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The synthesis, structure and reactivity of (α-trihalomethyl)carbinols

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ABSTRACT. Data on the methods of synthesis and chemical properties of (α-trihalomethyl)carbinols are correlated and systematised in the review. Features of the structure are considered and certain effects of the nature of the halogen on their reactivity and physicochemical properties are discussed. An important role has been shown for the (α-trihalomethyl)carbinols as intermediates and synthons.

The bibliography contains 153 references.

Contents

I.	Introduction	1318
II.	Methods of synthesising (α-trihalomethyl)carbinols	1318
III.	Conversions of (α-trihalomethyl)carbinols	1321

I. Introduction

Interest in the synthesis of (α-trihalomethyl)carbinols has been increasing since the first studies appeared on the preparation of this class of compounds.[1–3] Significant success has been achieved in the synthesis and practical application of these compounds. New degradable organochlorine pesticides have been synthesised, based on (α-trichloromethyl)carbinols, which do not accumulate in vertebrates and are decomposed by enzymic systems.[4–7] It has been established recently that systematic rapid changes in the toxic chemicals used enable the self-purification of the environment from their metabolites and residues to be maintained at a low level. The large number of compounds used for plant protection is increased by a range of (α-trichloromethyl)carbinols.[4]

(α-Trichloromethyl)carbinols are used in medicine as narcotics and analgesics and in recent years effective tranquillisers have been found among the (α-trichloromethyl)carbinols of the acetylenic series,[8,9]

(α-Trichloromethyl)arylcarbinols (ATMC) are converted by a one-stage method, dehydration–rearrangement reaction, into α,β,β-trichlorostyrenes which are co-monomers for heat- and light-stable polymers.[10,11]

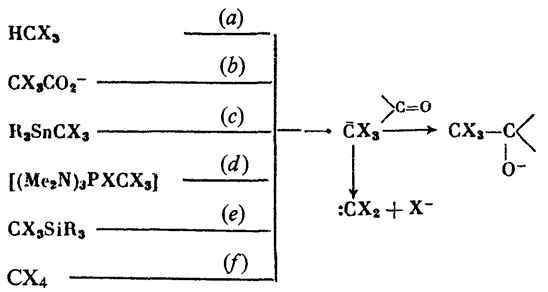
The current review is the first attempt in the Soviet and foreign literature to embrace completely all aspects of the chemistry of the (α-trihalomethyl)carbinols.

II. Methods of synthesising (α-trihalomethyl)-carbinols

1. Condensation of trihalomethyl anions with carbonyl compounds

The most widespread and general method of synthesising (α-trihalomethyl)carbinols is the condensation of trihalomethyl anions with carbonyl compounds. The generation of trihalomethyl anions (THA) is effected by various routes using a wide range of reagents, e. g. from haloforms in basic medium,[12–24] decarboxylation of trihaloacetic acids[25–27] or their salts,[28] from trihalomethyl-organotin compounds[29] and trihalomethylphosphonium salts,[30] from trihalomethylorganosilicon compounds[31] or the electrochemical reduction of carbon tetrachloride.[32–36] The resulting THA tend to dissociate into dihalocarbenes which is an undesirable process in the synthesis of (α-trihalomethyl)carbinols.[37] Experimentally this is readily prevented at relatively low (0 °C and below) temperatures in the presence of carbonyl compounds (Scheme 1).

Scheme 1



X = Cl, Br, combination Cl and Br

It has been shown that THA are formed from the majority of haloforms by a rapid reversible reaction. Many investigators,[12–24] using haloforms as a source of THA, have paid much attention to the choice of basic catalyst and to their proportion in the system of carbonyl compound–haloform–solvent. The generation of THA with almost the same success was effected with potassium and sodium hydroxides,[12,15,16,20,21] alkali metal alkoxides[13,14] and calcium oxide in dimethyl sulphoxide.[17,18] A serious difficulty in the process of simultaneously generating THA from haloforms and condensing them with carbonyl compounds is the inclination of the latter to undergo aldol condensation and Cannizzaro oxidation–reduction processes under the same base catalysis conditions. This hinders appreciably the synthesis of (α-trihalomethyl)carbinols. With the aim of suppressing the competing side reactions mentioned above, many authors have used various solvents, such as aliphatic acetals, ketals, vicinal glycols[38] or, which is particularly important, have tried to reduce the quantity of the basic catalyst to the minimum. In contrast to the early studies[12–19] where the catalyst was used in equimolar ratio to the aldehyde (or ketone), it was shown that the use of liquid ammonia as solvent was extremely convenient and it was possible to reduce the quantity of base (aldehyde : chloroform : potassium hydroxide = 1 : 1 : 0.3–0.5) and simultaneously provide low temperature conditions when the process of dissociative

fission of the THA into dihalocarbene is suppressed. The yield of the desired carbinol was 41–95%.[20] The yield of the desired carbinol was 41–95%.[20] A procedure, competitive at the technological level, has been described[21] in which it was shown that the optimum conditions for synthesising the narcotic chloretone, viz. (α-trichloromethyl)dimethylcarbinol, were a ratio of acetone : chloroform : potassium hydroxide = 10 : 1 : 0.1 without solvent at −5 °C. During the synthesis the excess of acetone was returned into the cycle and yield was 76%.

It was shown, using as example the condensation of benzaldehyde with mixed haloforms (dichlorobromo- and dibromochloromethanes) that under conditions of base catalysis the latter also generate the corresponding THA.[39,40] Condensation has been described with heterogeneous base catalysis (powdered calcium hydroxide) without solvent[39] and with homogeneous catalysis using potassium t-butoxide and t-butanol.[40]

The generation of THA from haloforms is also effected under conditions of phase transfer catalysis.[41,42] This method does not lead to a high yield of product, exceptions being only the higher representatives of aliphatic aldehydes and ketones and also certain aldehydes of the heterocyclic series (2-, 3-, 4-pyridyl-).[43] It must be noted that aromatic ketones do not react at all under phase transfer catalysis conditions.

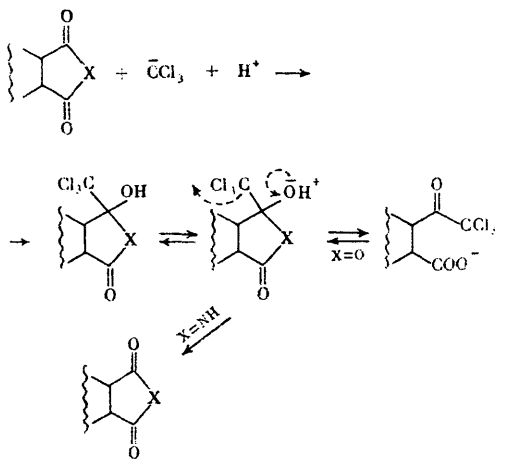
In 1959 Wagner[44] reported the generation of dichlorocarbene by the thermal decomposition of sodium trichloroacetate (TCAA) in 1,2-dimethoxyethane. However Winston and co-workers[28] under the same conditions succeeded in decomposing sodium trichloroacetate in the presence of aldehydes and isolating (α-chloromethyl)carbinols as products of the trichloromethylation of the carbonyl group, albeit in extremely modest yield (29–47%). Decarboxylation of trihaloacetate anions with the formation of trichloro(bromo)methyl anions (Scheme 1, *b*) takes place with comparatively low yields. The reason, in our opinion, is graphically illustrated in recently patented work where it was shown that, when using DMSO, DMF or other related compounds as solvent, spontaneous addition of $\bar{C}X_3$ and CO_2 takes place at the carbonyl group with the formation of the corresponding carbonates. Under specific experimental conditions the reaction may be directed completely to carbonate formation.[45]

$$>C=O + \bar{C}X_3 + CO_2 + Na^+ \longrightarrow >C(CX_3)OCO_2^-Na^+$$

It was shown recently by English scientists[25,27] that THA are readily generated at room temperature by dissolving trichloro- and tribromoacetic acids in DMSO. The use of halogenated acids as sources of THA completely excludes carbonate formation and the desired (α-trihalomethyl)carbinols are isolated in 50–80% yield.[25,27] It is interesting to note that 4-nitrobenzaldehyde does not react with haloforms[46] but 4-nitrophenyl(trichloromethyl)carbinol is formed in 80% yield with trichloro(bromo)acetic acid.[25] This experimentally observed fact is seemingly linked with the use of the highly polar DMSO solvent which in fact reduces the deactivating effect of the 4-nitro group on the α-carbon atom to zero.

This synthetic method enables several pyridinaldehydes to take part in the reaction but not furfural and its homologues, which are rapidly resinified in a TCAA medium. The problem of trichloromethylating these compounds was successfully resolved by the decarboxylation of trichloroacetates (K, Na) in a medium of DMSO or DMF.[47]

The trichloromethylation of cyclic anhydrides and imides in a TCAA–DMSO system is of interest. This reaction leads to a lactone or lactam containing a trichloromethylcarbinol structural unit in the γ-position of the heterocycle. It was shown[48] that either ring–chain isomeric conversions or partial haloform fission occur in this case.



By using various solvents the equilibrium system is successfully displaced in the direction of ring or chain isomers.

It must be noted in regard to the decarboxylation of TCAA into the trichloromethyl anion (TCA) that it is possible to use hexamethylphosphoramide (HMPA) successfully in place of DMSO, which while maintaining the pH of the medium close to neutral has certain advantages over DMSO from the preparative point of view.[49]

Trihalomethylphosphonium salts are also sources of THA. Tris(dimethylamino)trichloromethylphosphonium chloride, on reaction with aliphatic aldehydes and cycloalkanones, forms (α-trichloromethyl)carbinols in preparative yield.[30] Tributyl(trichloromethylstannanes, which are convenient synthons for generating THA, form (α-trihalomethyl)carbinols in 20–69% yield with aliphatic and aromatic aldehydes.[29] The authors excluded any effect of initiators and inhibitors of radical processes from the reaction and demonstrated strictly the heterolytic fission of the $-Sn-CCl_3$ bond with the formation of TCA.

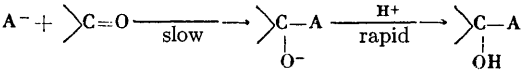
From the preparative point of view it is best to heterolyse the carbon–silicon bond in α-trichloromethylsilanes in a medium of tris(dimethylamino)sulphonium difluorotrimethylsilicate (TASX). This route provides a 75% yield of trichloromethylated carbinols.[31]

The method of generating TCA by the cathodic reduction of carbon tetrachloride in chloroform or DMF is interesting. In the presence of alkyl-, heteryl- or arylaldehydes the corresponding (α-trichloromethyl)carbinols are fomred in 11–92% yield.[32–36]

$$RCHO + CCl_4 \xrightarrow[CHCl_3 \text{ or } DMF]{2\bar{e}} RCH(OH)CCl_3.$$

The synthesis of several previously undescribed (α-trichloromethyl)carbinols has been achieved by this means although the complexity of the experimental conditions places the value of this method in use under some doubt.

The condensation reaction of TCA with aldehydes and ketones proceeds according to the widely known mechanism where the carbanion ($\overline{C}X_3$ in this case) attacks the carbonyl group.



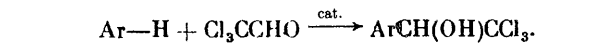
The first stage determines the rate of the reaction which makes it possible to make certain comparisons with the kinetically related Darzens (glycidyl condensation) and Perkin reactions.[50] Because of the absence of sufficient literature data on the kinetic parameters of the Darzens reaction, Reeve and co-workers[51] studied the reactivity of seven aryl aldehydes taking the kinetic data of the Perkin reaction as standard. The results obtained are in good agreement, and in several cases are even identical.

It must be noted that a neighbouring group effect or a secondary steric effect of an *ortho* substituent is observed in the condensation reaction of haloforms with aryl aldehydes. The displacement of the aldehyde group from the plane of the aromatic ring, accompanied by a disturbance of the conjugation, and consequently by the exclusion of the mesomeric effect of the substituent on the reaction centre, is the reason for the acceleration.

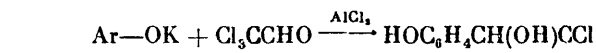
2. Syntheses based on chloral

The method of synthesis of (α-trichloromethyl)carbinols next in significance is based on chloral.

Chloral reacts under conditions of acid–base catalysis with aromatic hydrocarbons with the formation of aryl(trichloromethyl)-carbinols (ATMC) in good yield (70–91%). Both acidic (H_2SO_4, HCl, $AlCl_3$, $AlBr_3$, BF_3, $ZnCl_2$) [52–57] and basic catalysts (potassium hydroxide, pyridine, potassium carbonate) [58–60] are used for the condensation. Until recently it was considered that the method was effective only for benzene and its 1,4-disubstituted derivatives and in the remaining cases (monosubstituted benzenes) a mixture of 2- and 4-isomers is formed. It was shown, however, that this synthetic barrier was readily overcome on using a 10-fold excess of aromatic hydrocarbon relative to chloral.[61]

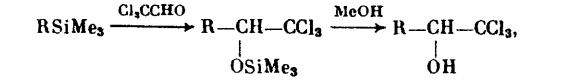


The hydroxybenzaldehydes do not take part in the condensation of haloforms with aryl aldehydes since the hydroxy group is converted into a phenoxide ion under base catalysis conditions, the electronic effect of which reduces significantly the positive charge on the carbon carbon and makes it inactive in relation to TCA. This synthetic gap in obtained 2-, 3-, and 4-hydroxyphenyl(trichloro-methyl)carbinols is eliminated by the reaction of phenoxides of the alkali metals with chloral.[62,63]



Many organometallic compounds also react with chloral with the formation of (α-trichloromethyl)carbinols, however, this method is not used widely due to low yields of the desired carbinols (< 50%) and the poor accessibility of the starting materials.[3,64–66] Furthermore the majority of alkylmagnesium halides react with chloral by an oxidation–reduction reaction forming trichloroethanol and the corresponding olefin (the Grignard reagent is a reducing agent). Exceptions are only the methyl- and benzyl magnesium halides which are not able to undergo such conversions and give adducts in good yield.[67] Vinyl- and substituted vinylmagnesium halides also react satisfactorily with chloral (30% yield) and the vinylcarbinols obtained are readily hydrogenated on palladium–carbon catalyst.[68]

In order to prepare new tranquillisers French scientists[8,9] have effected the synthesis of several(α-trichloromethyl)carbinols by the reaction of silylated hydrocarbons, in which the Si–C bond is activated by vinyl, acetylene and other electron-accepting substituents, with chloral in the presence of Lewis acids.

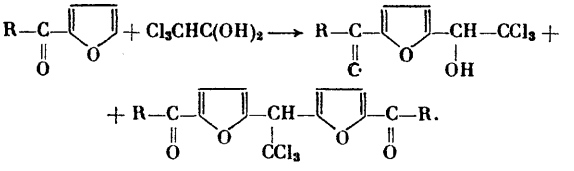


R=BuC≡C, $Me_3SiC{\equiv}C$, $Me_3SiCH_2C{\equiv}C$, PhC≡C, $EtOCOCH_2$, Et_2NCOCH_2,

pyrid-3-ylethynyl, 2-pyridyl, propargyl, allyl, vinyl.

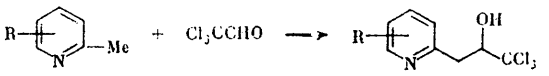
A series of interesting (α-trichloromethyl)carbinols containing α-ester groups has been synthesised by the reaction of chloral with orthoesters in the presence of mineral and Lewis acids.[69]

Studies[70,71] by Spanish scientists merit attention. These are devoted to the synthesis of substituted 2-furyl(trichloromethyl)-carbinols by the reaction of esters and amides of furane-2-carboxylic acid with chloral hydrate. In these studies, carried out for the purpose of obtaining effective pesticides, it was shown that, depending on the temperature and solvent, the reaction may stop at the required ratios of carbinol and the product with the bis structure.



R = NH_2, COOR'.

Chloral readily condenses with CH-acids. The condensation of picolines and lutidines with chloral is important from the applied point of view since the pyridomethyl(trichloromethyl)carbinols display local anaesthetic activity.[72,73]



Seemingly the ease of condensation is explained by the fact that the methyl and methylene substituents at the C(2) and C(4) atoms of the pyridine ring are potential centres for forming carbinols in view of their high CH-activity, which is readily stabilised by delocalisation, particularly if the heteroatom is quaternised. Such an approach is also substantiated by the fact that many authors have effected the condensation of chloral with picolines in the presence of Lewis acids.[74]

III. Conversions of (α-trihalomethyl)carbinols

(α-Trihalomethyl)carbinols are polyfunctional compounds. They react at the hydroxyl and trihalomethyl groups and it is interesting that anything affects one functional group leads to a modification of the other, i.e. there are very few reactions which are selective for one of these groups (exceptions are the partial and complete reduction of the trihalomethyl group and exchange of hydroxyl of halogen and acetoxy groups). Briefly, the numerous studies relate to the two types of conversions of (α-trihalomethyl)carbinols by reaction with basic and acidic reagents or by dehydrohalogenation and dehydration.

1. Reactions with acids

Acid hydrolysis of the isolated trichloromethyl group proceeds with the formation of an intermediate $R\overset{+}{C}Cl_2$ cation which is readily hydrolysed.[75] In sulphuric acid compounds of the type of $RCCl_3$ (R = Alk) at 90–100 °C form the $R\overset{+}{C}Cl_2$ cation,[76] which dissociates according to the scheme.[77]

$$RCCl_3+3H_2SO_4 \rightarrow R-\overset{+}{C}Cl_2+HOSO_2Cl+H_2O^+ +2HSO_4^-.$$

The formation of $R\overset{+}{C}Cl_2$ also occurs as a result of the thermal dissociation of the trichloromethyl group at high temperatures.[78,79]

$$RCCl_3 \rightleftarrows R\overset{+}{C}Cl_2+\overline{Cl}.$$

The hydroxyl group in the α position to the trichloromethyl group in (α-trichloromethyl)carbinols facilitates acidic hydrolysis, however, the reaction goes with complications. Alkyl trichloromethycarbinols form one product and aryl trichloromethylcarbinols form another.

On sulphuric acid hydrolysis of (α-trichloromethyl)carbinols the hydroxyl group is first involved in the reaction,[79,80] and it is possible to form the same $R\overset{+}{C}Cl_2$ cation by fission of hydroxyl and migration of a chlorine atom. Such a route of forming the $R\overset{+}{C}Cl_2$ cation occurs far more easily than through the difficult thermal dissociation of a C–Cl bond of the trichloromethyl group.

The first stage of the reaction of chloretone with 98% sulphuric acid is the protonation of the hydroxyl group with the formation of an oxonium cation, then follows elimination of water, the formation of the carbenium ion $Me_2\overset{+}{C}-CCl_3$, a 1,2-migration of chlorine atom and hydrolysis.[79]

$$Me_2C(OH)CCl_3 + H^+ \longrightarrow Me_2C(\overset{+}{O}H_2)CCl_3 \longrightarrow Me_2\overset{+}{C}CCl_3 \longrightarrow$$

$$\longrightarrow Me_2C\overset{Cl}{\underset{\odot}{\diagup\diagdown}}CCl_2 \longrightarrow Me_2C(Cl)\overset{+}{C}Cl_2 \xrightarrow{HOH}$$

$$\longrightarrow Me_2C(Cl)CCl_2\overset{+}{O}H_2 \longrightarrow Me_2C(Cl)COCl + HCl + H^+$$

With insufficient water the reaction stops at the stage of forming the acid chloride.

It is interesting that aryl[di(tri)chloromethyl]carbinols (ADMC, ATMC) do not give similar products on solvolysis with sulphuric acid.[81] In this case compounds of two types are formed, viz. a product of replacement of the hydroxyl group and a product of elimination of the HOCl fragment.[81]

$$ArCHCCl_2X \xrightarrow{H_2SO_4} ArCH(Cl)CCl_2 + ArCH=CCl_2,$$

$$\begin{matrix} | \\ OH \end{matrix} \qquad\qquad \begin{matrix} | \\ X \end{matrix}$$

X = H, Cl; Ar = *o*-, *p*-ClPh.

The reasons for the toxicity of diphenyldichloromethylmethane (DDD) have appeared in recent investigations and are a drawback for these medicinal preparations which have been approved for the treatment of adrenal neoplasia. It is proposed[81] that the increase toxicity of DDD and its analogues is linked with the formation of side products in their preparation by the condensation of the corresponding ADMC with chlorobenzene catalysed by acids.[82,83]

$$ArCH(OH)CCl_2X + PhCl \xrightarrow{H^+} Ar_2CHCCl_2X,$$

X = H, Cl; Ar = *o*-, *m*-, *p*-Cl, Alk-, AlkOPh.

Non-persistent analogues of DDD and DDT are obtained on an industrial scale by this reaction from readily available carbinols. Nevertheless yields are mainly low at 30–50% [82,83] and this already indicates the presence of side reactions. The products have been identified[81] and are formed by the action of concentrated H_2SO_4 on ADMC, ATMC and phenyltrichloropropanols. In contrast to ADMC and ATMC, 2,2-dichloro-1-(2-chlorophenyl)propanol forms only 1-(2-chlorophenyl)-1-chloropropanone with concentrated H_2SO_4. It is proposed that the reaction proceeds through an intermediate chloronium ion.

$$ArCH(OH)CCl_2Me \xrightarrow[-H_2O]{H^+} Ar-CH\overset{Cl}{\underset{\odot}{\diagup\diagdown}}CClCH_3 \xrightarrow[H^+]{H_2O}$$

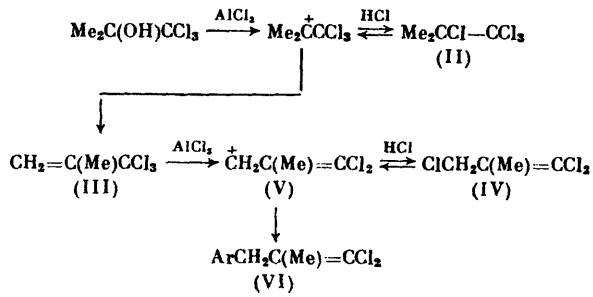
$$\longrightarrow ArCHClC(OH)ClCH_3 \xrightarrow[-HCl]{} \underset{(I)}{ArCHClCOMe}$$

It was shown by ^1H NMR using an acidified sample of carbinol that the quantity of water formed in the first stage of the reaction was sufficient for the transition into ketone (I). In fact the rearrangement occurs far more rapidly, condensations with chlorobenzene do not occur and ketone (I) is formed completely. On the other hand esterification in a sulphuric acid–acetic acid mixture occurs without anomaly with the formation of the acetoxy derivative of the starting carbinol.[81]

The use of Lewis acids for the dehydration of (α-trichloromethyl)-carbinols leads to a complex mixture of trichloroalkanes and tetrachloroalkanes.[84]

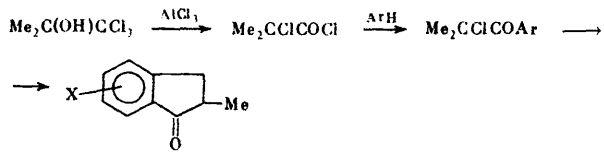
Even in the last century Willgerodt and Genieser[1] reported that on condensing chloretone with benzene, toluene and *o*-xylene in the presence of anhydrous $AlCl_3$ products of the replacement of a chlorine atom and the hydroxyl group were isolated in low yield. Kundiger and collaborators[84] repeated this reaction with toluene, chlorobenzene and anisole. The conclusions of the original authors[1] were not confirmed, alkylation of aromatic compounds by (α-tri-carbinols)carbinols by the direct replacement of chlorine atoms did not occur and neither did replacement of the hydroxyl. It was shown,[84] using chloretone as example, that dehydration occurs initially and the resulting 3,3,3-trichloro-2-methylpropene (III) is isomerised into 1,1,3-trichloro-2-methylpropene (IV). Compound

(IV) alkylates the aromatic nucleus via the allylic chlorine with the formation of 1,1-dichloro-2-methyl-3-arylpropenes (VI).



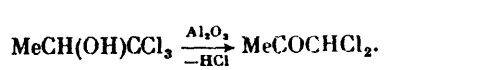
This scheme was confirmed by direct alkylation with individual (II)–(IV). Each of the intermediate products may give a carbonium ion of the type of (V) which forms the above-mentioned products in the course of the reaction.

On using chloretone under the conditions of the Friedel-Craft reaction the acid chloride of α-chloroisobutyric acid is formed together with the 1,1-dichloro-2-methyl-3-arylpropene.[84] If the experiment is carried out with small quantities of $AlCl_3$ it is possible to isolate the acid chloride mentioned above which condenses with aromatic hydrocarbons with an excess of $AlCl_3$ and gives 2-methyl-indanones.[84]



X = H, Cl

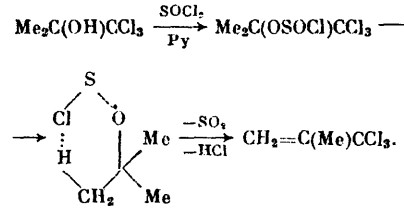
Primary and secondary trichloromethylated alcohols readily form alkoxy chlorides of the $ROAlCl_2$ type with $AlCl_3$,[85] which are comparatively stable. In this case alkylation by these carbinols proceeds not at the carbon linked with the hydroxyl but at the trichloromethyl group.[86] Seemingly the above-mentioned carbinols form mainly dehydrochlorination and not dehydration products under the action of zinc chloride and for the same reason. For example, it was shown[87] that 1,1,1-trichloropropan-2-ol forms 1,1-dichloroacetone on reaction with zinc chloride in hydrochloric acid solution. The same result was obtained on passing the same carbinol over a heated layer of aluminium oxide at 200–250 °C.[87]



Analysis of the available experimental data shows that under the influence of a trichloromethyl group all types of aliphatic α-carbinols should lose the ability to alkylate at a carbon atom linked with a hydroxyl group. Under the condensation conditions trichlorinated alcohols are either dehydrated with the formation of reactive compounds which lead to alkylation,[84] or the reaction proceeds at the expense of chlorine atoms of the trichloromethyl group.[85]

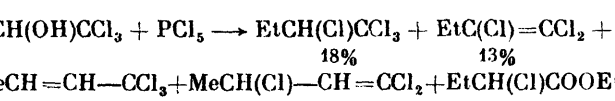
From the preparative point of view the dehydration reactions of (α-trihalomethyl)carbinols are attractive since interesting halogenated alkenes of various structures are generally obtained.

A mixture of thionyl chloride with various amines is used successfully for the dehydration of t-(α-trichloromethyl)carbinols.[88] The success of the dehydration depends critically on the molar ratio of thionyl chloride to amine. It was shown[89] that an increase in the quantity of amine leads to the formation of sulphates and chlorosulphonate esters. When using a catalytic quantity of amine (pyridine, aniline hydrochloride, t-butylamine, di-n-butylamine, *N,N*-dimethylaniline, triethylamine) 3,3,3-trichloro-2-methylpropene was obtained from chloretone in good yield.

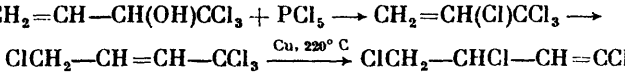


On the other hand the use of a catalytic quantity of tetramethylammonium iodide leads to the allyl isomer due to the catalytic action of the resulting molecular iodine causing isomerisation.[88]

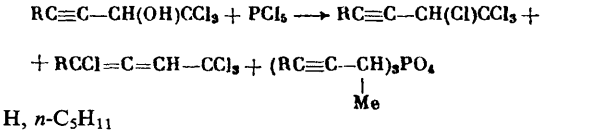
The introduction of a phenyl group into the α-position reduces the possibilities of dehydration. The absence of α-hydrogen atoms in phenyl(trichloromethyl)carbinol leads to the formation of α,β,β,β-tetrachloroethylbenzene (88%).[90] The latter was also obtained in 87% yield on using phosphorus pentachloride as dehydrating agent.[91] Replacement of the benzene ring by an aliphatic group leads to complications. In the case of ethyl-(trichloromethyl)carbinol Reeve[92] isolated the product of replacing the hydroxyl by chlorine in only 18% yield, the product of further dehydrohalogenation, viz. 1,1,2-trichlorobut-1-ene, in 13% yield and a high boiling mixture of phosphate and α-chloro-carboxylic acid ester.



In the case of vinyl(trichloromethyl) carbinol the reaction is accompanied by a double allylic isomerisation.



The products obtained by the reaction of alkynyl(trichloromethyl)carbinols with phosphorus pentachloride indicate the trivial course of the reaction. In this case the authors also identified the crystalline phosphate ester of the initial carbinols.[92]



R = H, n-C_5H_{11}

It is interesting that replacement of the hydroxyl group in phenyl(trichloromethyl)carbinol by chlorine by the action of hydrochloric acid in the presence of 20% (by weight) zinc chloride was unsuccessful, while in phenyl(methyl)carbinol exchange occurs by the action of gaseous hydrogen chloride.[91] Bis(trichloromethyl)carbinol also does not react with hydrochloric acid.[93] This phenomenon may be explained by the presence of the electron-accepting trichloromethyl group, the effect of which on the reaction of the hydroxyl group is extremely significant.

Acid dehydrating agents such as phosphorus pentachloride are used for the dehydration of alkyl(trichloromethyl)carbinols. It was shown[94] that chloretone is dehydrated with difficulty. Mainly, resinification occurs and the dehydration product, 3,3,3-trichloro-2-methylprop-1-ene is obtained in very low yield (8%), the isomeric 1,1,3-trichloro-2-methylprop-2-ene is formed in somewhat larger amounts (15%).

The dehydration of 1,1,1-trichloropropan-2-ol has been studied by many authors. Here the literature data are fairly contradictory. Only in one case do the data agree. Pierce and collaborators[87] and Kirrmann and collaborators[95] assigned the structure of 1,1,2-trichloroprop-1-ene to the dehydration product of 1,1,1-trichloroisopropanol, both studies giving the yield as very small (8–10%). The dehydration products, which distilled over a wide temperature range (11°), were divided into four fractions of which only one was identified as 1,1,2-trichloroprop-1-ene.[87]

$$MeCH(OH)CCl_3 \xrightarrow{P_2O_5} MeCCl{=}CCl_2.$$

While carrying out the dehydration under the same conditions Henne and co-workers[96] reported that mainly 3,3,3-trichloroprop-1-ene was obtained with very little of the isomerised 1,1,3-trichloroprop-1-ene.

$$MeCH(OH)CCl_3 \xrightarrow{P_2O_5} \underset{85\%}{CH_2{=}CH{-}CCl_3} + ClCH_2{-}CH{=}CCl_2.$$

Using the same reaction as an example Kharasch and collaborators[97] considered that they had a 1,1,1-trichloro-containing compound. Fractions were separated during the dehydration which were distillable over a wide temperature range. On a second distillation two products were separated. The first was assigned the structure 3,3,3-trichloroprop-1-ene and the second 1,3-dichloroallene (based on IR spectroscopy).

$$MeCH(OH)CCl_3 \xrightarrow{P_2O_5} CH_2{=}CH{-}CCl_3 + ClCH{=}C{=}CHCl.$$

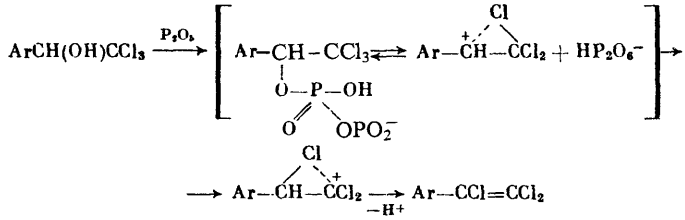
The constants for the first product agree with the data for the product obtained by Henry[98] but do not agree with the constants of Vitoria.[99] The authors[97] explain this by the fact that Vitoria most probably had a mixture of a propene and an allene and not the individual 3,3,3-trichloroprop-1-ene.

When generalising the results of all the studies in which phosphoric anhydride is used as the dehydrating agent in the reaction with alkyl(trichloro)carbinols (chloroetone, isopral), it may be concluded that dehydration occurs in this case by a mechanism leading to a complex mixture of isomeric chloroalkanes and allenes. It is quite probable that some products of the same dehydration process were successfully identified by one author and others by another. The low selectivity of this dehydration process is linked with the stabilisation of the intermediate carbenium ion simultaneously by several sources independently leading to one or other product, fission of the α-proton, shift of a double bond or skeletal rearrangement.

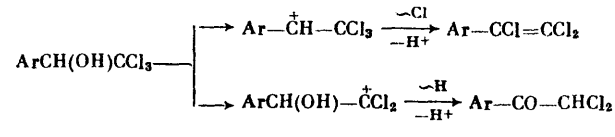
From the point of view of selectivity the considered reactions are only of theoretical interest, including the dehydration of aryltrihalo(chloro, bromo) methylcarbinols which leads to α,β,β-trihalo(chloro, bromo)styene in high yield (61–93%) by dehydration rearrangement with phosphorus pentoxide or oxychloride[10] and also on industrial aluminosilicates.[11]

$$ArCH(OH)CHal_3 \xrightarrow[Hal = Cl,\ Br.]{\text{dehydration}} Ar - CHal = CHal_2,$$

The dehydration of aryl(trihalomethyl)carbinols proceeds highly selectively compared with their aliphatic analogues because in this case the other means of stabilisation of the intermediate carbenium ion, which predominate in the aliphatic analogues, are suppressed. The relative reactivity of ATMC towards phosphorus pentoxide in cyclohexane was determined by the method of competing reactions.[100] The combination of the values for the ratio of the rate constants of substituted and unsubstituted carbinols (k/k_0) and the reaction constant ρ enabled the reaction mechanism to be established.



Industrial aluminosilicate (NBNZ) was also used as a dehydrating agent. Depending on its previous heat treatment this leads the process either towards dehydrochlorination with the formation of dichloromethyl aryl ketones[11] or towards a dehydration isomerisation reaction.



Evidently the previous heat treatment has a strong effect on the acid–base properties of the catalyst surface which also leads to a product of dehydration and dehydrochlorination.

The dehydration isomerisation reaction was used for a comparison of the migration properties of certain functional groups (halogens, alkyls) which form the series Br > Cl ≫ Alk in migrating ability under structurally identical conditions. Various α,β,β-trisubstituted styrenes, which are difficultly accessible by other methods of synthesis, were synthesised by the dehydration isomerisation one-stage method while of solving the theoretical problems.[101]

2. Reduction of the trichloromethyl group

The selectivity of the reduction of the trichloromethyl group in compounds of the $RCCl_3$ type depends on the nature of the initiator of the reduction reaction.

Carbon tetrachloride is selectively reduced by isopropanol to $CHCl_3$ on initiation by various peroxides,[102,103] by complexes of transition metal hydrides[104,105] or iron carbonyl $[Fe(CO)_5]$,[106] and further reduction of the resulting $CHCl_3$ to CH_2Cl_2 does not occur in practice. In the presence of $Mn_2(CO)_{10}$ and $Mo(CO)_6$ reduction occurs selectively with the formation of a mixture of $CHCl_3$ and CH_2Cl_2.

The reduction of the trichloromethyl group in compounds of the DDT type was the subject of several investigations with the aim of discovering new biologically active preparations.

The trichloromethyl group in DDT is exceptionaly inert towards the action of weak reducing agents. It is reduced by zinc in concentrated hydrochloric acid.[107] However it must be noted that the reduction proceeds non-selectively, the trichloromethyl group is reduced both to a dichloromethyl and to a methyl group with the formation of a mixture of 1,1-dichloro-2,2-di-(4-chlorophenyl)ethane, 1,1-di-(4-chlorophenyl)ethane and 4,4′-dichlorostilbene as the side product of the main reaction.

The selectivity of the reduction is significantly greater for the precursors of DDT, the (α-trichloromethyl)carbinols, however it also depends strongly on the character of the reduction initiator used and the substituent in the aromatic ring. Under the action of aluminium amalgam in alcohols, ATMC form the corresponding (dichloromethyl)carbinols in preparative yield.[108,109] Metallic aluminium (modified Meerwein-Pondorf method),[110,111] complexes of polystyrene with Ru, Rh and Ir containing organophosphorus ligands[112] and $Fe(CO)_5$ [106] in isopropyl alcohol have also been successfully applied for the same purpose.

$$ArCH(OH)CCl_3 \xrightarrow[iso-PrOH]{\text{reduction}} ArCH(OH)CHCl_2.$$

When reducing ATMC with zinc dust in acids or with lithium in liquid ammonia the selectivity of the process falls sharply.[113] The reduction of phenyl(trichloromethyl)carbinol with zinc dust in neutral or acid medium leads to a mixture of β,β-dichlorostyrene and β-chlorostyrene and in acetic acid to the methyl ether of phenyl(dichloromethyl)carbinol. Lithium in liquid ammonia gives α-phenylethanol in low yield and acetophenone and 2-phenylethan-1-ol as byproducts.

$$PhCH(OH)CCl_3 \begin{cases} \xrightarrow{Zn/H^+} PhCH{=}CCl_2 + PhCH{=}CHCl \\ \xrightarrow{Zn/AcOH} PhCH(OH)Me + CHCl_2 \\ \xrightarrow{Li/NH_3} PhCH(OH)Me + PhCOMe + PhCH_2CH_2OH \end{cases}$$

The introduction of a methoxy group into the 4-position of the aromatic nucleus in phenyl(trichloromethyl)carbinol increases the lability of the hydroxyl hydrogen. Reduction of the carbinol in isopropyl alcohol in the presence of $Fe(CO)_5$, $Mo(CO)_6$ or $Mn_2(CO)_{10}$ leads to a mixture of 4-methoxyphenyl(dichloromethyl)carbinol and 4-methoxyphenylisopropoxycarbinol in a ratio dependent on the nature of the carbinol and metal.[106] β,β-Dichlorostyrene is obtained as the main reaction on electrochemical reduction of the same carbinol.[114]

$$4\text{-}MeOC_6H_4CH(OH)CCl_3 \rightarrow 4\text{-}MeOC_6H_4CH{=}CCl_2.$$

There is even less selectivity on reducing the trichloromethyl group in alkyl(trichloromethyl)carbinols and in trichloromethylethanol. According to the data of Favorskii[115] a mixture of 1,1-dichloro-2-methylprop-1-ene and 1-chloro-2-methylprop-1-ene and isobutene, which are products of further reduction, is obtained from chloretone by reduction with zinc dust in ethanol.

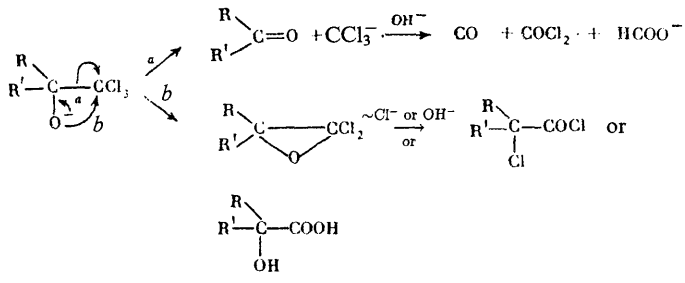
A dichlorocarbinol is obtained in 32% overall yield by the reduction of trichloroethanol in isopropyl alcohol in the presence of $RuCl_2(PPh_3)_3$.[116] The same dichloromethylcarbinol was obtained as a byproduct by electrochemical reduction when the main product was dichloroethylene.[117]

$$HOCH_2CCl_3 \longrightarrow CH_2{=}CCl_2 + \underset{\text{(byproduct)}}{HOCH_2CHCl_2}.$$

3. Reactions with bases

The isolated trichloromethyl group is inert to the action of nucleophilic reagents in general and of OH^- ions in particular.[118] The first studies devoted to the reaction of (α-trichloromethyl)carbinols with bases were carried out using as example dimethyl(trichloromethyl)carbinol (chloretone), however it turned out that in the course of the reaction chloretone is subject to alkaline decomposition with the formation of acetone, chloroform, carbon monoxide, phosgene and formic acid,[119] i.e. a reaction is observed which is the reverse of the chloretone synthesis with subsequent alkaline hydrolysis of chloroform. A similar decomposition was even observed by Iotsich in the reaction of phenyl(trichloromethyl)-carbinol with aqueous KOH.[2] In parallel, Willgerodt and collaborators[120] successfully isolated a small quantity of α-hydroxy-, and Ostropyatov[121] α-chloroisobutyric and methacrylic acids from the products of the reaction of chloretone with aqueous KOH. Seemingly both the decomposition and the formation of the acids mentioned proceeds through the same alkoxide ion of the (α-trichloromethyl)carbinol (Scheme 2).

Scheme 2



In numerous studies devoted to this reaction the molar ratios of carbinols and bases were selected which provide the maximum yields of α-chloro- and α-hydroxyacids, i.e. experimental conditions directed to the suppression of route *a*. This is successfully carried out at the expense of hydrolysis of the carbinols in aqueous dioxan in the presence of ion exchange resin[122] or by replacement of the aqueous by alcohol alkali, the use of which leads to α-alkoxyacids in preparative yields. The observed phenomenon is seemingly linked with the basicity of the RO^- formed from the initial carbinol, which further attacks selectively the electrophilic centre in the trichloromethyl group to a greater extent than is regulated by haloform decomposition.

It was shown that chloretone forms α-ethoxyisobutyric acid in 72% yield on reaction with three equivalents of sodium ethoxide in ethanol.[123] The mechanism by which this conversion occurs passes, "indisputably" according to Jacob,[124] through the intermediate dichloroepoxide which then undergoes alcoholysis. The author arrived at this conclusion from the reaction of chloretone with dimethylaniline and comparison of these results with data on the alcoholysis of the epoxide ring.[125]

$$Me_2C(OH)CCl_3 \xrightarrow[EtOH]{EtONa} Me_2C(O)CCl_2 \xrightarrow[EtOH]{EtONa} Me_2C(OEt)COOEt$$

The formation of α-alkoxyacids may be considered probable from the intermediate acid chloride of the α-chloroacid, the rearrangement product of the dichloroepoxide. However the high yields of the final products make this alternative variant less probable. The absence of the formation of unsaturated acid and of chlorine-containing products excludes the rearrangement of the dichloroepoxide before its alcoholysis.

α-Butoxyisobutyric acid is isolated on reaction with 4 M KOH in alcoholic medium or with potassium butoxide in butanol at 0 °C.[126]

$$Me_2C(OH)CCl_3 + KOH \longrightarrow Me_2C(O)CCl_2 + KCl + H_2O,$$

$$Me_2C(O)CCl_2 + 2KOH \longrightarrow Me_2C(O)C{=}O + 2KCl + H_2O,$$

$$Me_2C(O)C{=}O + ROH \longrightarrow Me_2C(OR)COOH.$$

At the same time the preparation of an alkoxyacid ester may take place without the participation of an α-lactone.

$$Me_2C(O)CCl_2 + ROH + 2KOH \longrightarrow Me_2C(OH)(OR)C(O) + KCl + H_2O,$$

$$Me_2C(OH)(OR)C(O) + ROH \longrightarrow Me_2C(OR)COOR + H_2O.$$

Reeve and collaborators,[127] while studying the reaction of ATMC with bases as though resuming their investigations on the study of the mechanism of the conversion in question, published stereochemical data on the reaction of (*S*)-(+)- and (*R*)-(−)-phenyl(trichloromethyl)carbinols with MeONa/MeOH at 40 °C leading to (*S*)-(+)- and (*R*)-(−)-α-methoxyphenylacetic acids respectively. It was shown that the conversion proceeds with 9% inversion of configuration and 91% racemisation of the initial carbinol. The mechanism considered does not differ appreciably from the mechanisms discussed by Bergman and Jacob. According to Reeve's mechanism HCl is eliminated from the initial carbinol by the action of methoxide ion with the formation of the dichloroepoxide, which then is subjected to methanolysis and hydrolysis with the formation of α-methoxyphenylacetic acids. The inversion of configuration occurs during methanolysis of the dichloroepoxide.

$$PhCH(OH)CCl_3 \xrightarrow[-HCl]{} PhCH(O)CCl_2 \xrightarrow{MeO^-} PhCH(OMe)COCl \xrightarrow{hydrolysis} PhCH(OMe)COOH$$

According to an alternative mechanism the dichloroepoxide is rearranged with migration of a chlorine atom to the acid chloride of α-chlorophenylacetic acid with inversion of configuration due to attack by the migrating chlorine atom at the α-carbon atom from the side opposite the epoxide oxygen. After hydrolysis of the acid chloride, replacement of chlorine by a methoxy group occurs.

$$PhCH(O)CCl_2 \xrightarrow{-Cl} PhCH(Cl)COCl \xrightarrow{hydrolysis} PhCH(Cl)COO^- \xrightarrow{MeO^-}$$

(inversion of configuration)

$$\longrightarrow PhCH(OMe)COO^- \xrightarrow{H^+} PhCH(OMe)COOH$$

It was shown experimentally[127] that under the reaction conditions the (*R*)-(−)-acid chloride of α-chlorophenylacetic acid is 96% racemised by the action of methoxide ion and the racemisation of the (*R*)-(−) configuration occurs more rapidly than that of the (*S*)-(+).

It is proposed that methanolysis leading to the α-methoxy ester also occurs through the intermediate gem-dichloroepoxide.[128]

The deacetoxychlorination of chloretone acetate leading to α-ethoxyisobutyric acid ethyl ester in 55% yield has been carried out[129] by boiling with an ethanolic solution of sodium ethoxide. The authors postulate the formation of this ester through the same intemediate dichloroepoxide.

α-Alkoxyarylacetic acids, obtained by the reaction of ATMC with alcoholic bases, have a high practical value (in analytical chemistry, agriculture).[130–134] Proceeding from this, a broad investigation was undertaken to optimise the synthesis of these acids.[130,135] The synthesis of aryl[trichloro(bromo)methyl]carbinols, their subsequent dehydrohalogenation and alcoholysis of the intermediate dihaloepoxide have been successfully combined in one stage.

$$ArCHO + CHHal_3 \xrightarrow[MeOH]{KOH} [ArCH(OH)CHal_3] \xrightarrow{KOH} ArCH(O)CHal_2 \xrightarrow{MeO^-}$$

(without isolation)

$$\longrightarrow ArCH(OMe)COHal \longrightarrow ArCH(OMe)COOMe,$$

Hal = Cl, Br.

It is interesting that the synthesis of phenyl(tribromomethyl)carbinol from an aldehyde and bromoform occurs with difficulty and in low yield (10–40%) but under the conditions of the reaction being considered (without isolation of the carbinol) the yield of the final α-methoxyarylacetic acids was 75% of theoretical. The condensation of 3-chlorobenzaldehyde with chloroform also proceeds with difficulty and the yield of the desired 3-chlorophenyl(trichloromethyl)carbinol was 12% overall.[15] Under the conditions of the given reaction α-methoxy-(3-chlorophenyl)acetic acid was isolated in 70% yield.

Replacement of methanol by liquid ammonia in the system aldehyde–haloform–potassium hydroxide–methanol leads to the formation of α-amino acids in low yield (29–48%) as a result of fission of the epoxide ring by amide ion.[14]

$$RCHO + CHCl_3 \xrightarrow[-33^\circ C]{KOH,\ NH_3} RCH(OH)CCl_2 \xrightarrow[-HCl]{} RCH(O)CCl_2 \xrightarrow{NH_3}$$

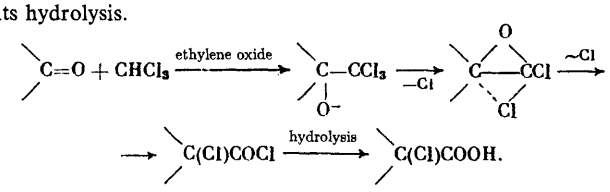
(isolation not obligatory)

$$\longrightarrow RCH(NH_2)COOH.$$

Although this method contradicts somewhat the synthesis of (α-trichloromethyl)carbinols under the same conditions,[20] it has been confirmed by recent work by Chinese authors,[136] in which a similar synthesis of amino acids was effected by the condensation of aliphatic aldehydes, ketones and cyclic ketones with chloroform and ammonia by phase transfer catalysis (dichloromethane–water, the catalyst was diethylbenzylamine ethochloride).

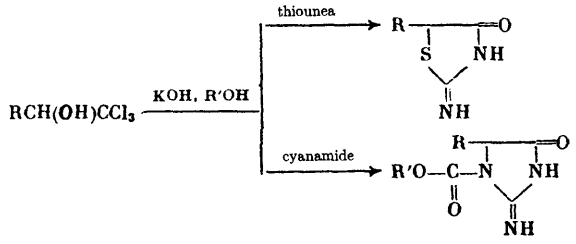
It should be mentioned that an analogous single-reactor method was used for the first time by Link.[137]

By a method similar to that of Link and Reeve, Buddrus and collaborators[138,139] carried out the condensation of isobutyraldehyde, acetone and cyclohexanone with chloroform taking ethylene oxide as base. The corresponding α-chlorocarboxylic acids were isolated in this case and are products of the rearrangement of the intermediate dichloroepoxide into the acid chloride of the α-chlorocarboxylic acid and its hydrolysis.

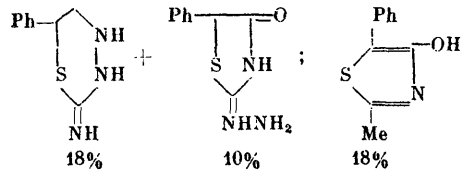


The high preparative value of α-haloacids and their acid chlorides in synthetic organic chemistry, particularly as synthons of α-amino acids and other functionalised α-carboxylic acids, was the reason for the in-depth study of the dehydrochlorination of (α-trihalomethyl)-carbinols. As was mentioned above the haloform fission of (α-trihalomethyl)carbinols (Scheme 2, route *a*) is the main obstacle to the dehydrochlorination process. It was established that the process depends strongly on temperature, reaction time and also on the alkali used.[140] Optimum conditions for obtaining α-chloroaryl-acetic acids were 0 °C, 10% aqueous KOH (10% aqueous NaOH forms a gel and the yield of product is reduced), the carbinol:KOH = 1:4 (yield 60–70%) and the reaction time was several days. The use of (tribromomethyl)- or mixed (chloro, bromo)carbinols leads to a significant reduction in the quantity of alkali, in the reaction time and to an increase in the yield of the desired α-haloacetic acids (17–100%).[141] Since the limiting stage of the process is the formation of the gem-dihaloepoxide, it is evident that the replacement of chlorine by bromine facilitates the intramolecular S_N2' substitution of halogen in the trihalomethyl grouping (Scheme 2, route *b*) with the formation of the epoxide ring and also rearrangement into α-haloacetic acids.

The single reactor method of Link and Reeve has limited application since the majority of the nucleophiles enter into direct condensation with carbonyl compounds with an incommensurably higher rate than does THA. For this reason the reaction of certain nucleophiles was studied directly on (α-trichloromethyl)carbinols. Cyanamide and thiourea[142–144] were tested with ATMC in various alcohols (methanol, ethanol, ethyleneglycol) and cycloadducts were isolated, viz. functionally substituted 1-imidazolinecarboxy imidates and thiazolidinones in low yields.

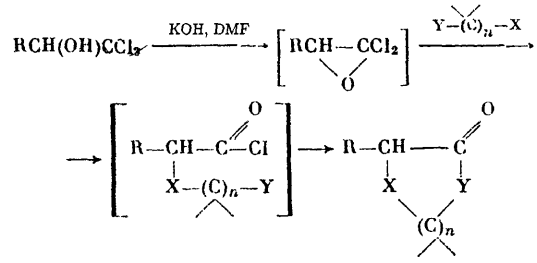


R was varied in (α-trichloromethyl)carbinols (alkyl, aryl, vinyl, ethinyl), but the yield of cycloadduct was not increased successfully. Replacement of nucleophiles (thiosemicarbazide, thioacetamide) also did not lead to the expected result. A mixture of dihydro-2-imino-6-phenyl-2H-1,3,4-thiadiazin-5-(6H)-one and 5-phenyl-2,4-thiazoldinedione-2-hydrazone in yields of 18 and 10% respectively was isolated from phenyl(trichloromethyl)carbinol by reaction with thiosemicarbazide. With thioacetamide by 4-hydroxy-2-methyl-5-phenylthiazole was isolated in 18% yield.[145]



The yield of cycloadduct was sharply increased on replacing a protic solvent by the dipolar aprotic solvent DMF. 2,5-Disubstituted thiazolidin-4-ones (a) were isolated from ATMC by reaction with thioacet(benz)amides in 40–85% yield,[146] tetrahydro-2-hydroxy-3-aryl-1,4H-quinoxalines (b) in 70–80% yield with *o*-phenylenediamine, 2-hydroxy-3-arylpiperazines (c) in 57–60% yield with ethylenediamine, 2-hydroxy-3-aryl-1,4-benzodioxans (d) in 63–84% yield from pyrocatechol and 2-aryl-3-hydroxy3,4-dihydro-2H-1,4-benzoxazines (e) from 2-aminophenol in 70–85% yield (Scheme 3).[147]

Scheme 3



R = Ar, Het;
X = S, Y = N, n = 1(a), X = Y = N, n = 2(b); X = Y = N, n = 2(c); X = Y = O, n = 2(d); X = P, Y = N, n = 2(e).

Since all the addition reactions considered above proceed through the intermediate gem-dihaloepoxide, the favourable influence of the dipolar solvent DMF on the dehydrochlorination of (α-trichloro-methyl)carbinols[146,147] is explained by the fact that the oxygen atom in DMF, being a centre of increased electron density, strongly coordinates potassium ions but the less effective positive portion weakly solvates the alkoxide ion. The weakly solvated anion possesses greater energy consequently the energy of activation of the intramolecular epoxidation is appreciably reduced in comparison with the use of protonated solvents.

The available literature data obtained by spectral methods in combination with quantum chemical calculations of the distribution of electron density in epoxides show that the epoxide carbon atoms, independent of the nature of the substituent, are extremely electron deficient. The value of the electron density on these atoms differs little.[148] This explains why the nucleophilic fission reaction of

epoxides occurs at both the α- and at the β-carbon atoms. However analysis of the total literature data on the fission of gem-dichloroepoxides by mono- and dinucleophiles shows that only the α-carbon atom is subject to nucleophilic attack. The reason for the observed regioselective fission of the ring may be attributed to shielding of the β-carbon atom by the bulky chlorine atoms. However the data on the X-ray structural analysis of the only stable gem-dichloroepoxide, 1,1,3,3,3-pentachloropropylenepoxide† gave a complete answer. According to X-ray structural analytical data the unfavourable conditions for the approach of a nucleophile to the β-carbon atom created both by the steric screening of the chlorine atoms, and by the strengthening of the C–O bond with the participation of the β-carbon atom which creates additional blocking from the side of the "adjacent" oxygen atom. On the other hand the O(1)–C(3) bond involving the α-carbon atom is longer than the O(1)–C(2) bond and is therefore weaker to a considerable extent (Fig. 1).[150]

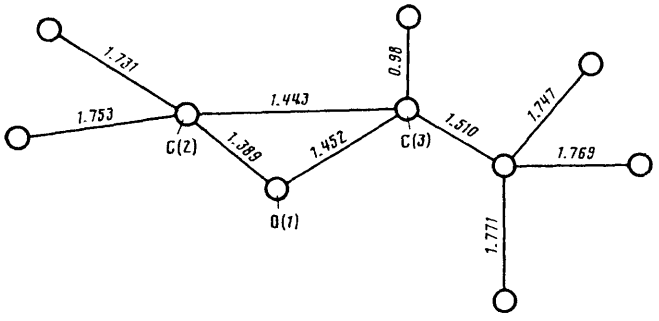


Figure 1. The structure of the 1,1,3,3,3-pentachloropropylene oxide molecule; σ = 0.003–0.004 Å.[150]

The reaction of aromatic and heterocyclic (α-trichloromethyl)-carbinols with mono-*C*-nucleophiles, viz. malonic, acetoacetic[151] and cyanoacetic[152] esters, has been studied with a view to clarifying the synthetic possibilities of gem-dichloroepoxides. It was established that adducts of vicinal structure are formed by the reaction and are the diethyl esters of substituted adipic acids which thermally, catalytically or spontaneously cyclise into substituted hetero- and carbocyclic ketones (Scheme 4).

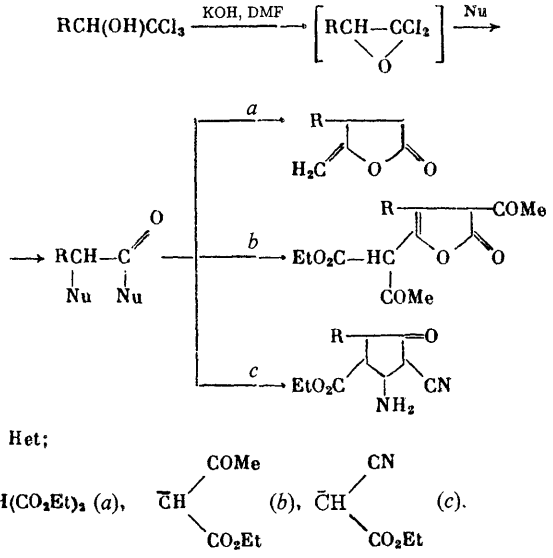
† 1,1,3,3-Pentachloropropylene oxide is the sole stable representative of the gem-dichloroepoxides. It is obtained by the reaction of bis-trichloromethylcarbinol with 2 N NaOH at 20 °C.[93]

$$Cl_3C{-}CH(OH){-}CCl_3 \xrightarrow{NaOH} Cl_3CCH{-}CCl_2$$

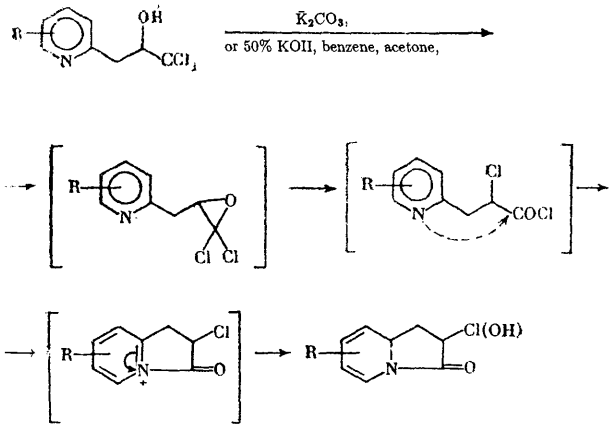
It is appropriate to mention that this dichloroepoxide was also obtained by Seyferth and collaborators[149] by the reaction of the carbenoid $PhHgCCl_3$ with chloral in boiling benzene and the physicochemical constants given agree exactly[93] although the author describes this compound as being synthesised for the first time.

In the studies considered the direction of the reaction of (α-trichloromethyl)carbinols of the aromatic and heterocyclic series with mono-*C*- and 1,3,1,4-dinucleophiles is the same and the difference consists only in the yield of the cycloadduct.

Scheme 4



It is interesting that the 2-pyridomethyl(trichloromethyl)carbinols are converted by base phase transfer catalysis (PTC) in the absence of external nucleophiles into [2,3H]-indolizines as a result of a rearrangement–heterocyclisation of the gem-dichloroepoxides generated as intermediates.



Depending on the type of PTC (liquid–solid, liquid–liquid) the product of heterocyclisation, the [2,3H]-indolizine, has either an α-chloro- or an α-hydroxyketone grouping. Since the indolizine structure forms part of the composition of the veratrum alkaloids, which are obtained by the multistage syntheses of Barret, Chichibabin and Shol'ts, the observed conversion acquires value in applied chemistry.[153]

In general the chemistry of [α-trihalo(chloro, bromo)-methyl]-carbinols is at the stage of promising development. The universal nature of these compounds for the solution of a whole series of problems of theoretical and practical chemistry has been demonstrated. The facile generation from them of highly reactive, little-studied gem-dihaloepoxides, which are synthons for a whole range of compounds with various properties, is just one factor indicating that the development of this field extends knowledge and creates new areas for using (α-trihalomethyl)carbinols.

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