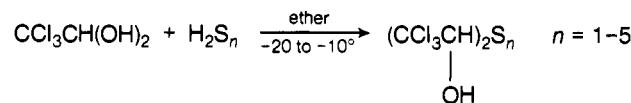
Glycolic, lactic, malic, tartaric, and other α -hydroxy acids²⁰⁸⁻²¹⁶ react with chloral in this way. In the case of α -tartaric acid two isomers of bis(chloralide) (with mp 160° and 173°) are formed, which can be separated by crystallization from benzene or toluene.²¹¹ The first chloralides were obtained by Wallach²⁰⁸ after long heating of the reactants in sealed tubes. Subsequently higher yields of chloralides were obtained by boiling the reactants in benzene or by heating them without solvent in the presence of sulfuric acid.

B. Interaction with Hydrogen Sulfide and Thiols

Hydrogen sulfide with chloral easily forms adducts of a composition 1:²¹⁷ and 1:2.²¹⁸ By treatment with H_2SO_4 the latter is transformed partly to acyclic trimer of thiochloral (yield ca. 2%) and to two isomeric 1,3,5-oxadithians (total yield up to 18%).²¹⁹

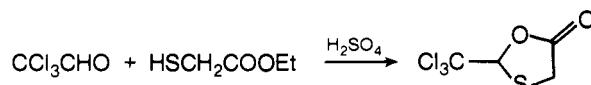


The stability of the reaction products diminishes with an increase in n .²¹⁸

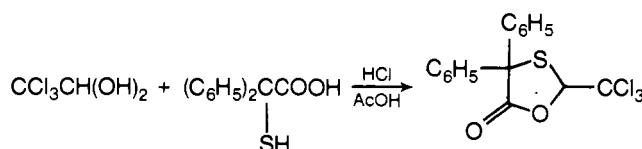


Chloral easily reacts with thiols either with or without acid catalysis. As a rule, the products are hemithioacetals in case of both aliphatic²²⁰⁻²²³ and aromatic²²⁴⁻²²⁷ thiols. For example, the reaction with dodecylmercaptan²²¹ in boiling methanol gives 88% of the hemithioacetal. Good yields (60-94%) arise by the interaction of chloral with para-substituted thiophenols²²⁵ at 20° in benzene. Thioacetals of chloral are formed²²⁶ with thiophenols in the presence of acidic catalysts. Dry hydrogen chloride improves the reaction between chloral and *p*-nitrothiophenol; the hemithioacetal is not stable, so it is preferable to carry out this reaction in acetic anhydride²²⁷ which acetylates the hemithioacetal to a stable product.

With ethyl thioglycolate, chloral reacts in refluxing benzene in the presence of H_2SO_4 , forming the monothio analog of chloralide with a yield of 90%.²²⁸

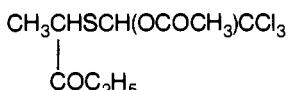


A product of similar structure was also obtained from the reaction between chloral and mercaptobenzilic acid.²²⁹

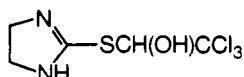


With a representative compound of α -ketothiols (2-mercaptopentanone), chloral reacts in ether in

the presence of pyridine, forming an acyclic hemithioacetal,²³⁰ which can be stabilized by acetylation:



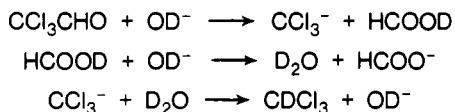
The melting of chloral hydrate with ethylenethiourea hydrochloride (with two nucleophilic centers, N and S) leads to the formation of an adduct of hemithioacetal structure²³¹



High nucleophilicity of the sulfur atom also allows adducts of a similar structure to be formed by the interaction of chloral with thioacetic and aromatic thiocarboxylic acids.²³²

C. Interaction with Alkalies and Aliphatic Nitrogen Bases

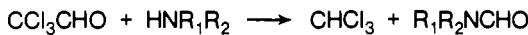
The decomposition of chloral and its hydrate under the influence of strong alkalies, to form chloroform and formates, is common knowledge; it is outlined in every course of organic chemistry and has found its application in the production of chloroform (notably of "chloroform pro narcosi") as well as for the quantitative determination of chloral hydrate as a drug.²³³ The use of D₂O as the solvent permits one to obtain^{234, 235} deuteriochloroform with a 90% yield and with isotopic purity up to 95%. The reaction apparently proceeds according to the following scheme:²³⁴



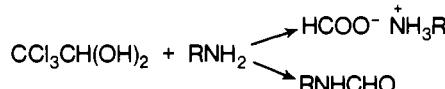
In 1948 Nesmeyanov and associates²³⁶ found that in the degradation of chloral hydrate to chloroform, potassium fluoride can play the part of the base (the base function being fulfilled by fluoride anion). (It should be noted for the sake of comparison that heating of chloral with anhydrous hydrogen fluoride with catalysis by chromium oxide leads to fluoral without C-C bond rupture.²³⁷) In this case the yield of chloroform is quantitative.

However, under certain conditions simultaneous hydrolysis of the trichloromethyl group is observed, forming glyoxylic acid.^{238,239} Similarly, in the alkaline hydrolysis of 4,4,4-trichloro-3-hydroxybutyric acid or its lactone,²³³ only malic acid is formed, without C-C bond cleavage to give chloroform. In the case of phenyltrichloromethylcarbinol²³⁸ the rate of trichloromethyl group hydrolysis depends only on the hydroxide concentration, and not on the nature of the cation; solvents with low dielectric constants hinder the reaction. These influences are of quite a different nature:²³⁸ the above solvents favor chloroform splitting off and the cation influence is in accordance with the series: Li < Na ≪ K ≪ Cs < Ca < Sr < Ba ≪ Tl; consequently with the use of excess potassium hydroxide, the reaction is greater than first order. In case of thallic hydroxide, the order of the reaction is greater than one if the base is in excess; with equivalent proportions of reagents C-C bond cleavage takes place with chloroform formation being second order. With excess chloral, hydrolysis to glyoxylic acid is the main reaction.

On treatment of chloral with strongly basic aliphatic amines, the main reaction is formylation with the simultaneous formation of chloroform.²⁴⁰⁻²⁴⁶ This appears to be one of the best methods for obtaining formamides, whose yields (in organic solvents) reach 80%.

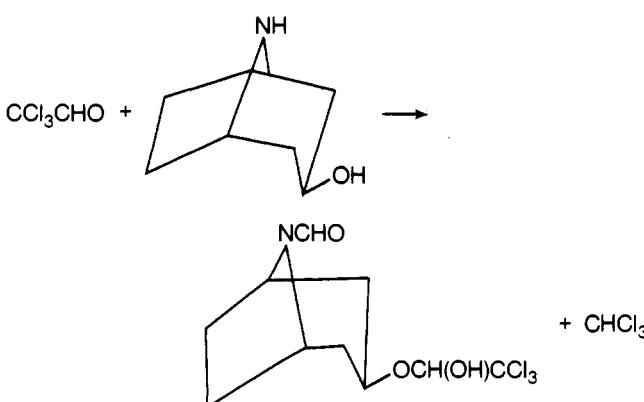


In water it is also possible to isolate ammonium formate;²⁴⁰ the nature of the reaction products is determined mainly by steric factors. For example, in the reaction between chloral and *tert*-butylamine, formamide is not formed at all.

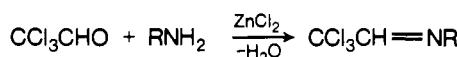


Yield, %	R = cyclo-C ₆ H ₁₁	R = n-Bu	R = <i>tert</i> -Bu
Ammonium salt	2	6	92
Formamide	72.5	73	0

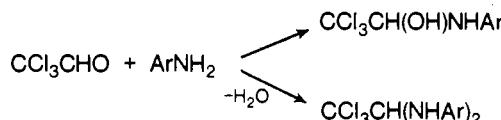
A kinetic study of the reaction between chloral hydrate and piperidine²⁴³ has shown that it is first order in the case of excess base, and is bimolecular with equimolar proportions or with an excess of chloral. With brief heating at 100° of the mixture of chloral and nor- ψ -tropine both formylation of nitrogen and hemiacetal formation²⁴⁵ take place:



Under conditions of azeotropic distillation of the water or still better with the use of a catalyst such as $ZnCl_2$, it is possible to obtain azomethines of chloral upon the interaction with several primary strongly nucleophilic amines²⁴⁷⁻²⁴⁹

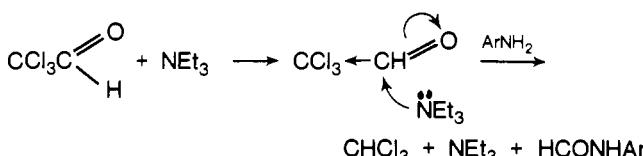


Amines of medium nucleophilicity may react with chloral in the ratio 1:1 or 2:1, as in the case of some substituted anilines:^{250,251}



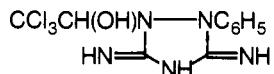
Upon boiling for 72 hr in a mixture of AcOH-AcONa products of both structures are formed, but no definite dependence of the reaction trend on amine structure²⁵ was revealed.

The interaction of chloral with aromatic amines in the presence of equimolar amounts of triethylamine²⁵² follows a different course; formamides are formed according to the following suggested scheme:

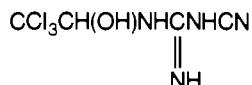


One should notice the difference between the reactions of aromatic alcohols and of amines with chloral: owing to the considerable nucleophilicity of the latter, chloral does not alkylate the carbon atoms of the benzene ring (as in the case of phenols; see section VI.E) but the nitrogen atom of the amino group. However *o,o'*-diaminobiphenyl is alkylated by chloral on the aromatic rings²⁵³ because of the steric hindrance to alkylation of the nitrogen atoms.

Boiling of chloral with phenylguanazole in an aqueous solution leads to alkylation in position 1 of the heterocycle²⁵⁴

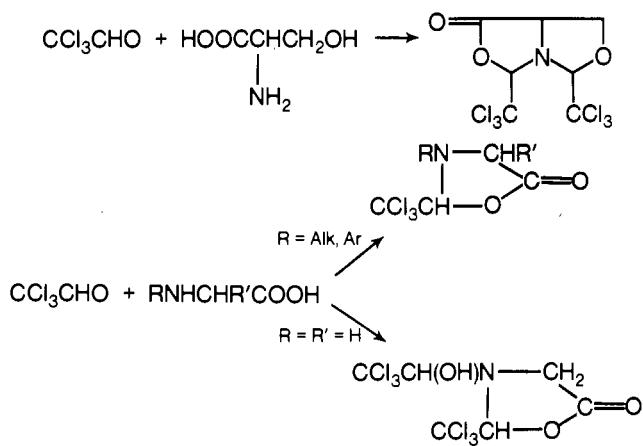


With dicyandiamide²⁵⁵ chloral reacts in boiling acetone with the formation of an adduct:

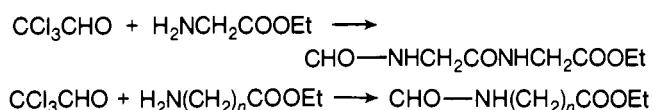


Treatment of chloral with weakly nucleophilic amino acids gives 5-oxazolidones;²⁵⁶⁻²⁵⁹ also, products of a peptide nature²⁵⁸ are formed. In the latter case catalysis by triethylamine²⁵² is advantageous (see Scheme IV).

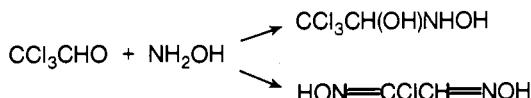
SCHEME IV



The esters of amino acids may be formylate on the nitrogen by chloral.^{258,259}



Chloral reacts differently with hydroxylamine. Naegele²⁶⁰ obtained, instead of the anticipated chloral oxime, chloroglyoxal dioxime ("chloroglyoxime"). Mayer²⁶¹ isolated chloral oxime (mp 39–40°) but Hantzsch^{262,263} failed to reproduce that result and obtained only a 1:1 adduct and chloroglyoxime.



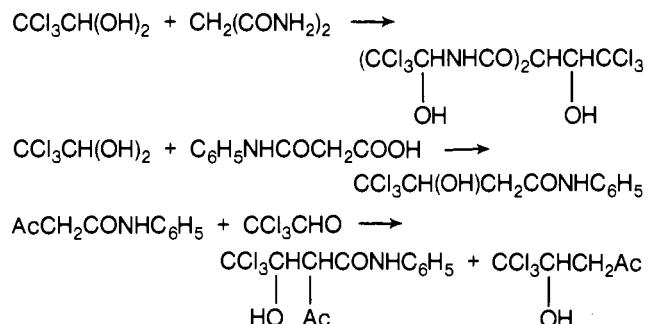
Recently methods have been suggested^{264,265} for obtaining chloral oxime in high yield by heating chloral hydrate with an aqueous solution of hydroxylamine hydrochloride in the presence of an excess of calcium chloride, which appears to play the part not only of a salting agent. By this method an isomer with mp 56° and bp

76–78° (11 Torr) is obtained.²⁶⁴ The test with β -trichloromethyl- β -propiolactone²⁶⁶ shows that the latter isomer is the anti oxime, in contrast with the syn oxime which has mp 39–40°.

There is a series of papers about the interaction of chloral with acid amides,²⁶⁷⁻²⁷⁷ resulting most frequently in 1:1 adducts ("chloralamides"):



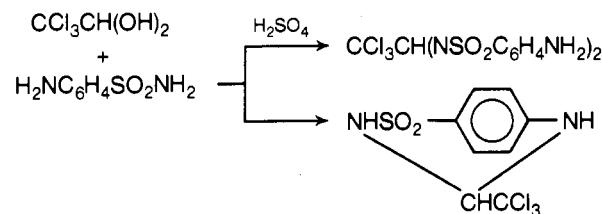
In the case of urea and similar bis-amides,²⁷² bis(chloralamides) are formed. Acid amides containing activated methylene groups are alkylated by chloral both on nitrogen and carbon atoms, or only on carbon if the nucleophilicity of the nitrogen is decreased by a substituent.²⁷⁴⁻²⁷⁶ (The results of Chattaway and James²⁷⁴ are in disagreement with those of Meldrum and Deodhar,²⁷³ who observed only N-alkylation of malonamide by chloral.)



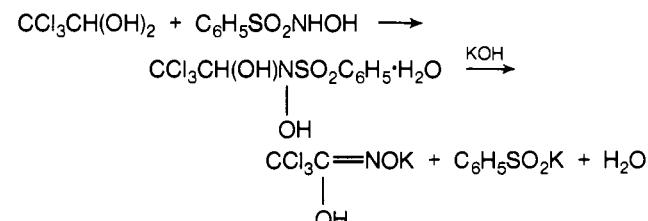
All the reactions of chloral with acid amides are realized upon prolonged heating of the reagents without a solvent, or under more mild conditions using an acid catalyst.

There are a few examples of the interaction between chloral and sulfonamides. Upon heating chloral hydrate with sulfanilamide in concentrated H₂SO₄, salt formation by the aromatic amino group causes chloral to alkylate the amidic nitrogen; the cyclic structure proposed for the condensation product formed²⁷⁸ in the absence of acid seems unlikely (Scheme V)

SCHEME V

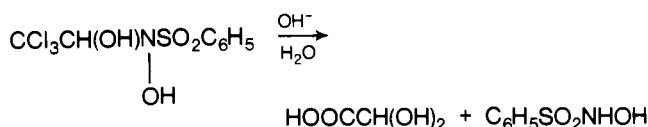


Ondo and Deleo,²⁷⁹ investigating the reaction between chloral hydrate and benzenesulfonylhydroxamic acid at 20°, have obtained an adduct which gave a negative reaction with FeCl₃ (hydroxamic acid test), but this reaction was positive after treatment of the reaction mixture with alkali. The investigators have proposed the following scheme of transformations:



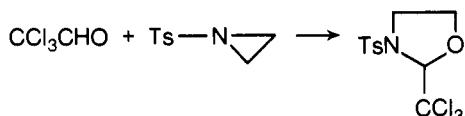
Such a decomposition of the adduct by alkali, with conservation of the trichloromethyl group, may be put to

question. More probable is a hydrolytic cleavage with regeneration of the sulfohydroxamic acid, thus rationalizing the positive FeCl_3 test:



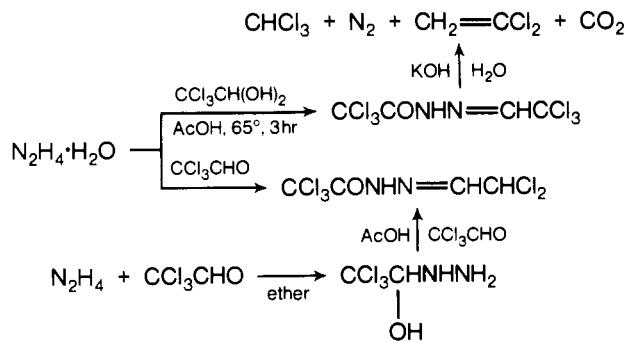
Furthermore, it is important to note that Cambi²⁸⁰ failed to reproduce the above results: during 8 days at 20° no changes in the reaction mixture were observed.

N-Tosylethylenimine reacts with chloral with the enlargement of its ring to an oxazolidine:²⁸¹



Eccentricity of chloral reactivity in comparison with other aldehydes is particularly displayed in its interaction with hydrazines. Knöpfer^{282,283} found that by treatment of chloral hydrate with hydrazine hydrate or with hydrazinium salts in acetic acid, depending upon the temperature, compounds $\text{C}_9\text{H}_8\text{Cl}_2\text{N}_2\text{O}$ or $\text{C}_4\text{H}_2\text{Cl}_6\text{N}_2\text{O}$ (named "anhydrochloral") are obtained; the latter is also formed on heating chloral hydrate and hydrazine salts in water. Only in 1968 did Karabinos and his associates²⁸⁴ ascertain that the structure of "anhydrochloral" is the *N*-trichloroacetyl-*N'*-hydrazone of chloral. As the reaction between hydrazine hydrate (or its sulfate) and chloral proceeds, a product is formed which differs from the above by a molecule of HCl; it is decomposed by aqueous alkali. In contrast, the formation of the identical compound was confirmed by the action of a second mole of chloral on the adduct obtained by the reaction of chloral with hydrazine in ether (Scheme VI).

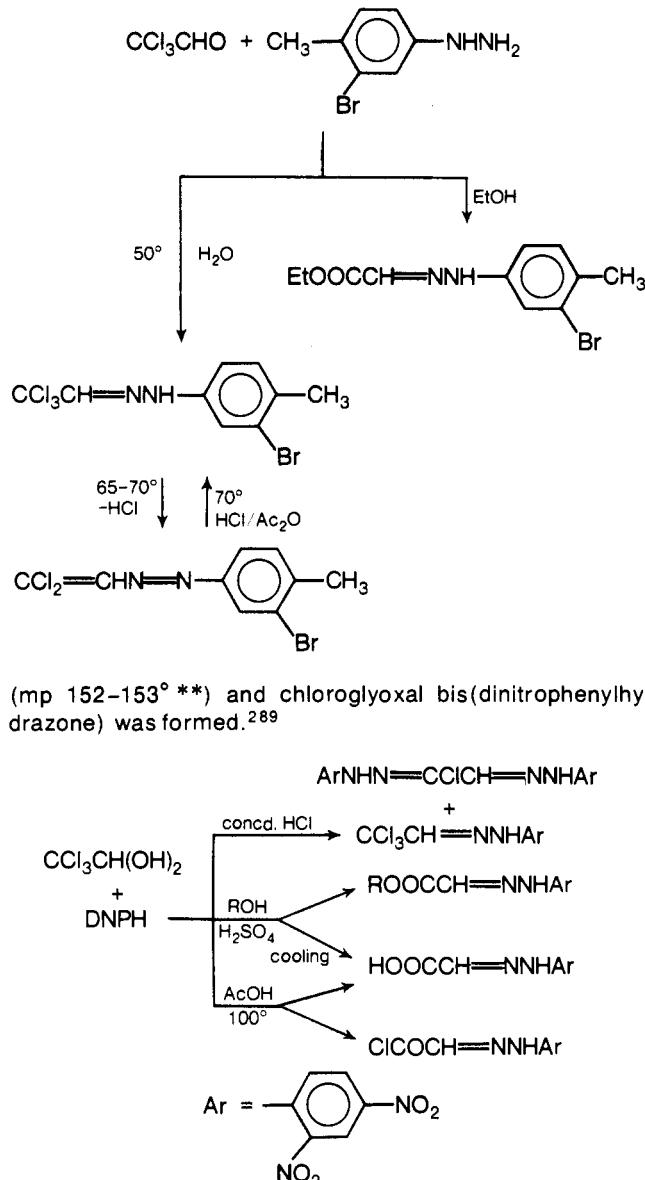
SCHEME VI



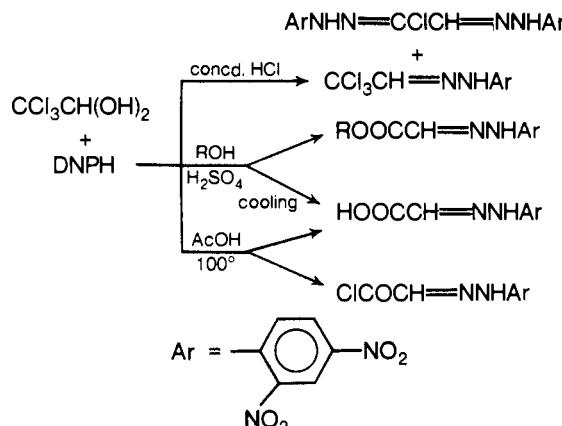
Substituted hydrazines react with chloral in various ways. Phenylhydrazines with electronegative substituents in the aromatic ring give unstable hydrazones which evolve HCl on heating. But this interaction is very specific and depends on many factors: the kind of substituent, solvent, medium acidity, proportion of reagents and temperature. For instance, with 3-bromo-4-methylphenylhydrazine, chloral reacts as shown in Scheme VII.²⁸⁵

The less nucleophilic 2,4-dinitrophenylhydrazine (DNPH) and 2,4,6-trichlorophenylhydrazine are even more receptive to the above-mentioned factors in their reaction with chloral.²⁸⁶⁻²⁹¹ Torres and Brosa²⁸⁶ and Rabbassa²⁸⁷ obtained, after briefly heating chloral hydrate with DNPH in acetic acid, a mixture of chloroglyoxal and glyoxylic acid dinitrophenylhydrazones. The latter was also obtained by treatment of a cooled mixture of the reagents with sulfuric acid in alcohol,²⁸⁹ on heating in concentrated HCl a mixture of chloral dinitrophenylhydrazone

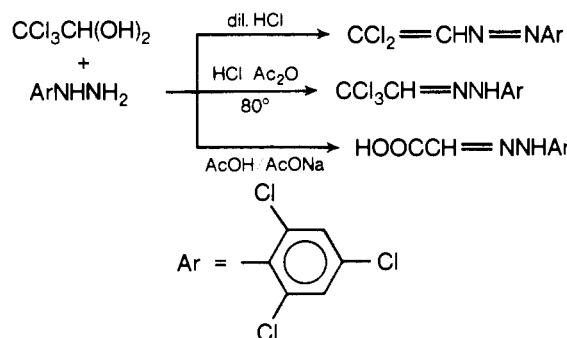
SCHEME VII



(mp 152–153° ***) and chloroglyoxal bis(dinitrophenylhydrazone) was formed.²⁸⁹



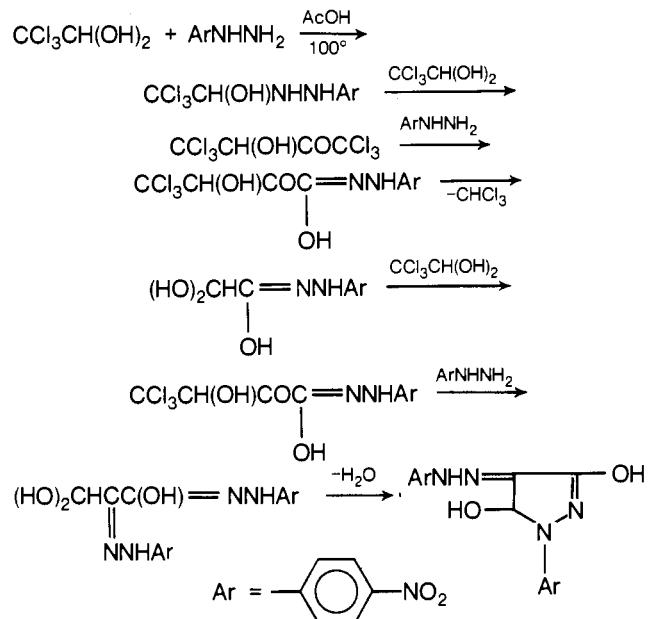
Products of the same structure were also obtained by the interaction between chloral and 2,4,6-trichlorophenylhydrazine:



Heating chloral hydrate with *p*-nitrophenylhydrazine in acetic acid, according to Stepanov and Kuzin,²⁹² leads to

** Ross and Ring²⁹⁰ confirmed that one obtains chloral dinitrophenylhydrazone with the same melting point by treatment of the reagents with 12 N HCl; meanwhile earlier²⁸⁸ it was communicated that the named compound was obtained, but with mp 131° by treatment of chloral with DNPH in methanol with H_2SO_4 catalysis. That erroneous melting point has been given by mistake in well-known references^{304,305} for identification of chloral in the form of its dinitrophenylhydrazone.

SCHEME VIII



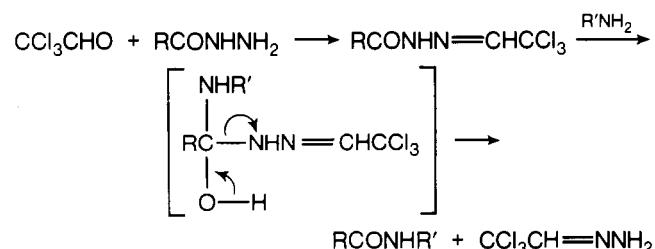
a product of composition $C_{15}H_{12}O_6N_2$, to which they assign the structure of a substituted pyrazoline, and propose the mechanism in Scheme VIII for its formation.

Torres and associates^{286,293} have doubted that mechanism and attempted to confirm the structure of the reaction product, but these investigators²⁹³ have succeeded only in isolating *p*-nitrophenylhydrazones of glyoxylic acid and dichloroglyoxal.

Interaction between chloral and acid hydrazides (benzoic,^{294,295} isonicotinic²⁹⁶) leads to appropriate *N*-acyl-*N'*-hydrazone of chloral.

Chloral with thiosemicarbazide forms thiosemicarbazone²⁹⁷ or its hydrate.²⁹⁸ The interaction with S-methylthiosemicarbazide has been used by Chang and Ulbricht²⁹⁹ for the synthesis of 6-azauracil. They have also obtained its 2-¹⁴C-analog through the interaction between chloral and ¹⁴C-semicarbazide (Scheme IX).

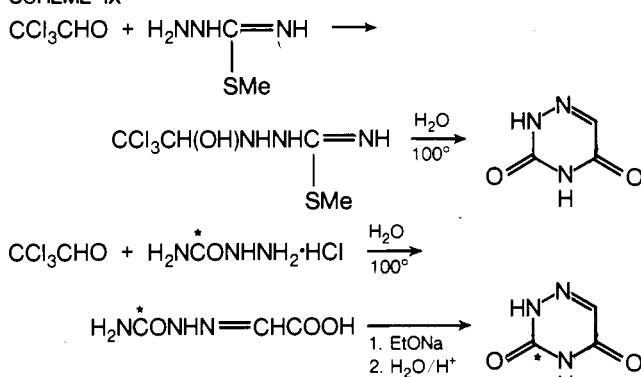
An interesting use of chloral was discovered by Kame-tani and associates.³⁰⁰⁻³⁰³ Appropriate acid amides or esters are formed by boiling chloral with acid hydrazides in the presence of nucleophiles (amines, alcohols). In the authors' opinion dehydrazination takes place through the intermediate chloral hydrazone which in some cases was isolated:



B. Interaction with HCN in Alkaline Media

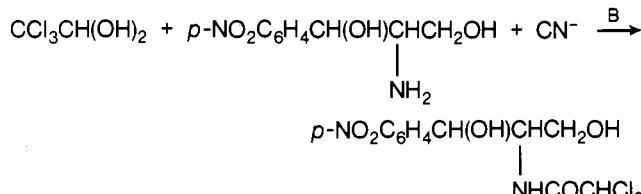
Wallach's discovery^{306,307} of the transformation of chloral hydrate into dichloroacetic acid or its esters by the action of aqueous or alcoholic potassium cyanide has much practical importance because of the limited accessibility of such compounds in other ways. This reaction (named sometimes "Wallach's reaction") plays a deci-

SCHEME IX^a



^a Upon interaction in water Wallach also isolated an adduct, $3\text{CCl}_3\text{CHO} \cdot \text{HCN}$.

sive role in dichloroacetylation, for instance in syntomycin and laevomycetin synthesis.³⁰⁸



B = base for neutralization of HCl (C_5H_5N , Et_3N , $CaCO_3$, $AcONa$, Na_2CO_3 , excess of CN^- itself)

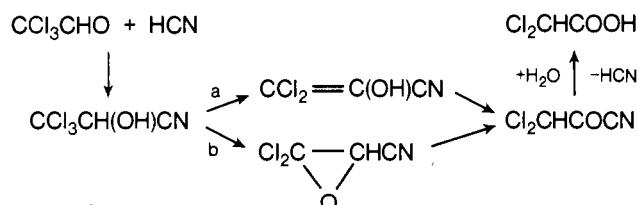
Instead of alkali cyanides, acetone cyanohydrin may be used;^{309,310} in this way the yield of syntomycin (at that stage) can be increased to 95.5%.

The mechanism of Wallach's reaction has been investigated only recently. Questions which arise are the following:

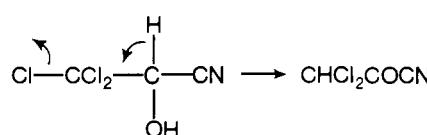
1. Does the carbonyl carbon atom of the dichloroacetic acid come from the chloral molecule or from cyanide ion?

2. What is the origin of the hydrogen atom in the dichloromethyl group of the acid molecule: is it a result of hydrogen migration from chloral or does it come from the protonic solvent in which the reaction is carried out?

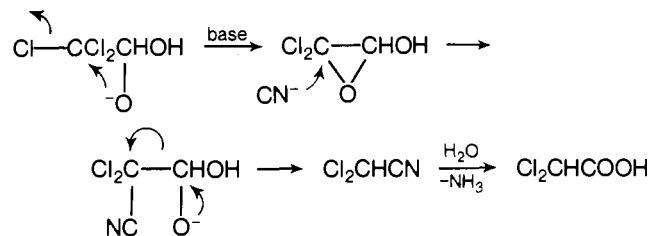
In particular it was supposed^{309,311-314} that cyanide ions perform only a catalytic function. Kötz³¹² and Pinner³¹³ thought that at first chloral cyanohydrin is formed, with two directions of reaction then becoming possible: "a" and "b", leading to dichloropyruvic acid nitrile with subsequent elimination of HCl:



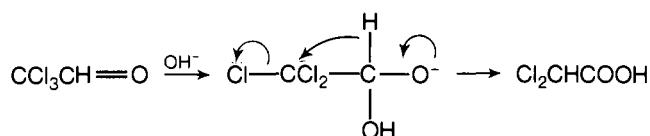
Francis and Davis³¹⁵ have confirmed the intermediate cyanohydrin formation; by carrying out the reaction in the presence of benzoyl chloride they obtained the benzoyl derivative of chloral cyanohydrin. Concerning the further transformation by path "a",^{309,311,316} the possibility of the following redistribution of electron density was supposed³¹¹:



Cram and Hammond³¹⁷ proposed a mechanism for Wallach's reaction that included attack by cyanide ion on an epoxide ring which is formed by basic catalysis:

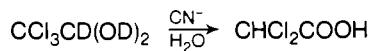


A mechanism proposed by Müller³¹⁸ neglects the participation of cyanide ion and foresees only hydride transfer in accordance with the scheme:



From the above discussion the viewpoints of investigators on two main questions are clear. Most of them agree that the carbonyl group of chloral is transformed into the carbonyl group of the dichloroacetic acid. In Cram and Hammond's opinion, the carboxyl group is formed by hydrolysis of the initially added cyanide ion.

Concerning the hydrogen atom of the dichloromethyl group in the acid, all investigators except Müller assume that the solvent is the hydrogen donor. The reaction between deuteriochloral hydrate and KCN and also the reaction between chloral and K¹⁴CN play a decisive role in resolving these questions. By NMR analysis the following course of the reaction⁴⁹ was suggested:



The isotopic purity of the hydrogen atom in the CHCl₂ group was ca. 90% protium. In this way, path "b" (of the Kötz and Pinner scheme) and the hydride transfer mechanism³¹⁸ were rejected.

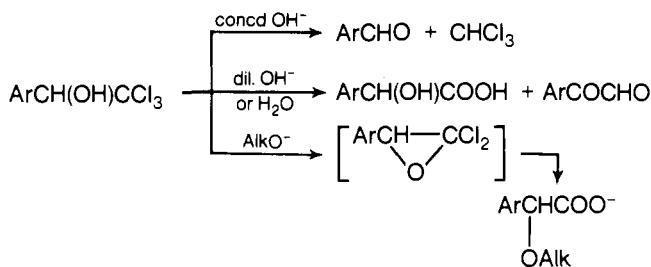
Interaction between chloral and K¹⁴CN in methanol³¹⁹ (by analogy with unlabeled KCN³²⁰) leads to methyl dichloroacetate without ¹⁴C in the carbonyl group. Thus the catalytic function of the cyanide ion was confirmed.

Finally, the research by Khaskin and associates³¹⁰ on the influence of amine structure on the yield of dichloroacetylated aromatic amines using chloral with acetone cyanhydrin is pertinent. These authors have shown that the yield of amide increases with increasing basicity of the amine, taking into account the hydrolysis of the intermediate dichloropyruvotriple in aqueous medium. In the case of β -naphthylamine and *o*-chloroaniline it is necessary to carry out the reaction in the absence of water (triethylamine is used to neutralize the HCl).

E. Interaction with Aromatic Compounds

Much research on chloral has been devoted to its interaction with aromatic compounds. But in some cases the structure of products and the reaction mechanism are still in doubt and constitute a subject for future research.

It is interesting that aryltrichloromethylcarbinols, which are obtained as a consequence of alkylating aromatic compounds by chloral, may be transformed into aldehydes and α -hydroxy acids by solvolysis of the trichloromethyl group.³²¹ These reactions have both preparative and industrial interest.

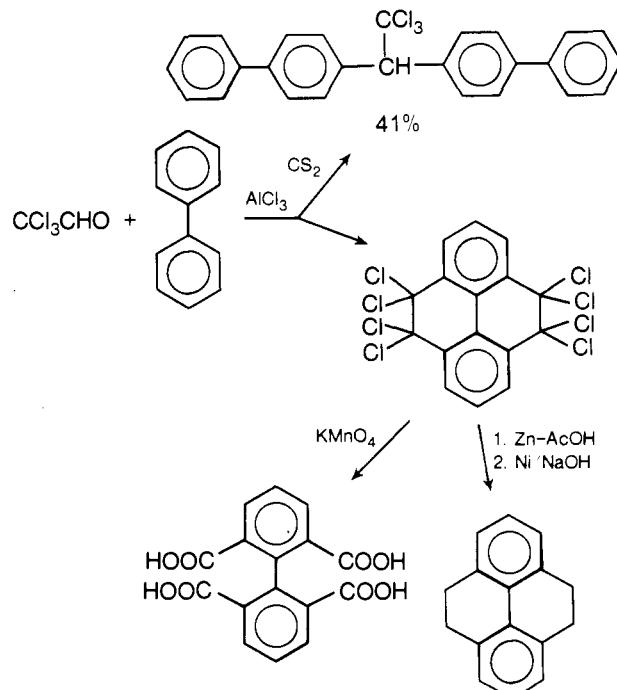


Chloral and its hydrate react with benzene and its alkylated homologs only in the presence of acidic catalysts. In concentrated H₂SO₄ or as the monohydrate, the reaction takes place with the formation of trichloroethane and trichloroethanol derivatives.³²²⁻³²⁸



In the presence of aluminum chloride the reaction with benzene leads to different products depending on the quantity of catalyst and the solvent. By heating in CS₂ mainly a mixture of the following compounds is obtained:³²⁹ (Ph₂CH)₂, Ph₂C=CPh₂, Ph₂CH₂, Ph₃CH, PhCH=CCl₂, Ph₂C=CCl₂. In the absence of CS₂ other products are obtained: CCl₃CHPh₂, PhCCl₂CHO, HCl;³³⁰ CCl₃CHPh₂, Ph₂CClCHPh₂³³¹ (in the last case a compound was also isolated which was assigned the structure of a "salt": C₆H₄(CCl₂CHPh₂)₂ · HCl).

Musante and Giraldi,^{332,333} who studied the interaction between chloral and biphenyl with AlCl₃ as a catalyst, depending on the solvent, have obtained either a condensation product (1:2) or a compound lacking a trichloromethyl group (its structure was established by reduction and oxidation to the known products).

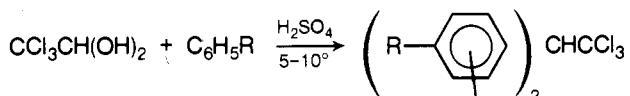


The reaction product from chloral and *p,p'*-dichlorobiphenyl in CS₂ in the presence of AlCl₃ also has no trichloromethyl group (as deduced by the test with alcoholic KOH³³²).

Treatment of chloral with naphthalene in the presence of Lewis acids³³⁴⁻³³⁷ leads to a mixture of 1- and 2-naphthyl derivatives of trichloroethanol and trichloroethane, whose composition depends upon solvent, temperature, and proportion of initial reagents. So by NMR analysis it

was detected that the main product is not β - (as claimed in earlier papers) but α -naphthyltrichloroethanol (up to 90%).³³⁷

It is clear that the course of the reaction between chloral and substituted aromatic compounds is subject to orienting influence of substituents. Bis(aryl)trichloroethanes are formed³³⁸ from chloral and monosubstituted benzenes in the presence of H_2SO_4 :



The aromatic ring reactivity decreases in the series $R = MeO, Me, Cl, NHAc, COOH, NO_2$.

The reaction between chloral and chloro- or other halobenzenes has been broadly investigated³³⁹⁻³⁵⁵ because of the practical use of DDT. The reaction proceeds under mild conditions with acid catalysis according to the above-mentioned scheme. For the synthesis of DDT, sulfuric acid or oleum was used^{343, 346-350, 352-354} as the preferred catalysts; however, in such cases the crude DDT may include up to 14 (!) by- and secondary products.³⁵² The use of solvents such as CS_2 , CCl_4 , chloroform, or petroleum ether hardly decreases the yield of DDT.³⁴⁶

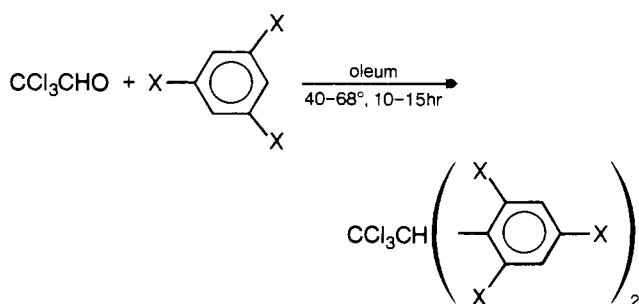
Concerning the use of Lewis acids such as $AlCl_3$ or $ZnCl_2$,^{334, 355, 356} there is a communication about obtaining DDT under such conditions; however, the main products were bis(*p*-dichlorodiphenylmethane) and *p*-chlorophenyltrichloroethanol; the last was also obtained by Ettel and Weichert.³⁵⁶ Musante and Parrini³⁵⁵ have isolated, using $AlCl_3$, a little 9-phenyltrichlorophenanthrene.

The following catalysts failed to give DDT in this reaction: $SOCl_2$, SO_2Cl_2 , P_2O_5 , H_3PO_4 ,³⁴⁶ and also hydrogen chloride.³⁴⁹ Up to 1947, in the presence of HSO_3Cl , the industrial yield of DDT was³³⁹ 67-69% (compared to 62% with H_2SO_4 and 58% with HF ³⁵¹ as catalysts). At the same time a method for DDT synthesis was published in which, on heating chloral with chlorobenzene at 30-50° in monohydrate medium, the yield increased to 80%. Later the use of oleum increased the yield of DDT up to 92-93%.³⁵⁴

There is an opinion³⁴⁹ that the role played by the H_2SO_4 involves formation of *p*-chlorobenzenesulfonic acid, which is then condensed with chloral to give DDT, but more probably one may account for the catalytic effect as a consequence of protonating the chloral carbonyl group by strong acid.³⁴⁰ However, the mechanism of catalysis in DDT synthesis seems not so simple or unique.

The acid-catalyzed reaction of fluorobenzene with chloral gives³⁴¹⁻³⁴³ the fluoro analog of DDT and also some *o*- and *p*-fluorophenyl derivatives of trichloroethane; the yield of "fluoro-DDT" decreases at lower temperatures.³⁴³

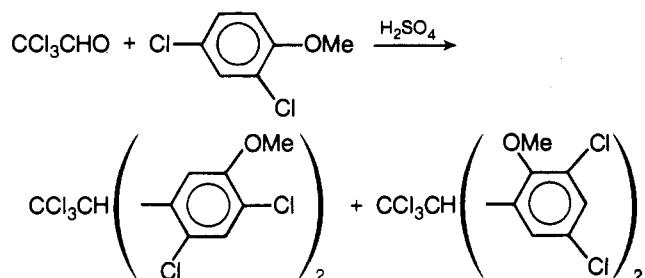
Polyhalobenzenes react with chloral to give trichloroethane derivatives, for example³⁵⁷



The temperature and yield increase in the series $X =$



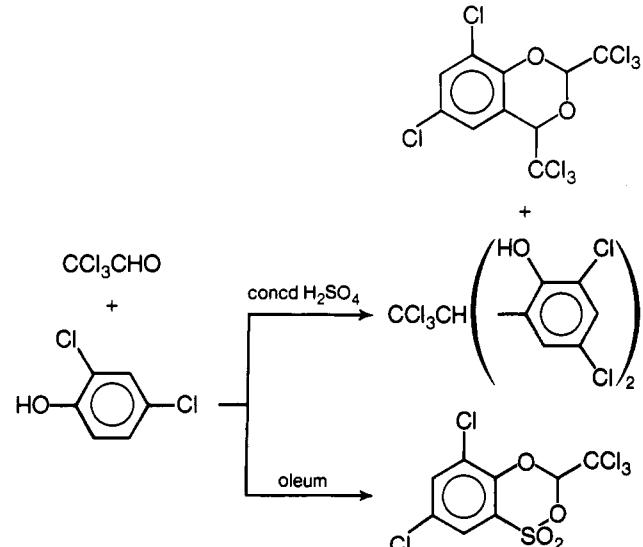
The interaction of chloral hydrate with 2,4-dichloroanisole in concentrated H_2SO_4 leads to alkylation in the 5 and 6 positions of the aromatic ring:^{358, 359}



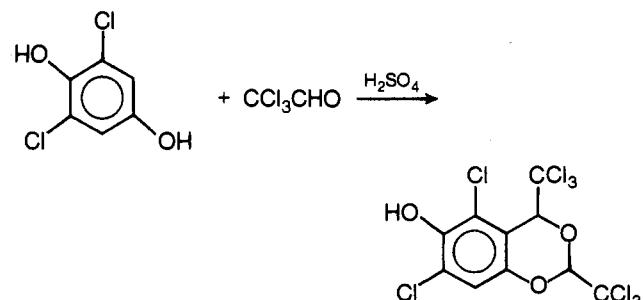
Hamada³⁵⁹ obtained the same compounds by the interaction between chloral and 2,4-dichlorophenol with subsequent methylation.

Ettel and Weichert found³⁶⁰ that in sulfuric acid, besides the products of alkylation by chloral, a condensation product was formed which has the benzodioxane structure; in oleum the reaction leads mainly to benzo-thiadioxane S,S-dioxide (Scheme X).

SCHEME X



2,6-Dichlorohydroquinone condenses with chloral in the presence of sulfuric acid to form a benzodioxane:³⁶¹



The reaction between chloral and 2,4-dichlorophenol with $AlCl_3$ catalysis³⁶² gives 1-(2-hydroxy-3,5-dichlorophenyl)-2,2,2-trichloroethanol.

Chlorinated acetophenones are not alkylated in the aromatic ring with chloral. On long boiling in acetic acid the activated methyl group reacts³⁶³ with the formation of a suitably ring-substituted 3-hydroxy-4,4,4-trichlorophenylbutanone.

The acid-catalyzed interaction of chloral with anisole has been studied by many investigators; H_2SO_4 ,^{364,365,368,370} BF_3 ,³⁶⁶ and $EtSO_3H$ ³⁶⁷ were used as catalysts. This reaction was investigated^{354,364-370} both at high temperatures (with azeotropic distillation of water) and at low temperatures. The product obtained is the appropriate bis(aryl)trichloroethane (bromal does not react with anisole to form a product with such a structure³⁶⁴), but an intermediate derivative of trichloroethanol may also be isolated.³⁶⁶

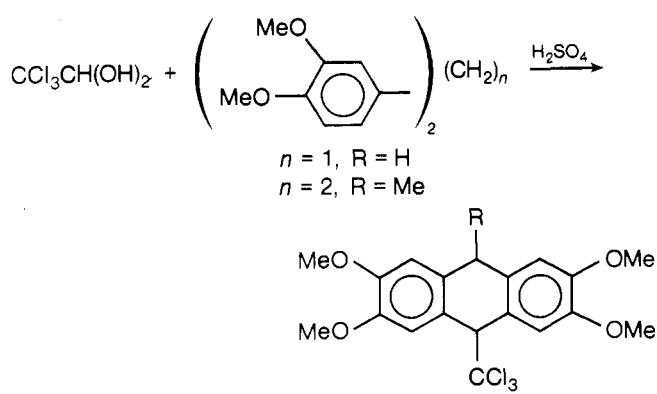
With electronegatively substituted anisoles (for example, *o*- or *p*-COOH, -NO₂) chloral reacts almost entirely in one way^{361,371-373} to give 2-methoxy-4-methyl-5-(1-hydroxy-2,2,2-trichloroethyl)benzoic acid. However, at high temperatures (100°) and by using a mixture of H_2SO_4 and HCl as a catalyst, the yield of that compound decreases because of by-product formation, particularly sulfonated derivatives.³⁷¹ *o*-Nitroanisole reacts easily with chloral in the presence of H_2SO_4 without heating,³⁷⁴ forming a mixture of aryltrichloromethylcarbinol and bis(aryl)trichloroethane derivatives (the latter predominates in the absence of a solvent) and also traces of 2,6-dimethoxy-3,7-dinitro-9,10-bis(trichloromethyl)dihydroanthracene.

Veratrol with chloral on heating in the presence of $AlCl_3$ forms bis(veratryl-4)trichloroethane, whereas on cooling the appropriate trichloroethanol derivative is formed.^{375,376} In CS_2 , bis(veratryl-4) dichloroethylene was obtained.³⁷⁷ Under the influence of H_2SO_4 this reaction is more complex.^{364,375,376,378-381} Arcleo and associates³⁷⁹ carried out this process in acetic acid and obtained, besides the main product, bis(veratryl-4)trichloroethane and also 4,5-bis[1-(3,4-dimethoxyphenyl)-2,2,2-trichloroethyl]-1,2-dimethoxybenzene, 1,1-bis{2-[1-(3,4-dimethoxyphenyl)-2,2,2-trichloromethyl]-4,5-dimethoxyphenyl}-2,2,2-trichloroethane, 2,3,6,7-tetramethoxy-9,10-bis(trichloromethyl)-9,10-dihydroanthracene, its 9,10-bis(dichloromethylene) derivative, and also a hydrocarbon (containing no chlorine) which was further³⁷⁹ characterized as an anthracene derivative.

By the action of twofold excess of veratrol up to 85% bis(veratryl-4)trichloroethane is formed and in case of excess chloral a large quantity of dihydroanthracene is obtained.^{375,376}

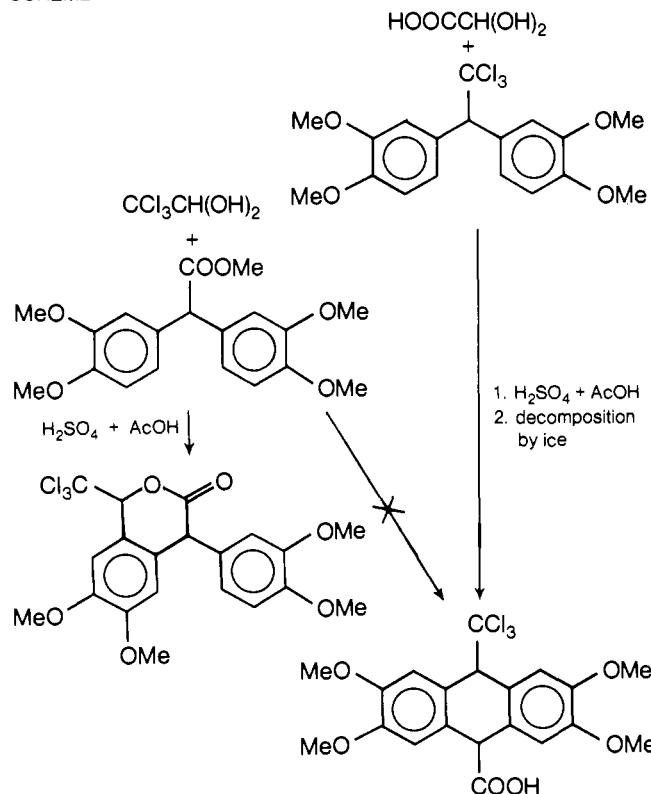
2,3,6,7-Tetramethoxy-9,10-dihydro-9-anthracene-9-carboxaldehyde has also been isolated as a reaction product from the interaction between chloral and veratrol with H_2SO_4 catalysis.³⁸⁰

Chloral reacts with 4-methylveratrol in a mixture of acetic and sulfuric acids to form mainly bis(aryl-5)trichloroethane.³⁸² With bis(veratryl)methane and -ethane, chloral hydrate yields anthracene derivatives.³⁸⁰



But with the methyl ester of bis(veratryl)acetic acid³⁸¹ the expected 2,3,6,7-tetramethoxy-9-trichloromethyl-

SCHEME XI



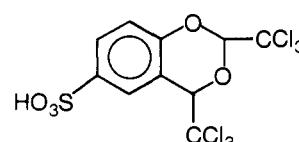
9,10-dihydro-10-carboxyanthracene is not formed; this has been confirmed by independent synthesis (Scheme XI).

Thioanisole^{383,384} and thiophenetole³⁸⁵ condense with chloral on cooling in the presence of H_2SO_4 or $AlCl_3$ in CS_2 with the formation of the corresponding *p*-bis(aryl)trichloroethanes in high yields. A publication³⁸⁶ about the analogous interaction between chloral and phenyl thiocyanate was disproved later by the same authors³⁸⁷ and also by Rimschneider and associates;³⁸⁸ in fact, the reaction takes the following course

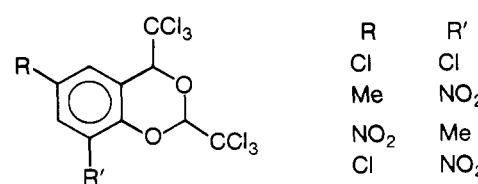


with a quantitative yield ($Ar = C_6H_5$) using the catalyst H_2SO_4 and in 57% yield in the presence of oleum.³⁸⁶

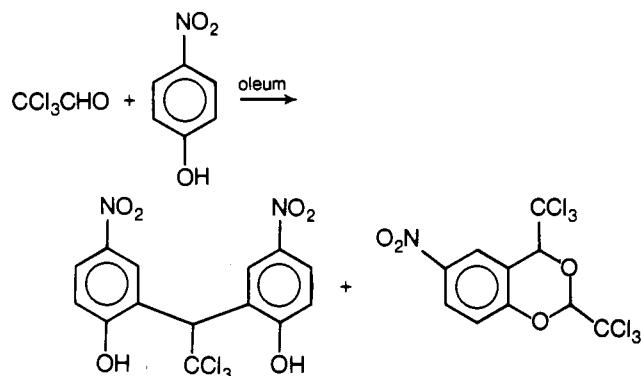
Reactions of chloral with aromatic alcohols have been investigated using both acid and basic catalysts. Chloral condenses with phenol in the presence of aluminum chloride to form bis(*p*-hydroxyphenyl)trichloroethane;³³⁴ if chloral hydrate is added to a solution of phenol in sulfuric acid,³⁸⁹ chloralidesulfonic acid is obtained:



Derivatives of chloralide are also obtained by the interaction of chloral with some 2,4-disubstituted phenols in the presence of H_2SO_4 .³⁹⁰



Backeberg³⁹⁰ failed, however, to obtain the products of established structure from chloral and hydroquinone: *p*-cresol, 4-chloro-, 2-chloro-4-nitro-, 2,4- and 3,4-dimethyl-, 4-bromo-2-methyl-, and 4-nitrophenols under the same conditions. Later Haskelberg and Lavie³⁹¹ obtained reaction products from chloral and 4-nitrophenol according to the following scheme:

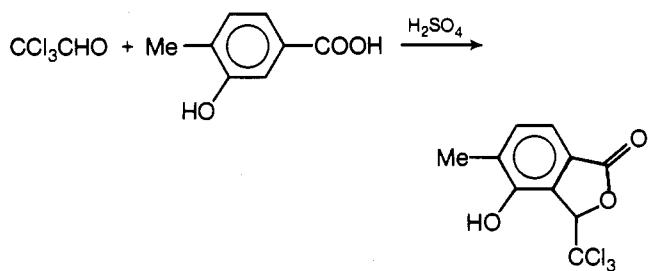


According to Chattaway,³⁹² the above formed benzochloralide has the 7-nitro structure.

The products obtained from the interaction of chloral with resorcinol depend on the acidic catalyst used. They include 4-resorcyltrichloroethanol,³⁹³ 1,1-bis(resorcyl-4)-2,2-dichloroethylene (in CS_2 in the presence of AlCl_3 ³³⁴), and 6-hydroxyfluorene-10-carboxylic acid.³⁹⁴

Guaiacol with chloral and an acidic catalyst forms the adduct 4-hydroxy-3-methoxyphenyltrichloroethanol^{393,395} (in yields up to 85%³⁹⁵) and bis(aryl)trichloroethane (at 0°, in acetic acid³⁹⁶).

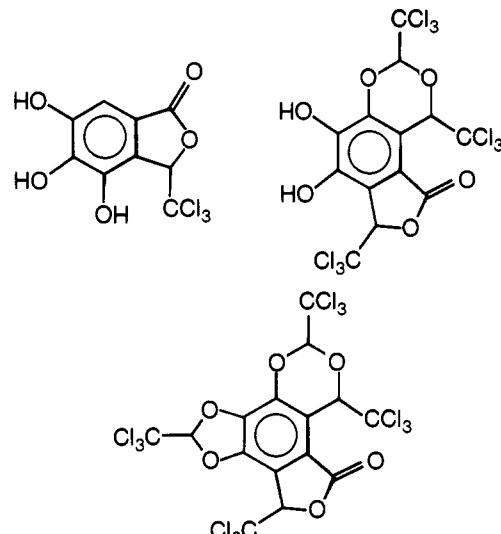
Phenolic acids react with chloral in the presence of strong mineral acids differently depending on the ring substituents. *p*-Hydroxybenzoic acid^{397,398} is condensed to a cyclic product, 2,4-bis(trichloromethyl)-6-carboxy-1,3-benzodioxane (similar to the reaction with 4-nitrophenol³⁹²). By the interaction with *m*-hydroxybenzoic acid³⁹⁹ chloral alkylates the aromatic ring in the 2-position.



The reaction between chloral and salicylic acid, its esters, and substituted derivatives^{371,372,400-403} in the presence of H_2SO_4 leads as a rule to the formation of 4-(1-hydroxy-2,2,2-trichloromethyl)salicylic acid and its substituted derivatives; with an excess of salicylic acid a derivative of trichloroethane is formed.^{401,402} In the presence of a mixture of H_2SO_4 and NaCl , suitable 1,2,2,2-tetrachloroethane derivatives are obtained.⁴⁰³ 4-Methylsalicylic acid is alkylated by chloral in position 5.⁴⁰⁴

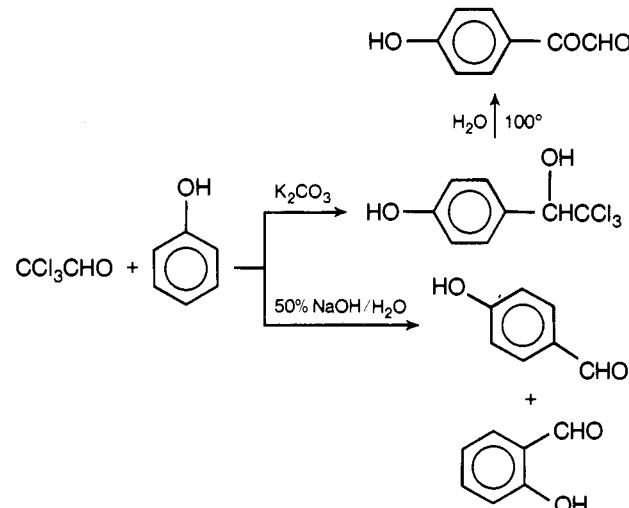
Gallic acid⁴⁰⁵ reacts with chloral (H_2SO_4 catalysis) to give, depending on proportion of reagents, the condensation products shown at the top of the next column.

Strongly electronegative substituents hinder such reactions. For example, 3- and 5-nitrosalicylic acids do not react with chloral even on heating with sulfuric acid in a sealed tube.³⁷²



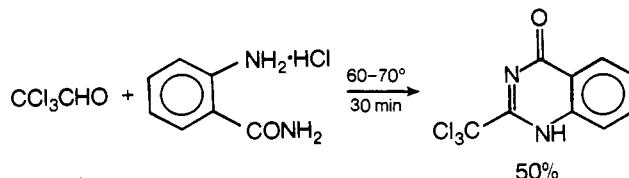
Base catalysis of the reaction of chloral with phenols leads to *p*-hydroxyaryltrichloroethanols⁴⁰⁶⁻⁴⁰⁸ (and some ortho isomer⁴⁰⁸) which, by boiling in water⁴⁰⁷ or reaction with aqueous alkali,⁴⁰⁸ leads to aromatic hydroxy aldehydes (Scheme XII). [Balfe and Webber,⁴⁰⁹ who car-

SCHEME XII

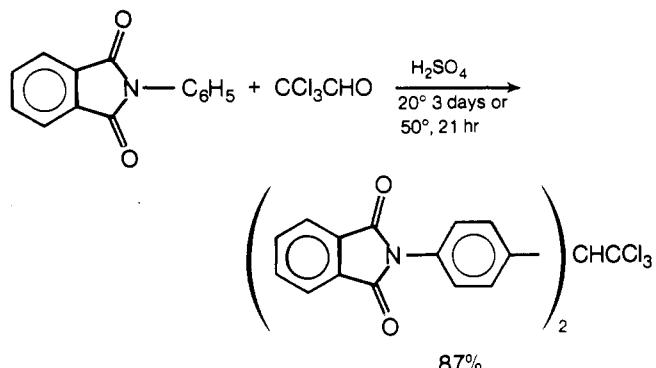


ried out the reaction between chloral and phenol in chloroform with potassium carbonate or acetate, obtained 7.5% chloral hemiacetal. They also obtained a hemiacetal in the reaction with *p*-cresol (yield 35%); in solution, it isomerized to (3-*p*-cresyl)trichloroethanol.] Thus chloral can successfully replace chloroform in the Reimer-Tiemann reaction; thus arises its use as a formylating agent, particularly in the vanillin synthesis.

The reaction of chloral with aromatic amides takes two paths. Heat without a catalyst leads to alkylation of the amidic nitrogen by chloral, for instance, with naphthoic acid amides⁴¹⁰ and substituted salicylic,^{411,412} toluyl-,⁴¹³ and some other acid amides.⁴¹⁴⁻⁴¹⁹ Chloral condenses with anthranilic acid amide⁴¹⁵ to give a quinazolone:



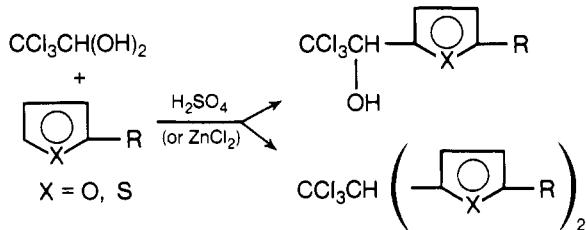
On the other hand, if the amide nitrogen is bound to an aromatic ring, it is not alkylated, but substitution of a hydrogen in the para position of the ring proceeds (when it is not hindered by other substituents),⁴²⁰⁻⁴²⁷ sulfuric acid plays a catalytic function, for example:⁴²⁶⁻⁴²⁸



Under such conditions succinimide does not react with chloral.⁴²⁶⁻⁴²⁸ With excess of phthalanilide, 1-(*p*-phthalanilido)-1,2,2,2-tetrachloroethane also has been isolated.⁴²⁸ Derivatives of the last compound are also formed by the interaction of chloral with acetanilide in the presence both of H_2SO_4 ^{424,427} and its mixture with phosphorus oxychloride.⁴²² The interaction with *N*-acetyl-*p*-toluidine^{420,421,423,428,429} is accompanied by many side reactions. *p*-Nitro- and *p*-bromoacetanilides do not react with chloral in the presence of H_2SO_4 .⁴²⁴

To conclude this part of the review we will discuss the interaction between chloral and heteroaromatic compounds.

Derivatives of furan^{430,431} and thiophene,^{432,433} under acidic catalysis and cooling, are alkylated with chloral in the α -position, forming trichloroethanol and trichloroethane derivatives, depending on the proportion of reagents and on the kind of substituent R:



With 2,5-dichlorofuran in oleum, bis(2,5-dichlorofuryl)-trichloroethane is obtained in 60% yield.⁴³² The reaction of chloral with 2-*tert*-octyl-, 2,5-di-*tert*-butyl-, and 2,3,5-trichlorofurans failed.⁴³²

2-Isothiocyanato-,⁴³⁴ -thiocyanato-, and -thiocarbamido-⁴³⁵ thiophenes react with chloral hydrate by the routes shown in Scheme XIII.

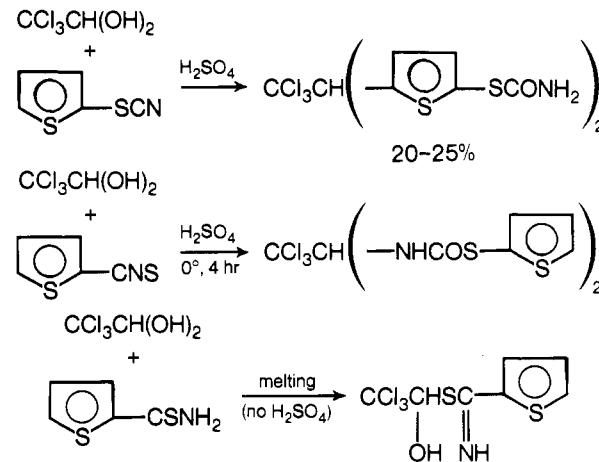
4-Hydroxycoumarin is alkylated by chloral in the 3 position to the corresponding trichloroethanol derivative.^{436,437}

Addition of chloral to 8-hydroxyquinoline also occurs, not on the weakly nucleophilic oxygen⁴³⁸ but on position 5 of the ring.⁴³⁹

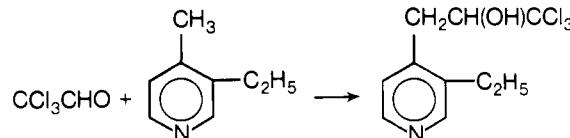
Heating chloral and 4-hydroxypyrimidines⁴⁴⁰ in pyridine gives hetero 5-trichloroethanols, from which one obtains pyrimidine-5-carboxaldehydes in a modified Reimer-Tiemann reaction.

Aromatic compounds with activated methyl groups react with chloral at that site rather than on the ring. Reactions of this type take place with collidine (both in the presence of soda as a catalyst⁴⁴¹ and by heating without a catalyst⁴⁴²), 3-ethyl- γ -picoline,⁴⁴³ 4-methyl-2-phenyl- and

SCHEME XIII

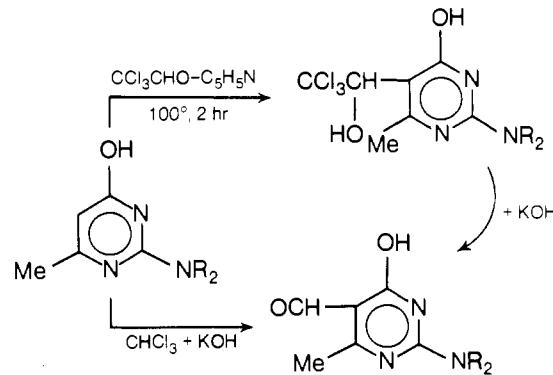


6-methoxy-4-methyl-2-phenylquinoline,⁴⁴⁴ 2-methylquinalzone-4,^{445,446} and 2-methylthiazole.⁴⁴⁷ The first stage of the synthesis of dihydroquinotoxine and dihydroquinine proceeds in such a way:⁴⁴¹



In contrast to these compounds, quinaldine reacts with chloral to form (2-methylquinolyl-3)-trichloroethanol,⁴⁴⁷⁻⁴⁵⁰ but 2-amino-4-hydroxy-6-methylpyrimidine and its N-substituted derivatives are alkylated by chloral in pyridine medium at position 5; this has been confirmed⁴⁵¹ with alternate synthesis via the Reimer-Tiemann reaction (Scheme XIV).

SCHEME XIV



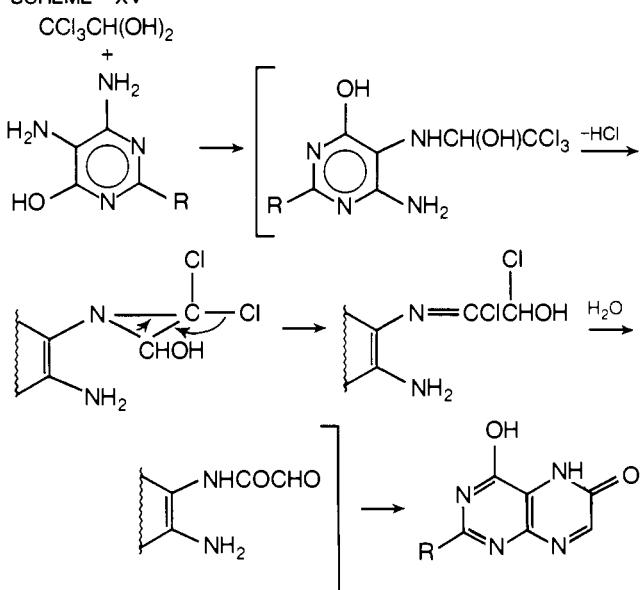
In the synthesis of pteridines from chloral and 4,5-diamino-6-hydroxypyrimidines with the acidic or basic catalysts, the investigators⁴⁵² proposed the following mechanism (through such a mechanism the above-mentioned results of Hantzsch in the reaction between chloral and hydroxylamine^{262,263} were explained). Scheme XV (based on the results of Fields and Sandri⁴⁵³ concerning chlorine transfer in aziridines).

Benzotriazole is alkylated with chloral in refluxing benzene to a (hetero-1)trichloroethanol.⁴⁵⁴

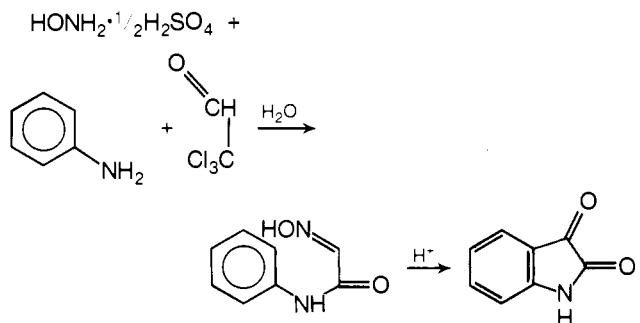
F. Synthesis of Isatin

By adding to an aqueous solution of chloral hydrate an equimolar quantity of aniline (the use of excess aniline leads to amidine,⁴⁵⁷ $HON=CHC(NHC_6H_5)=NC_6H_5$), followed by a hydroxylamine salt with subsequent boiling of reaction mixture, Sandmeyer⁴⁵⁵ obtained isonitrosoace-

SCHEME XV

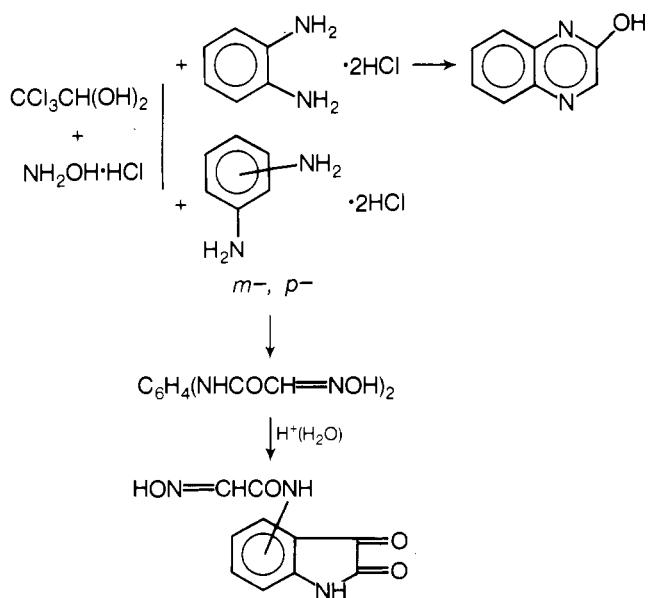


tanilide with a high yield; the product is transformed into isatin in acidic media:⁴⁵⁶



Instead of chloral and hydroxylamine one can use chloral oxime.⁴⁵⁸ The yield increases to 60–90%⁴⁵⁸ with an increase in the basicity of the aniline; a pH increase acts inversely as does the presence of salts with the same anion. Sandmeyer's reaction takes place in the presence of sodium sulfate, chloride, and bromide, but it does not take place in the presence of other sulfates or

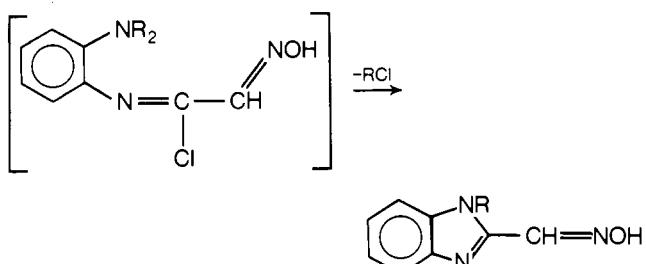
SCHEME XVI



sodium acetate, formate, citrate, fluoride, and dihydrophosphate. The salts may play a buffer role, but there is no firm understanding of their function.

Starting with *o*-, *m*-, and *p*-phenylenediamines, Morsch⁴⁵⁹ has shown that only the latter two react with chloral to give substituted isatins; *o*-phenylenediamine is cyclized to a hydroxyquinoxaline (Scheme XVI).

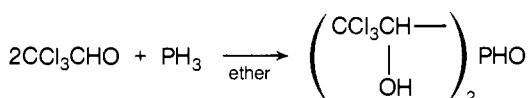
Petrov, Somin, and Kuznetsov,^{460–462} who studied the interaction of aromatic diamines with hydroxylamine and chloral or its oxime, have established that in the case of gem-N,N-disubstituted *o*-phenylenediamines the end product is a derivative of 2-formylbenzimidazole (as oxime) as a consequence of intermediate imidochloride formation:



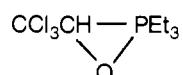
G. Interaction with Phosphorus Derivatives

With phosphorus derivatives chloral reacts as a rule as an oxidizing agent and transforms phosphorus from P(III) to P(V).

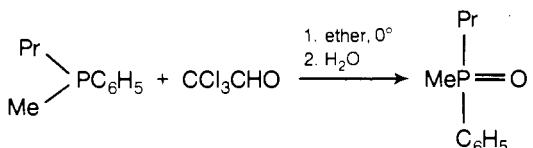
Phosphine adds two molecules of chloral⁴⁶³



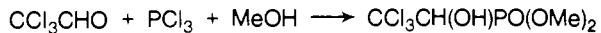
In contrast, Girard⁴⁶⁴ has assigned the product of the reaction between chloral hydrate and phosphonium iodide the structure bis(α -hydroxy- β,β,β -trichloroethyl)-phosphine. For the adduct of chloral and triethylphosphine, Collie⁴⁶⁵ has proposed the structure



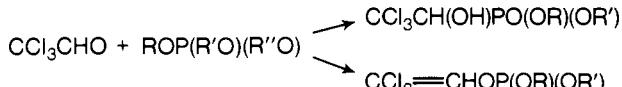
The reaction between chloral and methylpropylphenyl-phosphine⁴⁶⁶ produces a compound which, on hydrolysis, gives a pentavalent phosphorus product lacking chlorine:



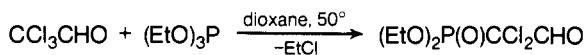
Most aldehydes, on being heated (190 – 200°) with phosphorus trichloride, condense to give $\text{RCHCl}-\text{PCl}_2$ (R = alkyl or, better, aryl). In contrast, chloral does not react even on heating to 270° for 5 hr.⁴⁶⁷ In methanol a reaction takes by the following path:⁴⁶⁸



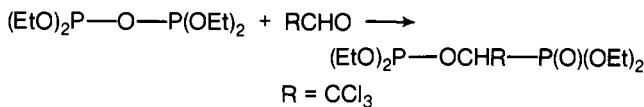
Compounds with the same structure or their dichlorovinyl derivatives are obtained by heating chloral with trialkyl phosphites, with or without a solvent;^{469–474} dichlorovinyl esters are preferred when there are different substituents in the initial phosphite:



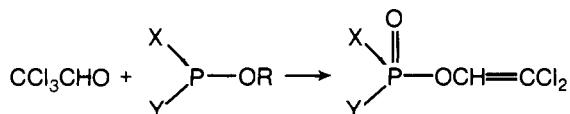
Before Perkov's⁴⁷³ and Kharasch's⁴⁷⁴ investigations (by analysis of ir spectra), it was considered⁴⁷⁵⁻⁴⁷⁷ that the above transformation involves an Arbuzov rearrangement⁴⁷⁵



The same result, in Arbuzov and Alimov's opinion,⁴⁷⁵ arises in the exothermic reaction between chloral and ethyl pyrophosphite, which usually reacts with other aldehydes in a different way:

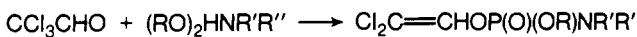


The reaction between chloral and mono- and diesters of di- and monoalkylphosphonic acids proceeds according to the following scheme, in good yields.^{473,478-482}



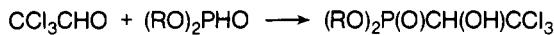
With dialkylphosphonic acid itself, according to Arbramov and D'yakonova,⁴⁸³ chloral forms the appropriate trichloroethanol derivative.

On the action of chloral with amidodialkyl phosphites, trans-esterification to dichlorovinyl derivatives⁴⁸⁴ takes place.



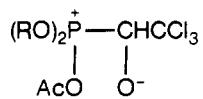
In this reaction, in the place of amido phosphites, one may also use dialkyl chlorophosphites, suitable amines, and triethylamine.

With organic compounds including a pentavalent phosphorus, chloral forms mainly trichloroethanol derivatives. Dialkyl phosphites add easily to the chloral carbonyl group:⁴⁸⁵⁻⁴⁹² basic catalysis, which is necessary for addition to other aldehydes,³ is not required.⁴⁹¹ The yield of the reaction



decreases from 100 to 56% on changing R from Me to Pr.⁴⁹¹ In alkaline media rearrangement takes place, leading to dichlorovinyl esters which accompany the main reaction product. Specific catalysis of the addition of chloral to dialkyl phosphites by ethylene oxide does not cause isomerization with hydrogen chloride elimination.⁴⁹²

The reaction between chloral and dibutyl acetyl phosphite⁴⁹³ gives dimers, whereas with other dialkyl acetyl phosphites mainly α -acetoxy- β,β,β -trichloroethyl- dialkyl phosphites are obtained (products from HCl elimination were not isolated). The authors⁴⁹³ proposed for the above reaction the following structure for the activated complex:



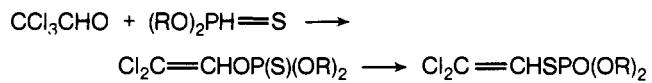
The reaction with pentavalent phosphorus acid amides⁴⁹⁴ results in nucleophilic addition of the amino group to the chloral carbonyl group.

Organic phosphates⁴⁹⁵ react with chloral on cooling to give reesterification products with hydrogen chloride elimination (mixed dichlorovinyl phosphates).

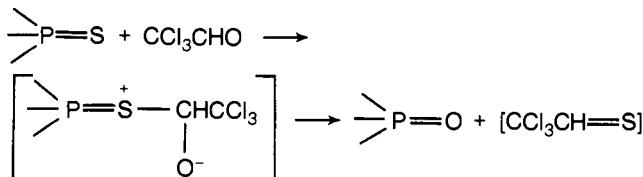
From the interaction between chloral and hypophos-

phorous acid, its potassium salt and esters, mono- and bis(α -hydroxy- β,β,β -trichloroethyl) phosphonites are formed.^{463,496,497} High yields of the latter are obtained on refluxing in an anhydrous solvent or by heating the reactants without a solvent.^{498,499}

Dialkyl thiophosphites differ from their oxygen analogs by forming, with chloral, dichlorovinylidic thioesters:^{498,499}



Sohr and Lohs⁵⁰⁰ have observed an interesting transformation of chloral with thio derivatives of pentavalent phosphorus leading to the replacement of the carbonyl oxygen by sulfur; the investigators proposed a dipolar intermediate:



VII. Interaction with Metallorganic Compounds

Metallorganic compounds as a rule add to the chloral carbonyl group to form an O-metal bond which, on hydrolysis, leads to a substituted trichloroethanol. For instance, from potassium acetylenide⁵⁰¹ α -hydroxy- β,β,β -trichloroethylacetylene is obtained in 27% yield. However, with phenyl- and methylolithium the trichloromethyl group shows greater reactivity than the carbonyl group, and interaction of those compounds with chloral at -30° leads to phenyl or methyl chloride formation; the authors proposed⁵⁰² the formation of an intermediate complex with charge transfer in the anion from carbon to oxygen. Such high reactivity of the trichloromethyl group has also been detected⁵⁰² in the reactions of chloral with butylmagnesium chloride and dibutylmagnesium; in both cases butyl chloride was obtained.

With dimethylzinc, chloral forms (depending on the ratio of reactants) trichloropropanol-2 or the reduction product, 3,3-dimethylbutanol-2.⁵⁰³

Interaction between chloral and aromatic and heteroaromatic magnesium derivatives^{335,337,504} gives 2-substituted trichloroethanols in high yields. Aliphatic Grignard reagents react with chloral differently, forming in addition to trichloroethanol and its 2-substituted derivatives some by-products whose proportion depends on the structure of the reagents, the order of mixing, the temperature, the solvent, and other factors. So on the treatment of chloral with methylmagnesium iodide the ratio of trichloroethanol/trichloropropanol-2 depends on the kind of catalyst and decreases in the series: FeCl_3 , CuCl , MnCl_2 .⁵⁰⁵ In the reaction with ethylmagnesium bromide, Gilman and Abbott,⁵⁰⁶ contrary to earlier data, failed to obtain chloral alcoholate; in many variations of the reaction conditions they isolated only trichloroethanol. However, Hamelin^{507,508} has contested the above conclusion and confirmed the formation of both named products and also of trichloropropanol-2; the ratio is sensitive to temperature changes.

With amyli⁵⁰⁹ and cyclohexylmagnesium bromide,^{509,510} chloral forms, besides trichloroethanol, the appropriate 1,2-dibromoalkenes. Compounds such as $\text{C}_6\text{H}_5(\text{CH}_2)_n\text{MgBr}$ ($n = 2-4$) with chloral lead to trichloroethanol, suitable phenylalkenes, and dimers with the formula $\text{C}_6\text{H}_5(\text{CH}_2)_{2n}\text{C}_6\text{H}_5$,⁵¹¹ but no substituted trichloromethylcarbinol. The latter, however, are formed in the

reaction with benzylmagnesium halides,⁵¹² but their yield is decreased with excess Grignard reagent because of bi-benzyl and polymer formation.

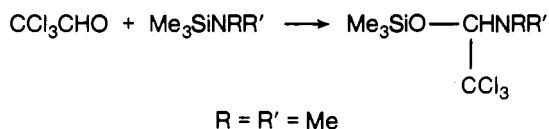
Two communications relate to the interaction between chloral and organic boron compounds. Triethylboron¹³³ reduces chloral to a trichloroethanol derivative in 90% yield:



Phenylboronic acid⁵¹³ forms, with chloral under mild conditions, a cyclic ester which by prolonged heating at 150–160° (under N₂) is dehydrated.

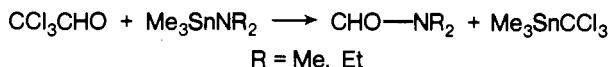
Silylacetals are formed on the interaction of chloral hydrate with mono- and dichloroorganosilanes in the presence of nitrogen bases;^{514–516} their SiO–C bond is strengthened by the inductive influence of the trichloromethyl group.⁵¹⁶ Substituted α-phenyl-β,β-trichloroethylsiloxanes are obtained by the successive action on chloral of phenylmagnesium bromide, then trialkylchlorosilanes at 2–30°.⁵¹⁷

Trimethylsilyldimethylamine adds exothermically to chloral with Si–N bond rupture:⁵¹⁸

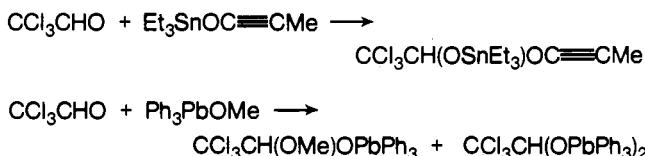


however, with R = R' = Et, Pr, (CH₂)_n or R = Me, R' = C₆H₁₁; R = Et, R' = C₆H₁₁, on heating (80°) trichloromethyltrimethylsilane is formed with β-elimination from the resulting siloxane; appropriate formamides RR'NCHO are also formed in that reaction. The ratio of the reaction products depends mainly on the steric nature of R and R'.

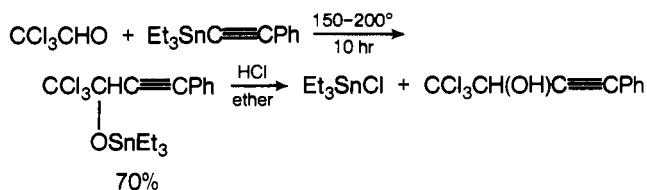
With trimethylstannylamines chloral forms only formamides and substituted stannanes⁵¹⁸ (the reaction takes in the same way as in the interaction with strong aliphatic nitrogen bases):



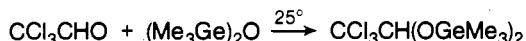
In contrast with the Si–O bond, the Sn–O⁵¹⁹ and Pb–O⁵²⁰ bonds are easily subject to heterolysis, adding to the chloral carbonyl group:



Under more severe conditions the Sn–C bond⁵²¹ is heterolyzed (providing a convenient route to ethynylcarbinols):

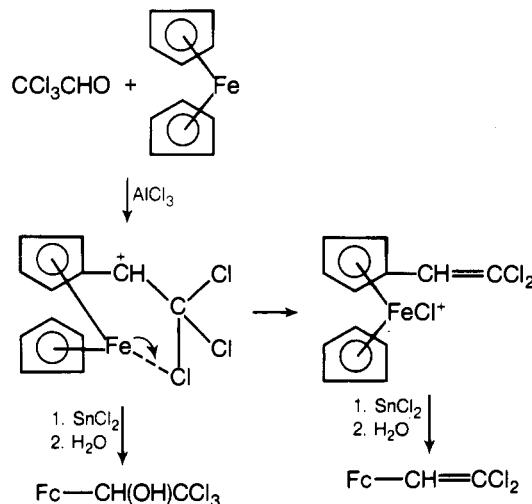


Organosilyl sulfides⁵²² form adducts with chloral with cleavage of the Si–S bond. With bis(trimethylgermyl) oxide chloral easily gives an adduct⁵²³ (by analogy with the interaction between chloral and acetic anhydride):



Ferrocene reacts with chloral in the presence of AlCl₃ (1:3:3 at 0°) to form a mixture which includes 5% ferrocenyltrichloromethylcarbinol and (after treatment of the reaction mixture with aqueous SnCl₂ solution) 21% ferrocenyldichloroethylene. The investigators²⁵⁴ proposed the reaction mechanism shown in Scheme XVII.

SCHEME XVII



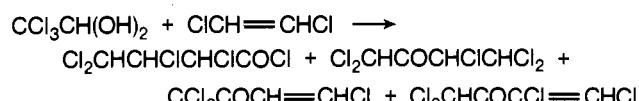
With the carbonyl derivatives of ferrocene⁵²⁵ chloral forms not carbinols but polymeric products (by interaction with the cyclopentadienyl fragments).

VIII. Interaction with Compounds Containing Multiple Bonds

A. Carbon–Carbon

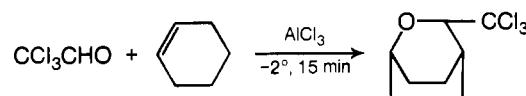
Chloral reacts with alkenes in the presence of acidic catalysts⁵²⁶ to form mainly 1-alkenyl-2,2,2-trichloroethanols.

sym-Dichloroethylene condenses with chloral in the presence of AlCl₃ to form trichloroacetyl-2-chloroethylene; under the same conditions with chloral hydrate, other products are also isolated:⁵²⁷



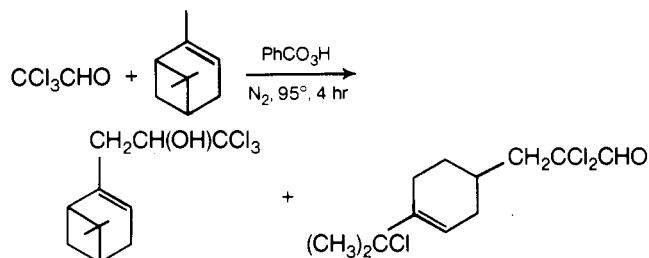
By the action of ethylene and Hg(OAc)₂ on chloral the hemiacetal $\text{CCl}_3\text{CH}(\text{OH})\text{OCH}_2\text{CH}_2\text{HgOAc}$ was obtained.⁵²⁸

Chloral reacts with mesitylene in the presence of H₂SO₄ to give the ester of 1-mesityl-2,2,2-trichloroethanol and 2-mesitylenesulfonic acid.⁵²⁹ Cyclohexene reacts with chloral to give a 2-oxabicyclo[2.2.2]octane derivative.⁵³⁰

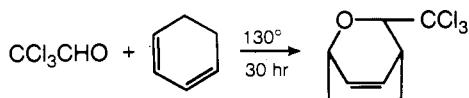


Activated olefins add easily to the chloral carbonyl group. Thus vinyl ethers react with chloral hydrate exothermically, forming 1:1, 1:2, or 2:1 adducts.^{531,532}

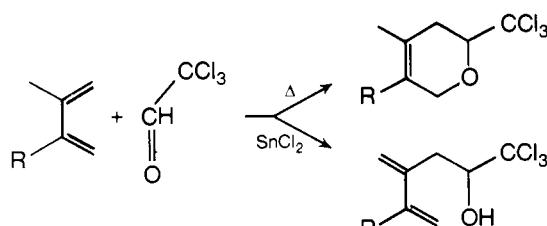
By heating (90°, 4 hr) chloral with β-pinene in the presence of benzoyl peroxide,⁵³³ a cyclohexene derivative is obtained; the same bicyclic product is formed by heating in a nitrogen atmosphere with perbenzoic acid:⁵³⁴



With 1,3-dienes chloral reacts as a dienophile,^{530, 535, 536} for example:⁵³⁰



Dale and Sisti⁵³⁵ obtained from chloral and isoprene, 2,3-dimethyl-1,3-butadiene, or piperylene under similar conditions (150° , 24 hr) the appropriate 2-trichloromethyl-2*H*-5,6-dihydropyrans in yields of 30, 53, and 32%, respectively. Recently^{536, 537} the products of the thermal and catalytic reactions of chloral with 2,3-dimethyl-1,3-butadiene and piperylene were determined; it was shown that both the dihydropyran derived from the Diels-Alder reaction and the acyclic trichloroethanol derivative are formed. The latter compounds are the major

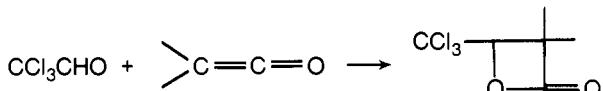


products on catalysis by SnCl_2 (20° , 18 hr) but they constitute only 10% of the product mixture in the thermal reaction (150°).

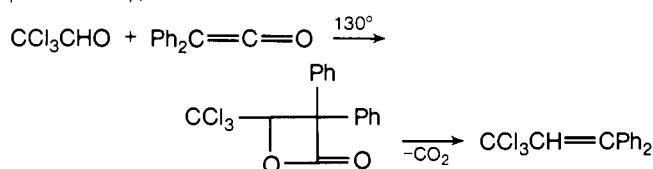
Dale and Sisti⁵³⁸ found that cyclopentadiene failed to add to chloral (100° , 21 hr). Polychlorocyclopentadienes react with chloral only at $200\text{--}300^\circ$ under high pressure;⁵³⁹ in that case compounds C_6Cl_8 or hexachlorobenzene were obtained from hexachlorocyclopentadiene and chloral (at $200\text{--}260^\circ$ or at $300\text{--}320^\circ$).

Heterolytic addition up to 30 molecules of chloral to 100 isoprene fragments with the formation of trichloroethanol derivatives⁵⁴⁰⁻⁵⁴² takes place on heating chloral with *cis*-1,4-polyisoprenes in the presence of Lewis acids.

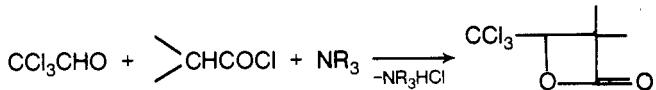
Chloral is one of the few carbonyl acceptors of the carbon-carbon double bond in ketenes. On the interaction between chloral and ketene, either with a catalyst (Lewis acids⁵⁴³) or without,^{544, 545} β -trichloromethyl- β -propiolactone is formed in yields up to 79% (in the presence of 2 equiv of ketene⁵⁴⁵). Other ketenes also form β -lactones with chloral, but in some cases only the appropriate ole-



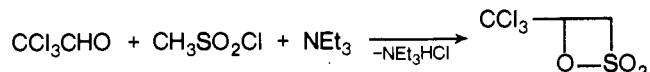
fins are obtained (as a result of decarboxylation of the β -lactones); for instance⁵⁴⁶



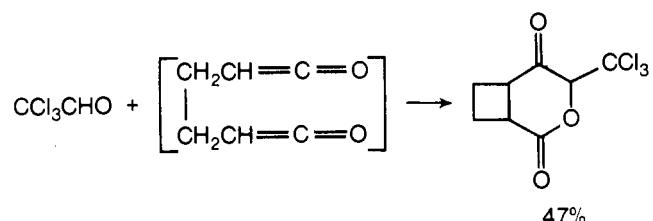
As the choice of stable ketenes is limited, methods have been proposed⁵⁴⁷⁻⁵⁵³ for obtaining β -trichloromethyl- β -propiolactones in high yields by using chloral to trap ketenes generated in situ by the reaction of acyl chlorides with strongly basic tertiary amines. Possible reaction mechanisms have been discussed.⁵⁵⁴



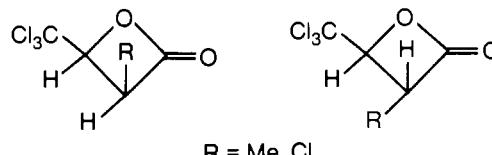
In the same way, sulfinic acids have been trapped with chloral as β -sultones.^{549, 550, 555, 556}



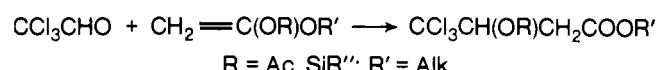
Some bis(ketenes) generated in situ may form cyclic adducts with chloral, for example:⁵⁴⁹



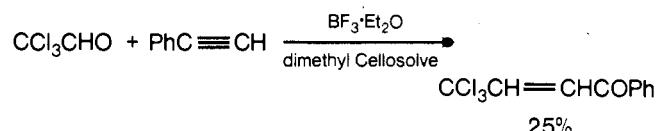
Brady and Smith⁵⁵⁷ have established by NMR analysis that methyl- or chloroketene generated in situ with chloral gives a mixture of isomeric β -lactones, with the *cis* isomer predominant:



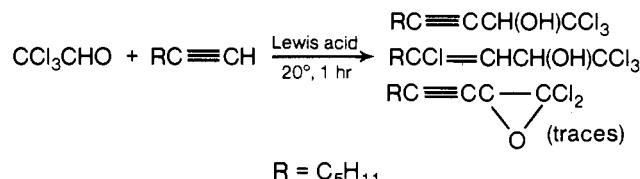
Ketene acetals react with chloral according to the scheme:^{558, 559}



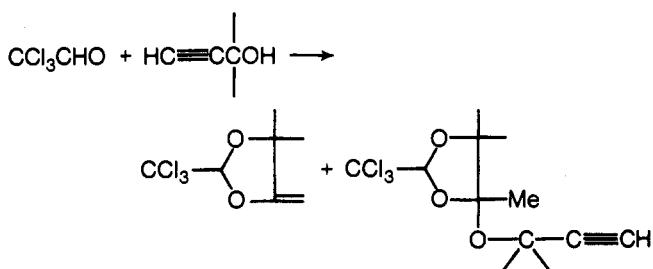
The interaction between chloral and alkynes may take place in two ways: chloral may add to the $\text{C}\equiv\text{C}$ bond to form α, β -unsaturated ketones,⁵⁶⁰ for example, with phenylacetylene:



On the other hand, 1-heptyne reacts with chloral in the presence of aluminum chloride or boron fluoride etherate to form a mixture of products (with acetylene derivatives among them⁵⁶¹):



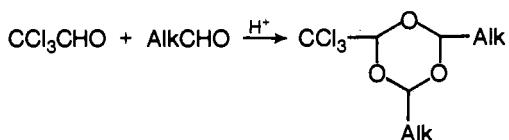
1-Substituted propargyl alcohols add to chloral in the presence of catalysts (HCl ,⁵⁶² BF_3 ,^{563,564 CaCl_2 ,⁵⁶⁵) to form hemiacetals, which in situ may exothermically cyclize⁵⁶³ to oxolanes (1:1 or 2:1, with prevalence of the latter on catalysis by BF_3)}



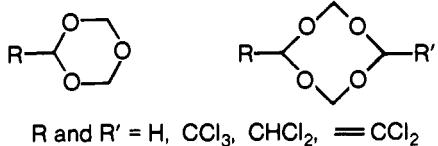
The $\text{C}\equiv\text{C}$ bond remains in the reaction products in the interaction between chloral and sodium⁵⁰¹ and tin^{519,521} alkynyl derivatives, as was noted in section VII.

B. Carbon–Oxygen

Chloral easily reacts with aliphatic aldehydes on catalysis by strong acids, usually forming trioxanes.^{566,567}



A more intricate reaction takes place between chloral hydrate and formaldehyde, from which Pinner^{568,569} has isolated many cyclic compounds such as the following

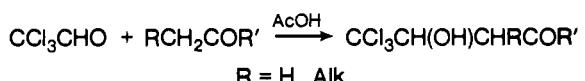


in addition to the monoadduct, chloral hydroxymethylacetal.

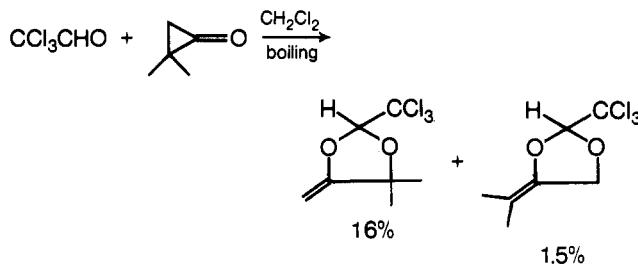
Products of unestablished structure were obtained⁵⁷⁰ by the interaction of chloral hydrate with terpenic aldehydes, in particular, with citral in the presence of H_2SO_4 .

Chloral reacts in a special way with anthrone.⁵⁷¹ In contrast with other aldehydes, which condense with dehydration (the oxygen from the carbonyl group of the aldehydes and the meso hydrogens of anthrone take part in this process), chloral reacts to form a mixture of α,β -bis(9,9'-anthronylidene)ethylene and dihydronanthrone (the catalysts are zinc chloride and tin or cupric acetate); in the presence of pyridine or sulfuric acid the latter product is obtained.

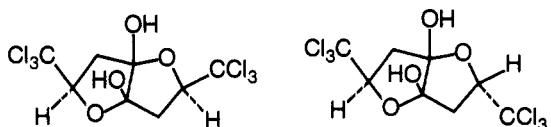
Methyl- and α -methylene ketones (the latter more difficultly; for reaction with acetoacetic acid derivatives see section IX) react with chloral as a consequence of their activated hydrogens^{572,573}



Cyclopropanones^{574,575} add chloral with ring enlargement to give dioxolanes:

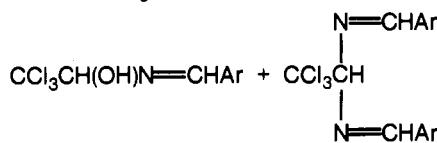


Research on the interaction of chloral or aromatic aldehydes with biacetyl in acetic acid in the presence of piperidine has given conflicting results. Schlenk⁵⁷⁶ assigned to all the reaction products the unique structure $[\text{CCl}_3\text{CH}=\text{CH}(\text{OH})_2]_2$. However, later⁵⁷⁷ this viewpoint was disproved; the products were assigned the structures *cis,cis,cis-* and *cis,cis,trans*-3,7-bis(trichloromethyl)-2,6-dioxabicyclo[3.3.0]octane-1,5-diol (their composition corresponds to Schlenk's compounds, $\text{C}_8\text{H}_8\text{Cl}_6\text{O}_4$):

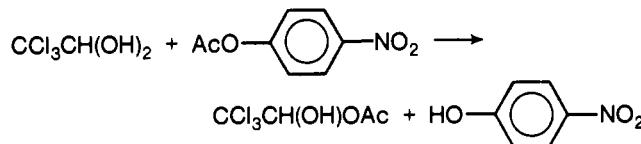


The interaction between chloral and acetyl- and *gem*-diacetylferrocene was discussed above.⁵²⁵

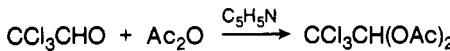
Spasov and Ivanov established⁵⁷⁸ an interesting specificity of aromatic aldehydes for chloral hydrate in the presence of ammonia; the products are azomethines:



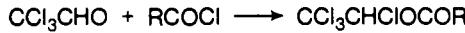
The reactions of chloral with carboxylic acids and their functional derivatives take place without the participation of their carbonyl groups (see also section IX). Most of the reactions involve the acetylation of chloral hydrate.^{579,580} A kinetic investigation of the reaction of chloral hydrate with acetyl-*p*-nitrophenol in water has shown⁵⁸⁰ that the reaction is first order in each reagent, according to the scheme:



In the presence of the base, chloral reacts with acetic anhydride in the following way:⁵⁸¹



Acyl chlorides add chloral according to the scheme:



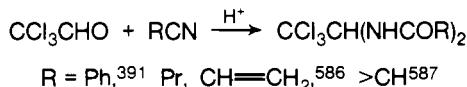
In this way the following reagents react with chloral: phosgene with tertiary-amine catalysis,⁵⁸² carbamoyl chloride,⁵⁸³ acetyl chloride with catalysis by silver malonate⁵⁸⁴ or by triethylamine.⁵³⁸

2,6-Bis(trichloromethyl)tetrahydropyron-4 is obtained⁵⁸⁵ on the treatment of chloral with bis(carboxymethyl) ketone.

C. Carbon–Nitrogen

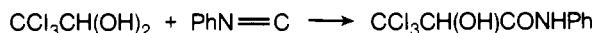
The interaction between chloral and nitriles was inves-

tigated in limited examples. Reaction is realized only on acidic catalysis according to the following scheme:

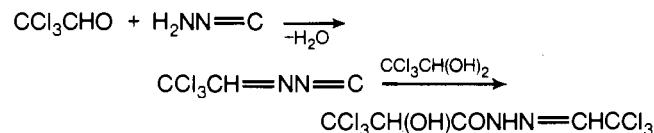


In the case of substituted acetonitriles⁵⁸⁷ the yield of such products varies (from 19 to 94%) and the appropriate acid amides are formed concurrently. These amides are not intermediates in the main reaction. Thus in the reaction with chloral, the C≡N bond itself takes part, with subsequent hydrolysis of the adduct.

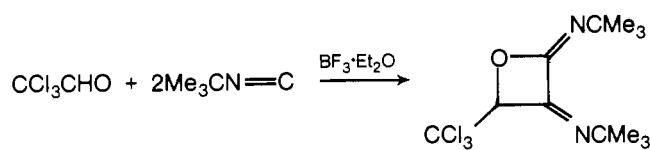
Isonitriles (phenylisonitrile,⁵⁸⁸ isodiazomethane⁵⁸⁹) add vigorously to chloral to form trichloroethanol derivatives. However, the mechanisms of these reactions differ. In the first case, chloral hydrate adds to the carbenic carbon atom and trichlorolactic acid anilide is formed:



In the reaction of chloral with isodiazomethane, it was supposed⁵⁸⁹ that condensation occurs first, followed by dehydration. Then a second chloral molecule (as hydrate) adds to the intermediate carbene (as shown for phenylisonitrile):



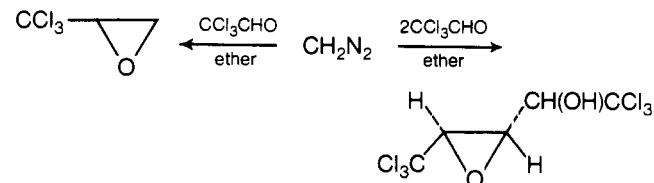
Kabbe⁵⁹⁰ established that chloral adds 2 equiv of *tert*-butyliodonitrile forming an oxacyclobutane derivative in 68% yield.



D. Interaction with Diazomethane and Diazoacetic Acid Ester

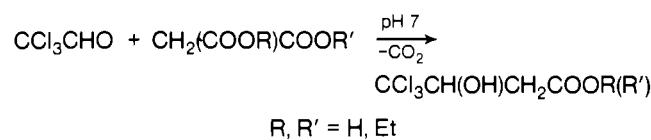
Schlotterbeck⁵⁹¹ has proposed that the reaction product of chloral and diazoacetic acid ester is ethyl trichloroacetacetate. Later, he⁵⁹² isolated a compound $\text{C}_3\text{H}_3\text{Cl}_3\text{O}$ (which he characterized as *gem*-trichloroacetone) from the interaction of equimolar amounts of chloral and diazomethane in cooled ether. A little α -hydroxy- β,β,β -trichloroethylacetone (using excess of chloral) was also isolated. This result was disproved by a series of later researches.⁵⁹³⁻⁵⁹⁵ By the action of diazomethane on chloral^{593,594} or on its hydrate⁵⁹⁵ the main product was trichloromethylethylene oxide. Besides that, Meerwein and his associates⁵⁹⁵ detected among reaction products also chlorine, methanol, dimethyl ether, chloral dimethyl acetal, and a nitrogen compound of unestablished structure.

The use 2 equiv⁵⁹⁶ of chloral leads to a substituted trichloroethanol:

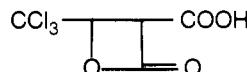


IX. Interaction with Activated C-H Bonds*

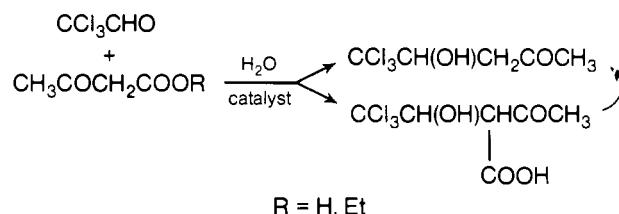
Malonic acid and its mono- and diethyl esters react with chloral with the participation of activated hydrogen atoms.⁵⁹⁷⁻⁶⁰²



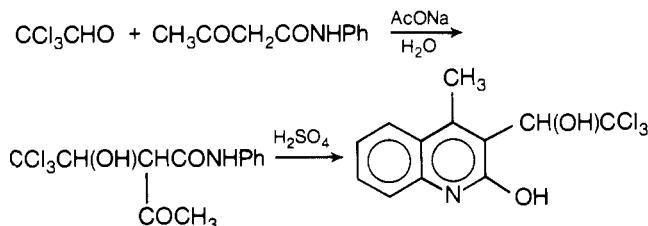
Vul'fson and Shemyakin^{603,604} incorrectly assigned a β -lactone structure to the product of interaction between chloral and malonic acid:



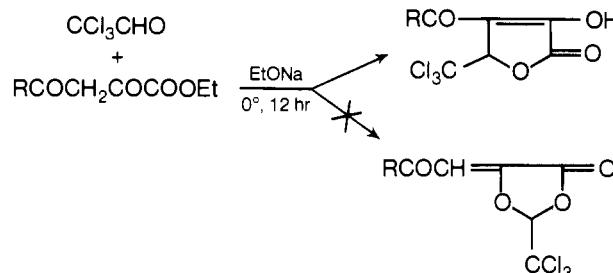
With acetoacetic acid and its esters, chloral reacts analogously in the presence of acidic or basic (pyridine)-catalysts.^{585,605,606} In all cases trichloroethanol (but not trichloroethane⁶⁰⁷) derivatives are formed, both with decarboxylation^{585,605} and without it.^{605,606}



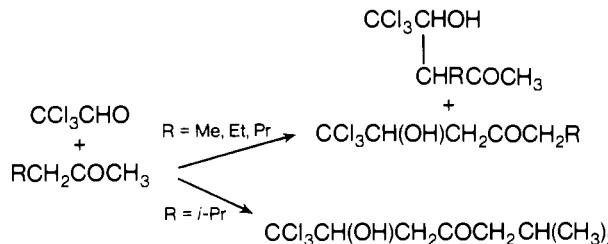
An adduct of chloral with acetoacetanilide⁶⁰⁸ obtained in this way (in the presence of sodium acetate) may be cyclized to a quinoline derivative with acid:



The interaction between chloral and ethyl esters of ketopyruvic acid leads to a α -butyrolactone⁶⁰⁹ (not to a ketodioxolane⁶¹⁰ as Bergel and associates had proposed):



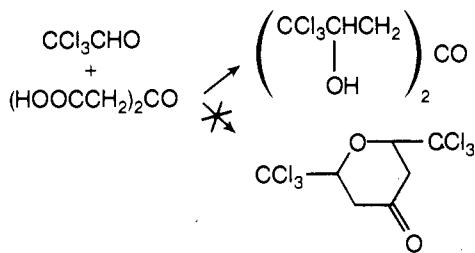
Methyl alkyl ketones add to chloral in two ways:⁶¹¹



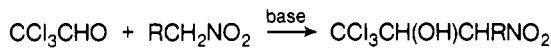
* See also section VI.E.

Indandione is alkylated⁶¹² in the 2 position by chloral hydrate.

Judging from its IR and NMR spectra⁶¹³ the product of the interaction of chloral with acetonedicarboxylic acid has the structure not of 4-ketopyran⁶¹⁴ but of a trichloroethanol derivative.

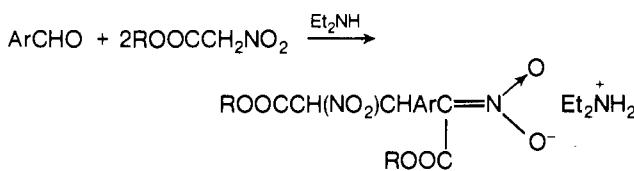


Reactions of chloral or its hydrate with aliphatic nitro compounds, as many investigators have shown,⁶¹⁵⁻⁶²³ are realized easily with basic catalysts both in water and in anhydrous media. 3,3,3-Trichloronitropropanol-2 derivatives are obtained in good yields; they can be dehydrated under more severe conditions.



R = H,⁶¹⁵⁻⁶²⁰ Me,⁶²¹ Et,⁶²² Pr,⁶²¹ COOR',⁶²³ and others.⁶²²

In contrast with chloral, other aliphatic and also aromatic aldehydes react directly to form nitro olefins.⁶²⁴ In further contrast to chloral, aromatic aldehydes can react with nitroacetic acid esters⁶²³ in the following way:



X. Stabilization, Polymerization, and Copolymerization

The high reactivity of the chloral carbonyl group as a consequence of the strongly negative inductive effect of the trichloromethyl substituent, also accounts for the low stability of monomeric chloral and for its capacity to homo- and copolymerize with other monomers (usually in the presence of ionic initiators). Chloral is kept with difficulty.

To stabilize chloral one uses formamide or dimethylformamide (0.2–1%,⁶²⁵) tetraalkylthiuram disulfide and azobisisobutyronitrile (0.1–0.2%).⁶²⁶

Sulfuric,⁶²⁷⁻⁶²⁹ phosphoric, and polyphosphoric⁶³⁰ acids induce the formation of polychloral with several degrees of polymerization—from tetrameric (2,4,6,8-tetrakis(trichloromethyl)-1,3,5,7-tetroxane⁶²⁸) to an amorphous polyether with a molecular weight up to 25,000.⁶³⁰ Chloral polymerization in the presence of aluminum chloride was patented,⁶³¹ but later⁶³² that catalyst was rejected as were NEt₃, Ph₃P, AsCl₃, MeONa, (i-PrO)₃Al, Fe(CO)₅.

Low-temperature polymerization of chloral is catalyzed by pyridine,⁶³³ magnesium and aluminum diethylamides,⁶³⁴ some organometallic compounds (as BuLi,^{635,636} Et₃Al,^{632,636-639} Bu₃B,^{636,638} Et₂Zn,⁶³⁸⁻⁶⁴³ sodium naphthalene⁶⁴⁴ and others^{636,638,640-642}), metal alkoxides,^{642,645} and also metal ketals (compounds of Mg, Ca, and Ba with benzil, benzophenone, Michler's ketone;⁶⁴⁶ Mn(II), Co, Mg, and Cu acetylacetones⁶⁴⁷).

In the catalysis by metal ketals, yields of polymers are decreased with an increase in temperature.⁶⁴⁰

A high degree of crystallinity of polychloral is achieved⁶³⁸ using MAIk_n (M = Mg, Zn, B, Al, Cd).

It was shown⁶³⁹ by IR spectra and X-ray diffraction that polychloral, which is obtained at -78° in the presence of Et₂Zn, Et₃Al, or BuLi, has an isotactic tetragonal structure. By these methods a spiral conformation was established⁶⁴⁸ for a polyether-alcohol obtained from chloral by several methods.

Chloral itself or its acetals are copolymerized with formaldehyde (as the monomer or as 1,3-dioxolane and 1,3,5-trioxane^{649,650}) in the presence of Et_xM_y (M = Zn, Al, Cd),⁶³² amines, phosphines,⁶⁵¹ diazonium salts,⁶⁵² Lewis acids,⁶⁵²⁻⁶⁵⁵ sulfuric acid,⁶⁵⁵ polyphosphoric esters,⁶⁵⁶ and other acidic catalysts.^{650,657-659} Attempts to copolymerize chloral and paraformaldehyde were unsuccessful.^{658,659}

At low temperatures copolymers of chloral with dichloroacetaldehyde are formed,^{629,660-662} the best catalysts are compounds such as Et₂Zn. Boron trifluoride etherate initiates the copolymerization of chloral with adipaldehyde (in a 1:1 ratio).⁶⁶³

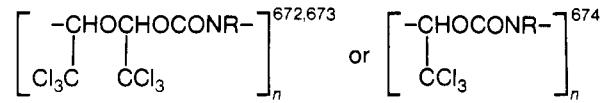
By heating at 100° with concentrated H₂SO₄,⁶⁶⁴ a copolymer of chloral with oxetane was obtained.

Vinyl monomers are copolymerized with chloral in the presence of M_xAlky⁶⁶⁵ (M = Li, Na, Be, Mg, Ca, Sr) and Lewis acids.⁶⁶⁶ Heating (150–220°) polystyrene or polystyrene-butadiene with chloral leads to the formation of polymer, including up to 20.6% α-hydroxy-β,β,β-trichloroethyl groups.⁶⁶⁶

Recently the high catalytic activity of the system CCl₃CH(OH)₂ with Et₃Al was established for the polymerization and copolymerization of vinyl monomers⁶⁶⁷ and acetaldehyde⁶⁶⁸ with chloral.

On interaction with some terpenic olefins, chlorine-containing polymeric resins are formed in addition to monomer adducts (trichloroethanol derivatives).⁶⁶⁹

Under the influence of ionic polymerization catalysts (BuLi, BF₃) at -78° a copolymer of chloral with ketene⁶⁷⁰ was successfully obtained. Other heterocumulenes such as isocyanates⁶⁷¹⁻⁶⁷⁴ and thionylaniline⁶⁷⁴ are also copolymerized with chloral in the presence of anionic polymerization catalysts: BuLi, NaCN, sodium fluorene,^{672,673} tertiary amines,⁶⁷⁴ with several ratios of monomers over a large temperature interval (-90 to +60°^{673,674}). The products have the structures (in case of isocyanates):



All polymers of chloral are characterized by high thermal stability, and they are fireproof.

XI. Identification

There is a series of well-established methods for identifying and detecting chloral in mixtures with other aldehydes or polyhalo compounds, used in analytic chemistry, pharmacology, and toxicology.

Among these, iodometric methods predominate: the oxidation of chloral by iodine to trichloroacetic acid in the presence of sodium thiosulfate⁶⁷⁵⁻⁶⁷⁷ or hydrazine hydrochloride⁶⁷⁸ as titrants. Several colorimetric methods⁶⁷⁹⁻⁶⁸³ are based on specific color reactions with chloral (for example, cyanine dye formation from chloral and quinaldinium ethyl iodide and ethylamine,⁶⁸¹ or the cherry-color obtained on treatment of chloral with hydroxylamine hydrochloride and diaminopyridine⁶⁸³) and also on general color reactions of polyhalo compounds (with

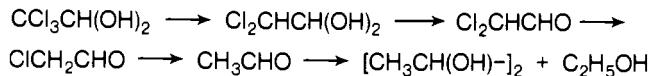
pyridine⁶⁸⁰ and resorcinol⁶⁸² in alkaline or acidic media); the latter obscure the detection of chloral by the named reactions in mixtures with chloroform, trichloroethanol, and so on.⁶⁸⁴⁻⁶⁸⁹

Additional color reactions for the identification of chloral include its interactions with fluoroglucine in alkaline solution,⁶⁹⁰ with molybdic acid and phenol,⁶⁹¹ with dimethylaniline,⁶⁹² with *m*-nitrobenzene (the violet color in alkali solutions is disguised by other aldehydes⁶⁹³), with sodium nitroprusside, and with ferric chloride (violet coloration, native to all polyhalo compounds⁶⁹⁴). Chloral does not form a complex with cupric ethylenediaminetetraacetate⁶⁹⁵ or a precipitate of AgCl with Ag⁺.⁶⁹⁶

Among different methods for the analysis of chloral one may notice potentiometric titration by alkaline solution,⁶⁹⁷ microcrystalloscopy (as *o*-, *m*-, and *p*-nitrophenylhydrazone⁶⁹⁸) and bichromatometric detection;⁶⁹⁹ in the last case the error is not more than 0.15%.

In spite of the high sensitivity (up to 5×10^{-9} mol)⁷⁰⁰ of some qualitative reactions of chloral, their low specificity in the presence of masking contaminants (which have been discussed above) requires the use of differential analytical methods for chloral in mixtures.

Elving and Bennett⁷⁰¹ failed to detect chloral with a polarographic method in the presence of chloro- and dichloroacetaldehydes; the investigators explained⁷⁰² that result by continuous multielectronic reduction of chloral on a dropping Hg electrode in accordance with the scheme:



This process is expressed by only one wave ($E_{1/2} = -1.4$ V). In the presence of hydroxylamine sulfate in the polarographic reduction of chloral, two waves are observed⁷⁰³ (-0.55 and -1.2 V), but they belong to the reduction of chloral oxime. The polarography of mixtures of chloral with other chloroacetaldehydes has been studied.^{704,705}

In the presence of dichloroacetaldehyde, chloral is determined by colorimetry of a phenylhydrazone mixture,⁷⁰⁶ or after alkaline work-up.^{680,707}

Lately chromatographic methods (mainly GLC) have been used to determine chloral in the presence of polyhalo compounds (aldehydes, alcohols, chloroform, and others);⁷⁰⁸⁻⁷¹⁰ these methods are used in particular as a control in chloral production by the chlorination of ethanol.⁷¹¹

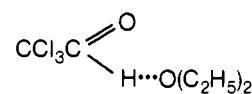
XII. Molecular Complexes with Chloral

Chloral's capacity to form molecular complexes with many compounds (especially those which are basic) is well known. So chloral hydrate gives complexes with some drugs: amidopyrine (1:1 or 2:1),⁷¹²⁻⁷¹⁴ phenacetin (3:1),^{715,716} antipyrine (1:1, 2:1),⁷¹⁷⁻⁷¹⁹ salol (3:1),^{715,720} quinine,⁷²¹ and others.^{715,719,722-724}

In the chloral hydrate-antipyrine system,⁷²⁵ the 2:1 complex was observed only at low temperatures; the 1:1 complex is more stable. According to Taboury,⁷¹⁸ the amino and carbonyl groups of antipyrine do not take part in its formation (based on Raman spectral investigations).

A subject for special review is the research on complexes of chloral in two- and three-component systems, made by measurements of surface tension,^{726,727} viscosity,⁷²⁸⁻⁷³⁹ ultrasonic velocity,⁷⁴⁰⁻⁷⁴² and other parameters.⁷⁴³⁻⁷⁵⁰

Data about the nature of the intermolecular bonding in chloral complexes are limited and contradictory. So Sandell⁷⁵¹ explained association between chloral and diethyl ether by a strong hydrogen bond:



but other investigators⁷⁵² have explained the same phenomenon by donor-acceptor interaction, with the chloral carbonyl group as the acceptor.

The interaction between chloral and iodine and its chloride and bromide is explained (by IR spectroscopy⁷⁵³⁻⁷⁵⁵) through the formation of a 1:1 charge-transfer complex.

XIII. Physical and Physical-Chemical Studies

Bond lengths and energies in chloral and its hydrate have been measured by several methods (see ref 54, 55, 64, 71, 756-758). Judging from the carbon-oxygen bond length,⁷⁵⁶ the chloral carbonyl group has a 100% C=O double bond; it is disposed in a pyramidal plane of symmetry formed by the trichloromethyl group.⁷⁵⁶ A molecule of chloral hydrate includes two chelate rings, formed with H...Cl hydrogen bonds (from osmometric data⁵⁴). According to the chloral dipole moment (1.58 D,⁷⁵⁷ 1.96 D⁵⁶), angles in a molecule have been enlarged. The dipole moment of chloral hydrate (2.07 D in benzene and 2.65 D in dioxane;⁵⁷ the increase is due to intermolecular hydrogen bonding between chloral hydrate and dioxane) once more confirms that chloral hydrate is a gem-diol, and not a molecular complex with water.

There are many measurements of the Raman,^{53,759-763} IR,^{60-62,764,765} UV,^{752,766-768} NMR,^{58,59,769} NQR,³⁵ Cl⁷⁷⁰⁻⁷⁷⁵ spectra of chloral and its hydrate, and of their polarographic behavior.^{701-705,767} It is interesting that the NQR spectrum⁷⁷² does not confirm the existence of H...Cl hydrogen bonds in the chloral hydrate molecule and that the nonequivalence of the three chlorine atoms in the trichloromethyl group is the result of a field effect.

Vapor pressure (from -20 to -240°), heat of vaporization (from -80 to +290°), heat of formation (from -80 to +1000°), heat of conduction (from -80 to +120°), viscosity (-80 to +500°), and surface tension (from -80 to +120°) of chloral are tabulated.⁷⁷⁶

XIV. Applications

In many pharmacopoeias chloral hydrate has been approved for many years as a hypnotic, sedative, and sleeping drug. The LD₅₀ is 710 mg/kg for mice.⁷⁷⁷ The biological activity of chloral and its hydrate has been studied in many aspects, but is outside the scope of the present review.

Besides the well-known uses of chloral—in the synthesis of dichloroacetic acid and its derivatives (syntomyctine among them), vanillin, DDT, organophosphorus insecticides—there are also many others. Chloral hydrate activates the bleaching of cotton and textile.⁷⁷⁸⁻⁷⁸⁰ It is used in the electroprecipitation of nickel,⁷⁸¹⁻⁷⁸⁷ for fungicidal wood protection,⁷⁸⁸ for the detection of a series of glucosides,⁷⁸⁹ for the detection of zinc in insulin,⁷⁹⁰ and for the isolation of water-soluble starch⁷⁹¹ and amylose⁷⁹² from potato starch. Similar to actinomycin D, chloral hydrate inhibits the synthesis of ribonucleic acid and proteins:⁷⁹³ it is also an inhibitor of steel, copper, and tin corrosion⁷⁹⁴ in perchloric acid solutions.

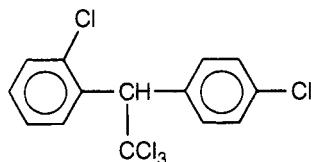
A modifying effect of chloral and its hydrate on polyenes,^{795,796} polyols,⁷⁹⁷⁻⁸⁰¹ polyamides,⁸⁰²⁻⁸⁰⁶ and also

on their high solvating capacity toward polyamide resins,⁸⁰⁶⁻⁸¹¹ polyalkylene terephthalates,⁸¹² and polysaccharides⁸¹³ has been found.

The behavior of chloral on radiolysis has allowed it to be used, on the one hand, as a radiopotentiator (on γ -irradiation of *Escherichia coli*^{814,815}) and, on the other hand, as a radioprotector⁸¹⁶ and also for detection and dosimetry of γ -irradiation;^{143,817-819} one can measure⁸²⁰ γ -irradiation up to 30 krads at pH 5-5.5.

High catalytic activity of chloral is recorded in the polymerization of alkenes⁸²¹ and other vinyl monomers,⁸²² in the preparation of urea-formaldehyde plastics,⁸²³ and in some dehydration reactions (in particular in the condensation of amines and ketones).⁸²⁴⁻⁸²⁶ Chloral is an activator of a catalytic π complex in cis-stereospecific butadiene polymerization.⁸²⁷⁻⁸²⁹

Still more common is the use of chloral transformation products. Chloral hemiacetals with polyols are used for the preparation of synthetic fibers and ion-exchange resins,^{188,191,204} and they also have a sedative action.^{187,192} Products from the interaction between chloral and hydroxy steroids have a selective biological activity.^{167,168,173} The strong oestrogenic action⁸³⁰ of so-called "ortho-para-DDT"



which constitutes up to 20% of crude (technical) DDT, does not except such action of the latter on warmblooded animals.

A sedative and hypnotic effect is associated with the reaction products from chloral with bromoisovalerylurea,²⁶⁹ cholin,⁸³¹ betaine,⁸³² and carnitine.⁸³³

Chloral itself has a little insecticidal and herbicidal activity; "meta-chloral" is, however, a good herbicide.⁸³⁴ High herbicidal properties have been exhibited by chloral adducts with amides and nitroparaffins,⁸³⁵ chloral 2,4-dichlorophenoxyacetylhydrazone,⁸³⁶ and some chloral mercaptals.^{231,235,837}

The known pesticides, "triphan",¹⁵² "methoxychlor",^{367,368} "methiochlor",³⁸¹ and *N*-(α -hydroxy- β,β,β -trichloroethyl)acetamide,⁸³⁸ are also chloral derivatives. An adduct of chloral with nitromethane was patented⁸³⁹ as a systemic fungicide.

Effective insecticides were synthesized from chloral and polychlorocyclopentadienes.⁵³⁹ Attempts to obtain analogs of DDT with enhanced activity by introduction of a series substituents into the aromatic rings or by their replacement with heteroaromatic rings did not lead to positive results.^{353,430,433,840}

Insecticides with strong activity have been obtained from phosphororganic derivatives of chloral including both trichloromethyl and dichlorovinyl groups (see ref 470, 490, 494, 495, 499, 841-844).

Nowadays chloral is used widely as a monomer for copolymerization because all its polymers have high thermal stability and fire resistance.^{655,660,661,666} For these purposes one uses some other chloral derivatives, in particular those which include multiple bonds^{181,845-847} and others.^{848,849}

Chloral acetals with dodecylmercaptan²²¹ are recommended for use in butadiene-styrene rubber production.

Reaction products between chloral and benzidine or *p*-phenylenediamine⁸⁵⁰ and also copolymers with several oxetanes⁶⁶⁴ are good adhesive additions to resins and

abrasives. *gem*-Diaryltrichloroethanes are excellent anti-corrosive agents for lubricants.⁸⁵¹

Chloral complexes including Fe^{852,853} are used in particular⁸⁵³ for dyeing of chromosomes.

To conclude, one may note that research concerning the use of chloral and its derivatives were based mainly on the properties of known model compounds.

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