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β-Ketovinylation

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The review deals with the methods of introduction into the molecule of the group RCOCR′=CR″, which has come to be called the β-ketovinylation reaction. It has been shown that the principal starting materials for these reactions are certain β-substituted vinyl ketones, which have surpassed all other activated ethylene compounds in their importance for synthetic organic chemistry. A systematic description of literature data has been given in accordance with methods for *C*-, *N*-, *O*-, *S*-, *P*-, *Hal*-, *Fe*-, and *Co*-ketovinylation. This made it possible to make generalisations and recommendations concerning the choice of the ketovinylating agent in particular cases. The possible mechanism of β-ketovinylation is discussed, particular attention being devoted to kinetic and stereochemical data. The bibliography comprises 300 references.

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I. INTRODUCTION

Cyanoethylation, the Michael condensation, and other reactions based on the capacity of the activated double bond to combine with nucleophilic reagents have played a considerable role in the development of synthetic organic chemistry. Among these reaction types, one of the most important is the β-ketovinylation reactions, despite the fact that the method hardly began to be developed until the 1950's. It is noteworthy that the main advances in this field have been achieved by Soviet chemists.

Ketovinylation reactions involve the introduction of a preformed RCOCR′=CR″ group into the molecule[1]. These reactions have led to a new synthesis of αβ-unsaturated ketones, and a very wide variety of β-substituted vinyl ketones, in which the RCOCR′=CR″ group is linked with the atoms of various elements, have become available. Among the compounds obtained particular mention should be made of the σ complexes of the RCOCR′=CR″ group with the atoms of transition metals such as iron and cobalt. The availability of these derivatives extends the possibilities of the synthesis of organometallic compounds, since the RCOCR′=CR″ fragment is bifunctional. The high activity of the carbonyl group in β-substituted vinyl ketones had led in turn to the development of methods for the preparation of many heterocycles. The extensive studies of the properties of β-substituted vinyl ketones have shown that these compounds are not only of interest in connection with synthesis but can serve as convenient models for the elucidation of certain theoretical questions associated with the mechanisms of nucleophilic substitution and addition to an activated double bond.

The RCOCR′=CR″ group may be introduced into the molecule in two ways. 1. By nucleophilic substitution of X in compounds of the type RCOCR′=CR″X:

$$RCOCR'=CR''X + Y^- \rightarrow RCOCR'=CR''Y + X^-,$$

where X = Hal, OR, OH, NR_2, $\overset{+}{N}R_3$, etc. 2. By the addition of nucleophilic agents to the triple bond of ethynyl ketones

$$RCOC{\equiv}CR' + Y^- \xrightarrow{H^+} RCOCH{=}CR'Y .$$

The first method is used more often, and its development has been particularly intense after general methods for the synthesis of β-chlorovinyl ketones have become available[2-4].

Despite the large number of studies on the chemistry of β-substituted vinyl ketones, a systematic account of β-ketovinylation methods has not been published so far. There are several reviews in the literature dealing with syntheses on the basis of β-chlorovinyl ketones[1,5-8] or their derivatives—β-ketoacetals[9]. In 1961 Kochetkov and coworkers published a review on the *C*-ketovinylation of β-dicarbonyl compounds[10]. In the present review the authors attempted to give a systematic account for the first time of other methods of β-ketovinylation, including *C*-, *N*-, *O*-, *S*-, *P*-, *Hal*-, *Fe*, and *Co*-ketovinylation. Examination of the literature data in this context permits certain generalisations and recommendations for the choice of the method of synthesis of αβ-unsaturated ketones in particular cases. The review includes literature data up to 1st January 1968.

II. METHODS OF β-KETOVINYLATION

1. *C*-Ketovinylation

Among other β-ketovinylation reactions, the methods for the formation of a carbon–ketovinyl bond (*C*-ketovinylation) occupy one of the most important places. The development of these methods not only led to the ready availability of all possible αβ-unsaturated aliphatic, aromatic, and heterocyclic ketones, but has also permitted the synthesis of certain cyclic compounds and also stable organic anions and polymers with a conjugated system of double bonds.

It would appear that carbanions should undergo ketovinylation most readily. However, with powerful nucleophilic reagents such as the carbanions of the organometallic compounds of Group I elements and magnesium, complications arise due to the additional possibility of reaction at the carbonyl group. It is noteworthy that numerous investigations of the reactions of αβ-unsaturated ketones with these nucleophilic reagents have not so far provided a definite answer to the question why 1,2- and 1,4-addition takes place. However, with β-substituted vinyl ketones it is possible to follow the effect of the nature of the β-substituent on the mode of attack on the carbanions. It has been found that β-chlorovinyl ketones cannot be used for the ketovinylation of aliphatic and aromatic carbanions. In this case the carbonyl group is mainly attacked and the reaction yields carbinols. It is noteworthy that the rearrangement of such carbinols in an acid medium is used for the preparation of αβ-unsaturated aldehydes of type (I)[11-16]:

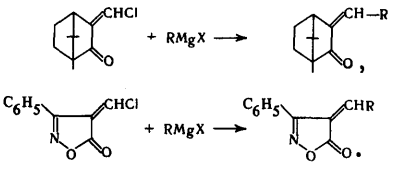
$$RCOCH{=}CHCl + R'M \rightarrow \overline{O}{-}CRR'{-}CH{=}CHCl \xrightarrow{H_3O^+} \underset{(I)}{RR'C{-}CH{=}CH{-}O} .$$

β-Chloroacrolein[17] and its polyhalogeno-derivatives[18-20] react similarly and this was used by Skoldinov et al.[17] in the synthesis of the *cis*- and *trans*-isomers of β-chlorovinyl methyl ketone (see p. 450).

However, in reactions with organometallic compounds having a less polarised metal–carbon bond, such as cadmium derivatives, the successful use of β-chlorovinyl ketones is also possible[21,22]:

$$RCOCH{=}CHCl + \overset{\delta-}{R'}{-}\overset{\delta+}{Cd}{-}R' \rightarrow R{-}\underset{\underset{O}{|}}{C}{-}CH{=}CHR' .$$

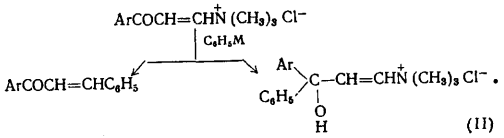
Furthermore, normal ketovinylation of RLi and RMgX by β-chlorovinyl ketones is possible in those cases where the approach to the carbonyl group is sterically hindered (for example, when the carbonyl group is in a ring)[22-25]:



The replacement of the chlorine atom in substituted β-chlorovinyl ketones by a phenoxy-group favours the formation of ketovinylation products and their derivatives, but the yields are only 20–40%:[26]

$$CH_3COCH{=}CHOC_6H_5 \xrightarrow{CH_3MgBr} [CH_3COCH{=}CHCH_3] \xrightarrow{CH_3MgBr} \rightarrow CH_3{-}\underset{\underset{OH}{|}}{\overset{\overset{CH_3}{|}}{C}}{-}CH{=}CH{-}CH_3 \rightarrow CH_2{=}\underset{\underset{CH_3}{|}}{C}{-}CH{=}CH{-}CH_3 .$$

Vinyl ketones containing a powerful electron-acceptor group such as the quaternary ammonium group in the β-position relative to the carbonyl group react with C_6H_5Li to form a mixture of *C*-ketovinylation and 1,2-addition [compounds (II)] products in almost equal amounts†. When C_6H_5MgBr is used, the yield of *C*-ketovinylation products is much higher:[27]



(II)

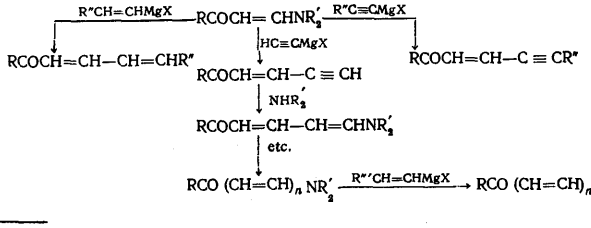
Thus, despite the pronounced electron-acceptor properties of the quaternary ammonium group, which should apparently intensify the electrophilicity of the carbonyl carbon atom, *C*-ketovinylation products are formed in appreciable amounts. This is probably because the $\overset{+}{N}(CH_3)_3$ group attracts electrons by an inductive effect, so that the positive charge appears also at the carbon atoms of the double bonds. In this connection it is interesting to note that the sulphonyl group, which exhibits a powerful I-effect, is also substituted on interaction of organomagnesium compounds with phenyl β-phenylsulphonylvinyl ketone[29]:

$$C_6H_5COCH{=}CHSO_2C_6H_5 + C_6H_5MgX \rightarrow C_6H_5COCH{=}CHC_6H_5 .$$

On the other hand, in most cases β-dialkylaminovinyl ketones[30,31], which are less reactive than β-chlorovinyl ketones, are convenient reagents for the ketovinylation of RLi, RNa, and RMgX:

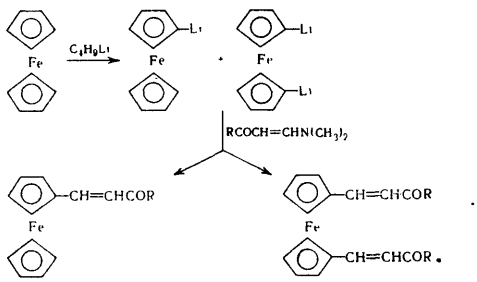
$$RCOCH{=}CHN(CH_3)_2 + R'Li \rightarrow RCOCH{=}CHR' .$$

This was shown experimentally by Benary for the first time[30] and later Normant and coworkers[31] developed an elegant method for the synthesis of conjugated keto-polyenes and keto-enynes:

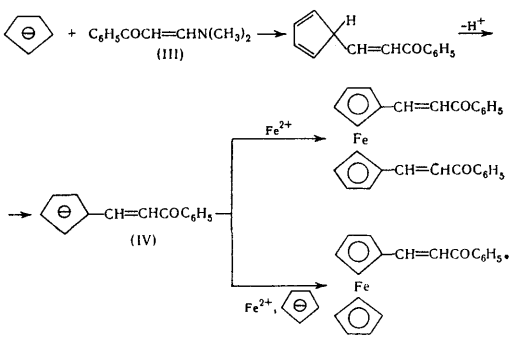


† It has been found[28] that the salts (II) may be used to synthesise the hitherto unknown quaternary ammonium salts containing the indenyl group.

Nesmeyanov and coworkers[32] used this method for the preparation of mono- and di-ketovinylated ferrocenes by the following procedure:



The same compounds were obtained[33] by the ketovinylation of the cyclopentadienide ion with β-dimethylaminovinyl phenyl ketone (III) followed by treatment of the reaction mixture with anhydrous iron(II) chloride:

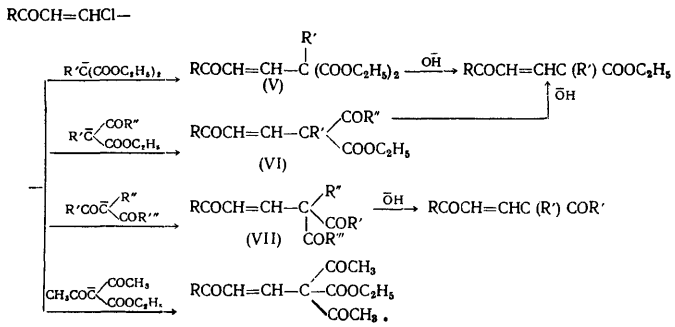


The yield of the ion(IV), which amounted to about 40 mole %, may be estimated from the amounts of mono- and di-ketovinylated ferrocenes produced. Thus the ketovinylation method developed may be used for the synthesis of αβ-unsaturated ketones of the ferrocene series.

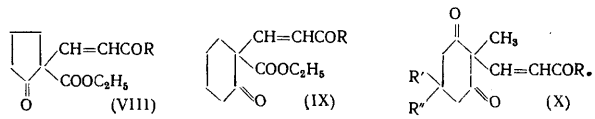
Ketovinylation reactions have assumed particular importance in the synthesis of heteroannular dicarbonylvinyl derivatives of ferrocenes. The very possibility of synthesising such derivatives was discovered solely owing to the development of these methods.

It is interesting to note that β-chlorovinyl ketones can also be used in the reaction with the cyclopentadienide ion‡, but in this case the process does not stop at the first stage and polyketovinylation products are formed[34].

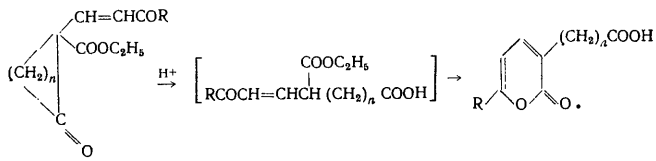
The ketovinylation of carbon-containing ambident anions takes place very readily. Such ions include in the first place the anions of β-dicarbonyl compounds, ketones, nitro-compounds, etc. The reactions with β-dicarbonyl compounds (β-diketones, β-keto-esters, malonic ester, and their derivatives) have been investigated in detail by Kochetkov and coworkers[10]. β-Chlorovinyl ketones were used as ketovinylating agents. It was found that β-dicarbonyl compounds are normally ketovinylated only when they contain one labile hydrogen atom[35-39]:



Methods for the synthesis of unsaturated keto-acids and diketones have been developed on the basis of these reactions. For example, under the action of bases, compounds of type (V) eliminate the ethoxycarbonyl group and are converted into δ-keto-βγ-unsaturated acids[40] and compounds of type (VI) readily undergo the ketonic decomposition[41]. The same reactions were observed with the triketones (VII).[37] Cyclic β-keto-acids[42] and β-diketones[37,43] are of course ketovinylated without complications, compounds of types (VIII)-(X) being formed:



It is noteworthy that the rearrangement of compounds (VIII) and (IX) and analogous compounds under the action of acids has been proposed as a method for the synthesis of α-pyrones[44,45]:

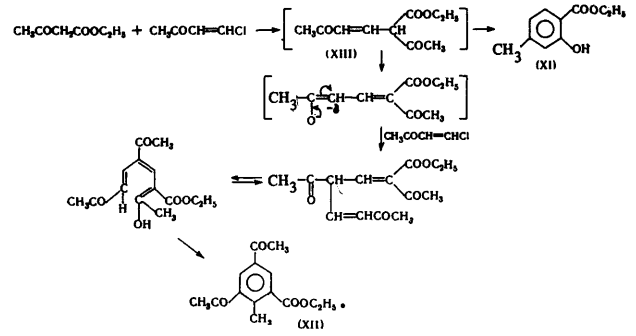


It has been found that the yields of ketovinylation products vary appreciably depending on the nature of the β-dicarbonylcompound: esters of alkylmalonic and α-substituted acetoacetic acids reacts with higher yields than β-diketones, while the diacetylacetic ester does not react at all[10]. Probably the decrease of the yields of ketovinylation products in this series may be attributed to the increase of the stability and hence the decrease of the nucleophilicity of the attacking mesomeric anions formed from the corresponding carbonyl compounds.

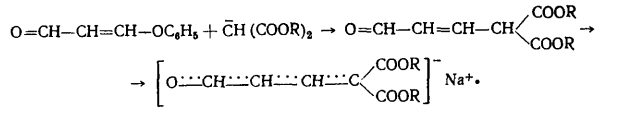
In contrast to the single-proton β-dicarbonyl compounds, the two-proton (with two labile hydrogen atoms) malonic and acetoacetic esters react with β-chlorovinyl ketones under analogous conditions to form a complex mixture of products. For example, when β-chlorovinyl methyl ketone reacts with acetoacetic ester in the presence of potassium carbonate, two compounds are formed: ethyl 4-methylsalicylate (XI) and the ester of 3,5-diacetyl-2-methylbenzoic acid (XII).[46,47] The amounts of the two products, (XI) and (XII), in the mixture depend on the ratio of the starting

‡ In contrast to aliphatic and aromatic ions, the cyclopentadienide ion is not a very powerful base, becoming readily polarised, and therefore it reacts with β-chlorovinyl ketones via the β-carbon atom of the ethylene bond (see page 446).

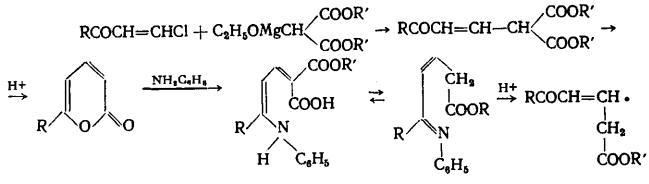
materials. The formation of compounds (XI) and (XII) may be accounted for by the following mechanism:



Under the reaction conditions the mono-ketovinylation product (XIII) undergoes further cyclisation to compound (XI). However, since the intermediate (XIII) is a stronger acid than the initial acetoacetic ester, it readily produces an anion which is capable of being ketovinylated. In turn compound (XII) is formed as a result of the cyclisation of the ketovinylation product. It is interesting to note[48] that, when hydroxymethylene ketones, the double bond of which is less electrophilic than in β-chlorovinyl ketones, are employed in this reaction, the process stops at the mono-ketovinylation stage[48] and only 4-methylsalicylic acid (XI) was isolated. Of course, the capacity for subsequent ketovinylation depends not only on the electrophilicity of the β-carbon atom of the ketovinylating agent but also on the stability of the anion formed as the result of mono-ketovinylation. Thus, in the interaction of sodiomalonic ester with β-phenoxyacrolein[49], the product is the stable anion of an acid with a strength approximately equal to that of acetic acid ($K_a = 1.4 \times 10^{-5}$). The nucleophilicity of this anion proved to be too low for it to react again with β-phenoxyacrolein and the reaction stops in the first stage:

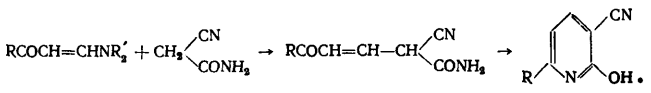


In order to avoid complications associated with successive ketovinylation, Kochetkov and Kudryashov[50] employed the ethoxymagnesium derivative of malonic ester in benzene in the reaction with β-chlorovinyl ketones. In this case the reaction takes place fairly smoothly and α-ethoxycarbonyl-δ-keto-βγ-unsaturated acids are formed in high yields. It proved possible to convert these acids into α-pyrones and further into the vinylogues of acylacetic esters[51]:



It is noteworthy that under these conditions the reaction with acetoacetic ester did not yield satisfactory results[50].

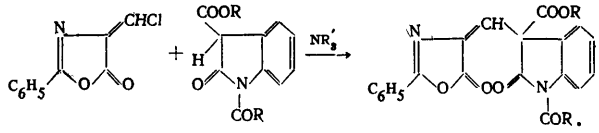
The reaction of β-dialkylaminovinyl ketones with cyanoacetamide can also be regarded as monoketovinylation with subsequent cyclisation—the nitriles of 6-alkyl-2-hydroxynicotinic acids were obtained[52]:



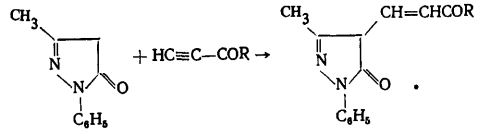
The reaction of ethyl β-diethylaminovinyl ketone with cyclic ketones was achieved by Abe[53].

Ketovinylation with β-hydroxyvinyl ketones[54], β-methoxyvinyl ketones[55] or their derivatives, and also acetals of β-keto-aldehydes[56] requires the use of catalysts, for example piperidinium acetate.

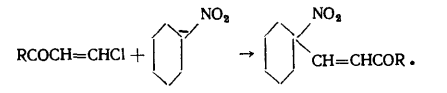
Behringer and coworkers[22,25] used tertiary amines as condensing agents in the reaction of heterocyclic analogues of β-chlorovinyl ketones with various compounds containing a methylene group with labile hydrogen atoms:



Probably quaternary carbonylvinyl ammonium salts, which are very powerful ketovinylating agents, are formed in this case as intermediates. However, the explicit use of the open-chain quaternary salts $RCOCH{=}CH\overset{+}{N}(CH_3)_3Cl^-$ in the ketovinylation of the anions of the malonic and acetoacetic esters did not yield satisfactory results[50]. Ethynyl ketones have also been used for the ketovinylation of heterocyclic compounds[57]:

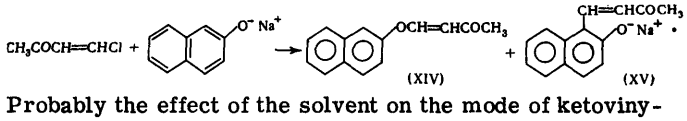


The possibility in principle of the ketovinylation of nitro-compounds with one labile hydrogen atom in the α-position has been demonstrated for 2-nitropropane[58] and nitrocyclohexane[59,60]. The choice of these nitro-compounds was again dictated by the possibility of further ketovinylation in the presence of two labile α-hydrogen atoms:



Unfortunately the yields of ketovinylation products in these cases are low.

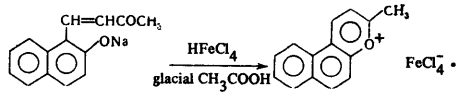
Yet another example of the ketovinylation of an ambident ion is the reaction of sodium β-naphthoxide with β-chlorovinyl ketones. The authors of the present review showed[61] that their reaction yields both series of derivatives§, the ratio of the products of *C*- and *O*-ketovinylation depending markedly on the solvent. In an aqueous alkaline medium the main product is methyl β-(2-naphthoxy)vinyl ketone (XIV) (63%) and only 10% of sodium 1-(β-acetylvinyl)-2-naphthoxide (XV) is formed, while in dioxan the main product is compound (XV) (50.5%) and the yield of compound (XIV) is only 19%:



Probably the effect of the solvent on the mode of ketovinylation is due to the fact that in an aqueous alkaline medium the oxygen of the β-naphthoxide is mainly attacked, while in the reaction in dioxan the oxygen atom is blocked by the cation, since here only the closely linked ion pairs $\beta\text{-}C_{10}H_7O^-Na^+$ exist. For this reason, the *C*-ketovinylation product is formed preferentially in dioxan. The structure

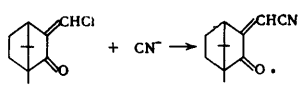
§ We may note that only the *O*-derivative is formed in the ketovinylation of the phenoxide anion[61,62].

of compound (XV) was demonstrated by its ready ring closure to form a salt of 2-methylnaphthopyrylium:



It is noteworthy that the same salt was obtained[61] by the direct reaction of β-chlorovinyl methyl ketone with β-naphthol (see p. 438).

The importance of the correct choice fo the ketovinylating agent is well illustrated by the cyanide ion as an example. The ketovinylation of the cyanide ion with chloromethylenecamphor was achieved for the first time by Bishop et al.[63] as early as the end of the previous century:



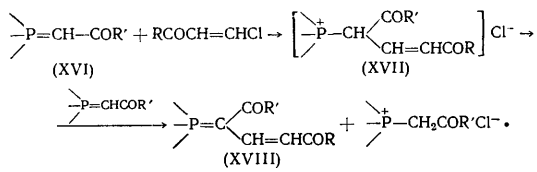
However, the reaction of open-chain β-chlorovinyl ketones with cyanide ions proved to be quite impossible. In his study of this reaction using β-chlorovinyl phenyl ketone in non-polar media, Pannizzi[64] isolated the starting material. The attempts to ketovinylate alkali metal cyanides in polar solvents (water and alcohol) also proved to be unsuccessful. In this case the reaction takes place extremely vigorously and the initial β-chlorovinyl ketones vanish completely, but dark coloured resins are formed instead of the expected products. The ketovinylation of copper cyanide also failed. It is noteworthy that the attempt to replace the chlorine atoms in β,β-dichlorovinyl ketones by CN groups was also unsuccessful[65].

The ketovinylation of the cyanide ion was achieved only when quaternary carbonylvinylammonium salts were employed[66]:

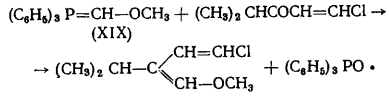
$$RCOCH{=}CH\overset{+}{N}(CH_3)_3 + CN^- \rightarrow RCOCH{=}CHCN + N(CH_3)_3.$$

The ready solubility in water of the initial salts and the sparing solubility of the resulting β-cyanovinyl ketones play a significant role in this synthesis. The successful ketovinylation of the cyanide ion lead to the development of a new synthesis of β-aroylacrylic acids and their amides[67].

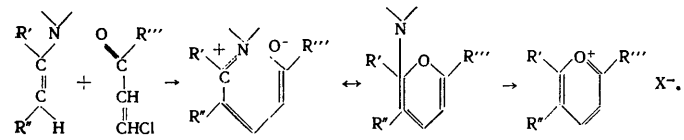
Phosphorylides, which may be regarded as dipolar ions, react in different ways with β-chlorovinyl ketones, depending on the structure of the phosphorylide. Stabilised phosphorylides of type (XVI) probably form intermediate phosphonium salts (XVII), which react further with the second molecule of the phosphorylide and are converted into a ketovinylated phosphorylide (XVIII):



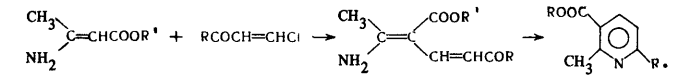
On the other hand, methoxymethylenetriphenylphosphorane (XIX) undergoes the normal Wittig reaction[68]:



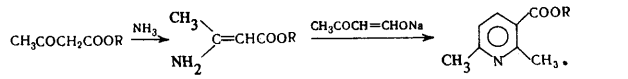
Ketovinylation can be achieved also with neutral unsaturated molecules having a multiple bond with enhanced electron density. Thus it has been found[69] that enamines react very readily with β-chlorovinyl ketones, dipolar ions, from which pyrylium salts were subsequently obtained, being formed as intermediates:



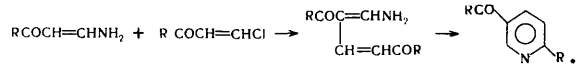
Probably the reaction of β-chlorovinyl ketones with methyl β-aminocrotonate is also accompanied by initial *C*-ketovinylation[70]. A method for the synthesis of 2,6-dialkyl-3-ethoxycarbonylpyridines was developed on the basis of this reaction:



β-Dicarbonyl compounds[70,71] in an excess of ammonia may be used in the reaction instead of the actual enamines. For example, Rabe[71] obtained 3-ethoxycarbonyl-2,6-dimethylpyridine by the reaction

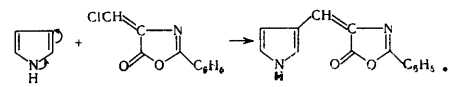


β-Aminovinyl ketones are also capable of undergoing *C*-ketovinylation. A method for the synthesis of 2,6-dialkyl-3-acylpyridines was developed on the basis of this reaction[72,73]:

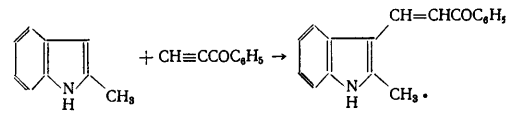


The method is convenient for the synthesis of fusaric acid[74,75].

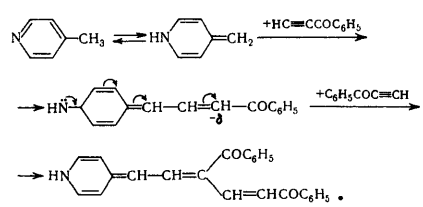
The reaction of β-chlorovinyl ketones and related compounds with pyrroles and indoles may be regarded as a special case of ketovinylation of enamines[22,76]:



Ethynyl ketones have also been used for this purpose[77]:

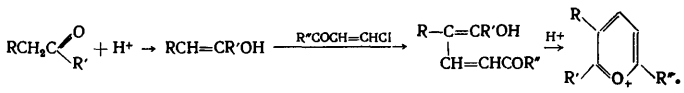


γ-Picolines react with ethynyl ketones like enamines with a longer conjugation chain; the reaction does not stop at the first stage and coloured diketovinylated products are formed[77] (see the section dealing with the ketovinylation of β-dicarbonyl compounds having two labile methylene hydrogen atoms):



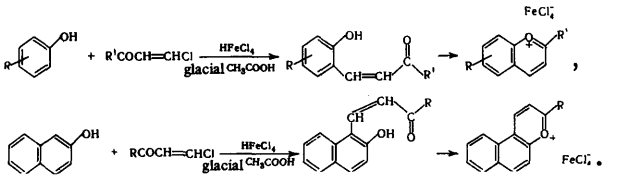
The ketovinylation of the system $\rangle C{=}C{-}OH$ was studied in many instances. The reaction of ketones with hydroxymethylene ketones in an acid medium was discovered[78] as

early as 1924 but was ignored for many years and its systematic study began only recently. It was found that under these conditions not only hydroxymethylene ketones [79-82] but also β-chlorovinyl ketones [83] can enter into the reaction. As a result, a general method has been developed for the synthesis of pyrylium salts:

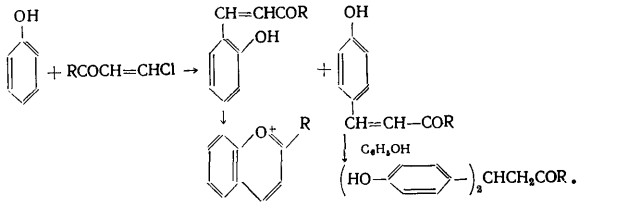


It is interesting to note that, according to the data of Zakharkin and Sorokina [84-87], in the case of ββ-dichloroacrolein the carbonyl group is attacked.

β-Chlorovinylketones react very readily with phenols and β-naphthol in the presence of a condensing agent—a mixture of iron(III) chloride and hydrochloric acid. On the basis of this reaction, Nesmeyanov, Kochetkov, and Rybinskaya developed a preparative method for the synthesis of benzopyrylium [88,89], flavylium [89], and naphthopyrylium salts [88,90]:



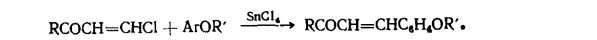
In the case of phenols with a free *para*-position, other products are formed from the phenols ketovinylated in the *para*-position together with the benzopyrylium salts. The former combine with a further phenol molecule at the double bond under the reaction conditions [91]:



A strongly activated system, such as phloroglucinol reacts with β-chlorovinyl ketones even in the absence of catalysts. This led to the development of a very simple synthesis of the methyl ester of a natural anthocyanidine—hesperidin chloride [89]. The reaction with pyrogallol requires heat [22].

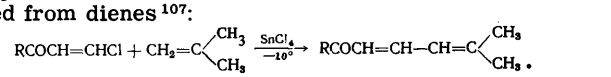
The methods for the synthesis of salts with a pyrylium ring using β-hydroxyvinyl ketones (β-diketones capable of enolisation) were investigated in greater detail [92-100].

Phenolic ethers can also be made to undergo the ketovinylation reaction and best results are achieved when tin(IV) chloride is used as the catalyst. The attack of the ketovinylating agent is mainly directed to the *para*-position and, if the latter is occupied, to the *ortho*-position [101-105]:

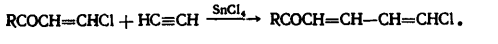


It is noteworthy that thiophen reacts under these conditions like phenolic ethers [106].

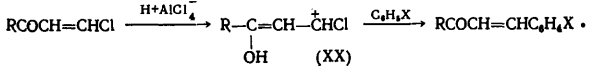
Tin(IV) proved to be an extremely active catalyst also in the condensation of β-chlorovinyl ketones with olefins having alkyl substituents at the double bond. This reaction takes place so easily with isobutene that fairly pronounced cooling (−10°C) is required. The reaction yields ketones derived from dienes [107]:



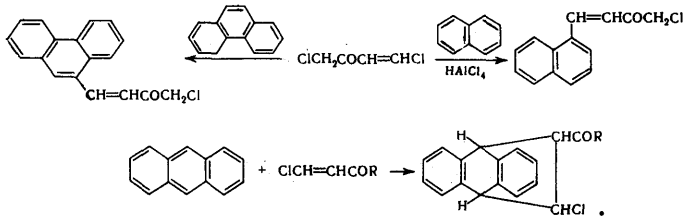
In this connection it is noteworthy that, in the presence of tin(IV) chloride, it even proved possible to achieve the reaction of acetylene with β-chlorovinyl ketones [107]. This reaction is interesting because it permits the preparation of the vinylogues of β-chlorovinyl ketones:



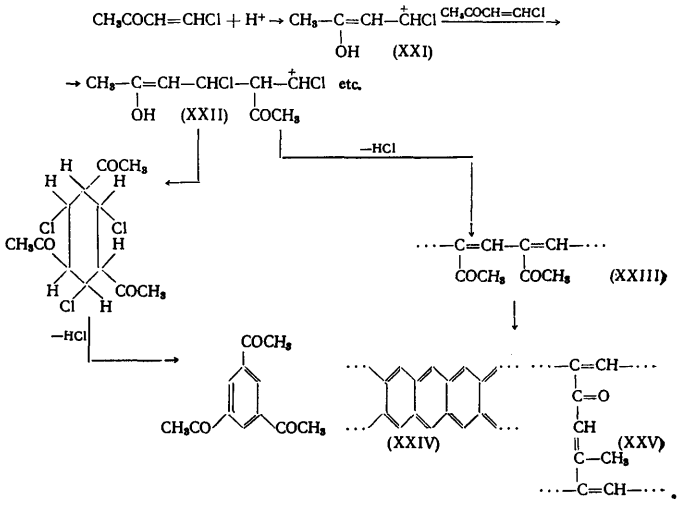
However, with very weak nucleophilic agents such as benzene and its homologues ketovinylation does not occur even in the presence of Friedel–Crafts catalysts. Probably this is because the double bond in β-chlorovinyl ketones, even when it is additionally polarised by the action of the catalyst, is still insufficiently electrophilic. In order to increase the positive charge at the β-carbon atom of the double bond, a stream of moist hydrogen chloride was passed into the reaction mixture containing aluminium chloride. In this case the reaction took place extremely readily and even chlorobenzene could be made to react [108]. It is suggested that the active species in this reaction is the intermediate carbonium ion (XX):



Naphthalene and phenanthrene [34] reacted readily under the same conditions and only in the case of anthracene [109] were diene condensation products obtained instead of the ketovinylated derivatives:



The unusual polyketovinylation or, more correctly, polycondensation of β-chlorovinyl methyl ketone, which is accelerated in the presence of acid reagents, should also be classified as a *C*-ketovinylation reaction. Depending on the reaction conditions, a cyclic trimer (triacetylbenzene) or a polymer with a conjugated system of bonds can then form [34,110]. The active species in this process is probably the carbonium ion (XXI). This ion attacks the next molecule with formation of a new carbonium ion (XXII), etc.:



Condensation in solution yields a cyclisation product, while in the absence of solvent a polymer is formed, which, as a result of spontaneous dehydrochlorination, yields the polyene (XXIII). The polymer (XXIII) changes slowly on heating in a vacuum with evolution of water, which is probably due to the crotonic condensation of the acetyl group in the chain or between the chains. As a result, the polymer may contain units consisting of condensed aromatic rings (XXIV) and units of type (XXV). According to infrared spectroscopic data, fragments of type (XXIV) probably predominate in the polymer. The study of electrical and magnetic properties showed[111,112] that the polymers may be regarded as "organic" semiconductors. Their ability to catalyse certain reactions, in particular the oxidation of toluene to benzaldehyde and benzoic acid[111], proved to be specially interesting.

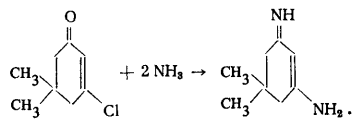
In conclusion it should be noted that the formation of triacetylbenzene was observed also in the polycondensation of other compounds of the type $CH_3COCH=CHX$, for example with X = OH, OCH_3, OCOR, etc. It was found that here too polycondensation is facilitated by acids[113-115].

2. *N*-Ketovinylation

Ammonia and primary, secondary, and tertiary amines readily undergo ketovinylation. The principal ketovinylating agents in these processes are β-chlorovinyl ketones[116-119]:

$$RCOCH=CHCl + NH_3 \rightarrow RCOCH=CHNH_2.$$

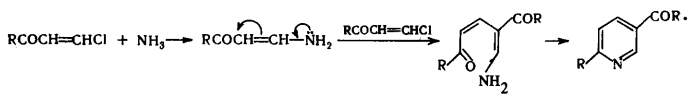
Information about this reaction appeared for the first time in the patent literature[120-121], where it was suggested that β-aminovinyl ketones be used as antidetonators and as intermediates for the synthesis of dyes and insecticides. In some cases two molecules of ammonia enter into the reaction simultaneously (at 100°C), which results in the formation of imines derived from β-aminovinyl ketones[122]:



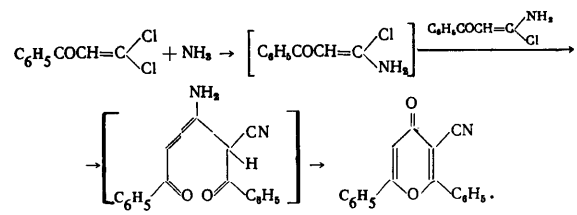
Since ammonia and amines are fairly powerful nucleophilic reagents, hydroxymethylene ketones and their enolates and ethers may take part in *N*-ketovinylation[123]. β-Aminoacrolein was also obtained by the treatment of β-methoxyacrolein with ammonia[124]. Ethynyl ketones were used successfully in this reaction[125]:

$$RCOC\equiv CH + NH_3 \rightarrow RCOCH=CHNH_2.$$

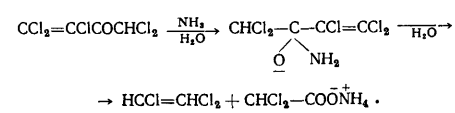
When aqueous ammonia reacts with an excess of β-chlorovinyl ketones[126-128] and ethynyl ketones[129], 2-alkyl-5-acylpyridines are formed. Possibly the intermediates in this reaction are β-aminovinyl ketones, which cyclise with the excess of the initial reagent to form the corresponding pyridine derivative[72,126,129]:



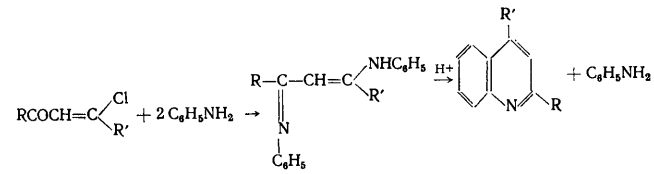
A similar mechanism may be proposed for the reaction of ammonia with ββ-dichlorovinyl phenyl ketone[8], which led to the formation of the nitrile of 2,6-diphenyl-γ-pyrone-3-carboxylic acid:



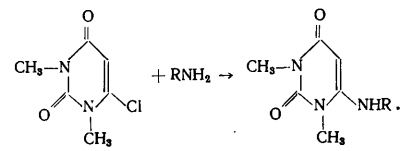
However, the situation changes fundamentally when polychloro-substituted αβ-unsaturated ketones are employed. Roedig and Maier[130] found that this results in the fission of the initial compound into trichloroethylene and a carboxylic acid salt. Probably in this case nucleophilic attack is directed to the carbonyl group:



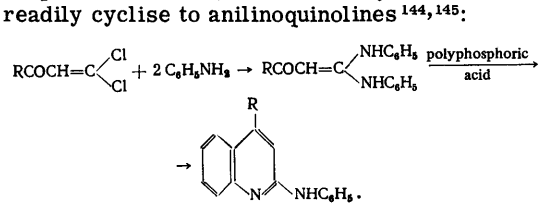
Under conditions analogous to those of reactions with ammonia, primary amines are ketovinylated with β-chlorovinyl ketones[64,120,131-137] and hydroxymethylene ketones[123,138]; ethynyl ketones can also be used[5,125]. In the presence of an excess of aromatic amines, the Schiff bases of β-arylaminovinyl ketones are formed as a rule[122,134,139-142]; they have been used for the synthesis of quinolines[139,140]:



Cyclic β-chlorovinyl ketones with a fixed *S-trans*-conformation react very readily with primary amines[122,143]:



In the reaction with amines ββ-dichlorovinyl ketones rapidly exchange both chlorine atoms very rapidly even in nonpolar solvents and it has been found that in the presence of polyphosphoric acid the ββ-diaminovinyl ketones formed very readily cyclise to anilinoquinolines[144,145]:



Similar results were obtained also with di- and tri-chloroacrolein[146]. In a number of cases the transamination of β-aminovinyl ketones was achieved[147,148]:

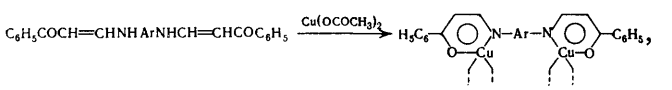
$$C_6H_5COCH=CHNHC_6H_5 + C_{10}H_7NH_2 \rightarrow C_6H_5COCH=CHNHC_{10}H_7 + C_6H_5NH_2.$$

The products of the ketovinylation of aromatic amines with aryl β-chlorovinyl ketones are difficult to purify by recrystallisation from the initial ketones. Therefore in

the synthesis of β-aminovinyl ketones of this kind water-soluble quaternary β-aroylvinyltrimethylammonium salts may be used as the ketovinylating agents [149,150]:

$$ArCOCH{=}CH\overset{+}{N}(CH_3)_3 + NH_2C_6H_5 \rightarrow ArCOCH{=}CHNHC_6H_5.$$

Carbonylvinylammonium salts have played a particularly important role in the synthesis of *NN'*-bisketovinylated aromatic diamines [149]. A synthesis of chelate polymers has been developed on the basis of such diamines:

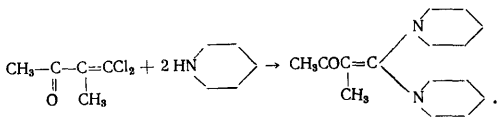


where Ar = $-C_6H_4-$ or $-(C_6H_4)_2-$. Using ammonium salts of the type $RCOCH{=}CH\overset{+}{N}(CH_3)_3Cl^-$, it proved possible to develop a method for the synthesis of hitherto unknown *N*-(β-acylvinyl)-substituted glycines and their ethyl esters [151]. The interaction of quaternary salts with the sodium salt and ester of glycine takes place very vigorously in aqueous solution.

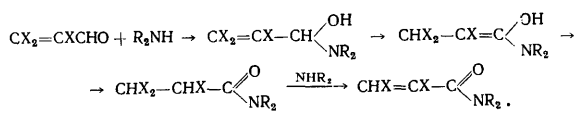
It is noteworthy that tautomerism of an interesting type, ketimine–enol ⇌ enamine–ketone, has been investigated in β-aminovinyl ketones obtained by the ketovinylation of ammonia and primary amines. Tautomerism of this type was investigated in detail by Nesmeyanov and coworkers [117,118,152,153], Potapov et al. [135], and Kazitsyna et al. [154]

Among secondary amines, aliphatic amines and saturated heterocycles are very readily ketovinylated. When they react with β-chlorovinyl ketones [64,120,155-157], ethynyl ketones [125,158], and hydroxymethylene ketones [123,159-162], β-dialkylaminovinyl ketones are formed.

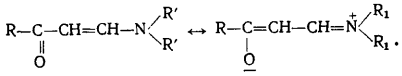
In the reaction with secondary amines both chlorine atoms of ββ-dichlorovinyl ketones [144,163] and dichloroacrolein [164] are substituted, but their α-alkyl derivatives react very slowly due to the breakdown of the coplanarity of the carbonyl group and the double bond [144,163]:



It is interesting to note that with polychlorinated acroleins the secondary amine attacks the carbonyl group. The subsequent allyl rearrangement and elimination of HX leads to the acid amide [165]:



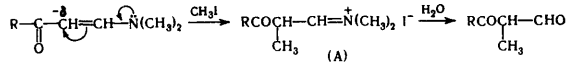
β-Dialkylaminovinyl ketones have high dipole moments [166]. For example, the dipole moment of methyl β-dimethylaminovinyl ketone is 5.67 D.



The capacity of these compounds to react with nucleophilic reagents is very weak (they react only with powerful nucleophilic reagents¶) and conversely their reaction with electrophilic reagents takes place readily. The electrophilic agent attacks the α-carbon atom of the double bond.

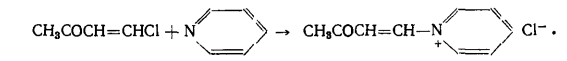
¶ For further details see pp. 434 and 447.

Thus, instead of the expected quaternary β-acylvinyltrimethylammonium salts, the methylation of β-dimethylaminovinyl ketones led to the isolation after hydrolysis of the decomposition products of salts of type (A) [156,167]. The synthesis of α-substituted β-keto-aldehydes is based on this reaction:

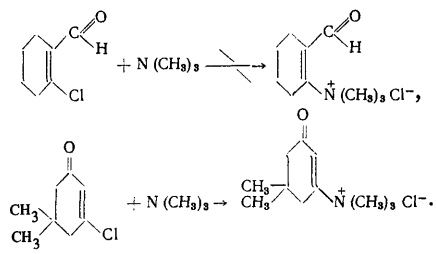


In an acid medium β-dialkylaminoacroleins [160] and β-dimethylaminovinyl ketones [168] exchange the α-hydrogen atom at the double bond for deuterium. Their capacity to enter into the ketovinylation reaction has already been mentioned (see p. 434).

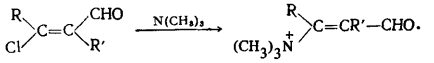
The ketovinylation reaction of tertiary amines occupies a special place, primarily because extremely powerful ketovinylating agents—β-acylvinylammonium salts—were obtained on its basis. A quaternary salt of this type was obtained for the first time by Yakubovich and Merkulova [169] by the action of pyridine on β-chlorovinyl methyl ketone:



Subsequently Kochetkov, Skoldinov, and coworkers [170,171] found a general method for the ketovinylation of tertiary amines with β-chlorovinyl ketones†. Nesmeyanov and Rybinskaya [66] suggested that the same trimethyl- and triethyl- ammonium salts be used without preliminary purification for the ketovinylation of the cyanide ion. It is interesting to note that cyclic β-chlorovinyl carbonyl compounds known to have the *cis*-configuration hardly react with tertiary amines [172,173], while ketones with a fixed *trans*-configuration are converted into quaternary salts with almost quantitative yields [172]:



αβ-Dialkyl-β-chlorovinylaldehydes react with trimethylamine very slowly and the quaternary ammonium salts are then obtained with very low yields [173-175]:



The possibility, in principle, of synthesising quaternary salts by the reaction of ethynyl ketones with tertiary amine hydrochlorides has been demonstrated for ethynyl phenyl ketone as the sole example [127]:

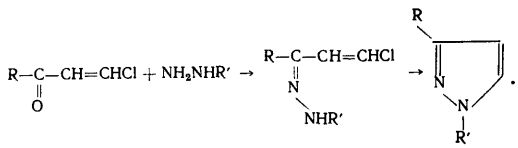
$$C_6H_5COC{\equiv}CH + N(CH_3)_3 \cdot HCl \rightarrow C_6H_5COCH{=}CH\overset{+}{N}(CH_3)_3\,Cl^-.$$

Hydrazines, semicarbazide, and hydroxylamine are much more powerful bases and nucleophilic agents than amines because of the additional electron transfer to the

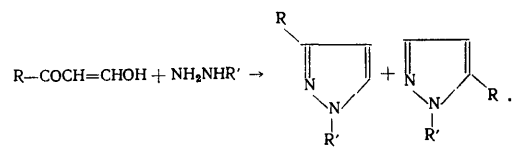
† Because of a number of disadvantages of experiments with β-chlorovinyl ketones, largely due to the high toxicity of these compounds, the above workers suggested that the ketones be converted into quaternary ammonium salts without being isolated from the reaction mixture [171].

nitrogen atom by the adjacent NH_2 and OH groups. It has been found that, in contrast to amines, these reagents are capable of attacking a second electrophilic centre in the β-chlorovinyl ketone molecule, i.e. the carbonyl group (cf. the reactions with RLi and RMgX, p. 434). The capacity to attack the carbonyl group is more pronounced in hydrazines and semicarbazides than in hydroxylamine. The latter is a weaker base and nucleophilic agent and reacts simultaneously with both electrophilic centres. It is noteworthy that the ketovinylation of these compounds leads in most cases to heterocyclic pyrazole and isoxazole systems, the position of the substituents in which shows the direction of the primary attack by the nucleophilic agent.

Nesmeyanov et al.[2] have shown that alkyl β-chlorovinyl ketones react with hydrazine and alkyl hydrazines with formation of 3-alkyl- and 3-alkyl-1-aryl-pyrazoles:

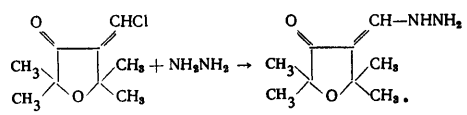


This result is evidence in the first place that the reaction begins with attack on the carbonyl group. This was subsequently confirmed by the isolation of the intermediate hydrazones[16,176,177], which subsequently cyclised to the pyrazole ring. Furthermore, the use of the β-chlorovinyl ketones in this reaction is of practical value, since it provides a preparative method for the synthesis of 1,3-disubstituted pyrazoles. The hydroxymethylene ketones employed previously yield a mixture of 1,3- and 1,5-disubstituted pyrazoles.[178]



Subsequently the reaction was extended also to other aromatic, aliphatic,[90,176] and barene[179] β-chlorovinyl ketones and αβ-disubstituted β-chlorovinyl aldehydes[180,181]. The unsubstituted pyrazole was obtained with the aid of β-halogenoacroleins[182-184]. The reactions with polyhalogenoacroleins and poly(chlorovinyl ketones) also yield hydrazones, which are converted into the corresponding pyrazoles on boiling[185-187], the yield of pyrazole increasing with the degree of chlorination of the ketovinylating agent[187]. In this connection it is interesting to note that cyclic *cis*-β-chlorovinyl ketones (for example, 1-acyl-2-chlorocyclopent-1-ene) readily form hydrazones, which, however, do not cyclise to pyrazoles[188]. This is because of the lower lability of the halogen in the *cis*-configuration.

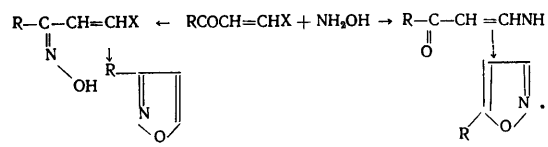
The only known case of *N*-ketovinylation of hydrazine is the reaction with a β-chlorovinyl ketone, the approach to the carbonyl group of which is sterically hindered[189]:



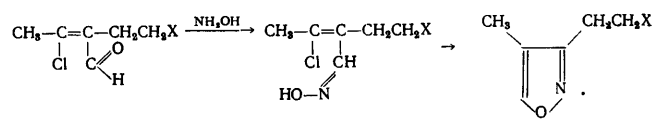
In this connection we may recall that a powerful nucleophilic agent such as RMgX also does not usually react with the carbonyl group of β-chlorovinyl ketones if the approach to the latter is hindered, and attacks the β-carbon atom of the double bond[22-25]. Finally, it should be noted that ethynyl ketones have also been used for the synthesis of pyrazoles[190].

Semicarbazide also reacts with β-chlorovinyl ketones at the carbonyl group with formation of semicarbazones[16,169,191-193]. Like hydrazones, semicarbazones can probably cyclise to the corresponding 1-carbamoylpyrazoles, since it was found that they undergo a change on recrystallisation[169].

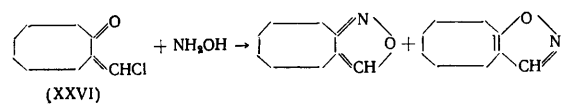
Hydroxylamine is less basic and less nucleophilic and therefore in the reaction with β-chlorovinyl[179,194-196], β-phenoxyvinyl[196], β-phenylthiovinyl[196], and β-hydroxyvinyl[197] ketones it attacks both electrophilic centres simultaneously. Subsequent cyclisation leads to the formation of a mixture of 3- and 5-substituted isoxazoles. Similar results were obtained also with barenylmethyl β-chlorovinyl ketones[179]:



β-Halogenoacroleins have been suggested for the synthesis of unsubstituted isoxazoles[182-184,194]. It is interesting to note that in the reaction of β-alkyl substituted β-chloroacroleins under mild conditions it is possible to isolate oximes[172], while on heating isoxazoles are formed immediately[180,181]:

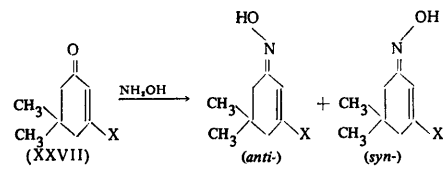


The cyclic β-chlorovinyl ketone (XXVI), with a fixed cisoid conformation, reacts with hydroxylamine to form a mixture of isoxazoles similar to that obtained in the reaction with the corresponding hydroxymethylene ketone[198,199]:



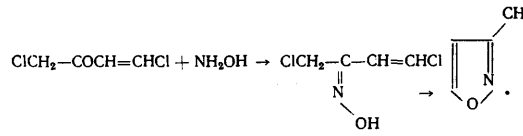
(XXVI)

However, in the reaction of hydroxylamine with the β-chlorovinyl ketone (XXVII), which has a fixed transoid conformation, only oximes (*syn*- and *anti*-isomers) are formed. In this case attack on the electrophilic centre of the double bond is hindered, since the double bond is located in the ring. Furthermore, the fixed transoid conformation prevents cyclisation[172]:

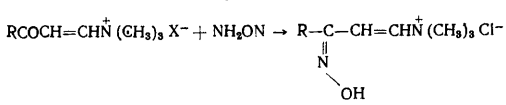


By varying the ketovinylating agents, it is possible to alter the mode of reaction with hydroxylamine. An increase in the electrophilicity of the carbonyl group in alkyl β-chlorovinyl ketones by the introduction of electron-acceptor substituents in the α-position of the alkyl group

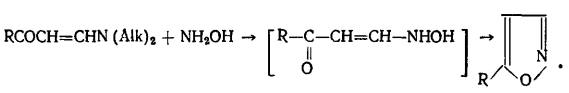
leads to the preferential formation of 3-substituted isoxazoles [195,200]‡. This shows that an oxime is formed as an intermediate in the main reaction:



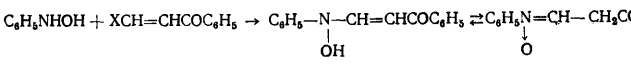
A similar effect can probably be achieved by replacing the chlorine atom in β-chlorovinyl ketones by a quaternary ammonium group. In this case the corresponding oximes could be obtained under very mild conditions [172]:



On the other hand, by introducing into the α-position a powerful electron-donor group $N(Alk)_2$ (instead of chlorine), which suppresses the electrophilic activity of the carbonyl group, the entire process may be reduced to the formation of 5-substituted isoxazoles only, i.e. products of the *N*-ketovinylation of hydroxylamine will form in the first stage of the reaction [52,196]:

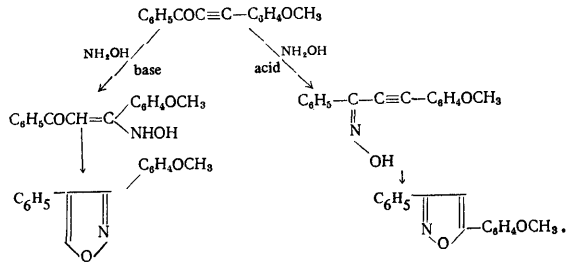


When *N*-phenyl-substituted hydroxylamine is used, only *N*-ketovinylation products are formed [147]:

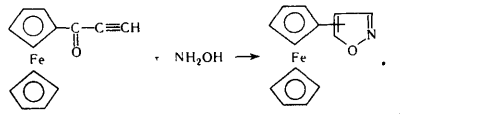


where X = Cl or NHC_6H_5.

It was found that ethynyl ketones can also react with formation of isoxazoles [202]. As in the case of β-chlorovinyl ketones, this reaction takes place in two ways, but, by varying the conditions, the process can be driven one way or another. In an acid medium attack on the carbonyl group is facilitated and in an alkaline medium the 1,4-addition (*N*-ketovinylation) product is formed as an intermediate:



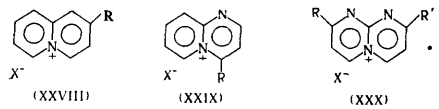
Ferrocenyl-substituted isoxazole was obtained in the same way [190]:



‡ We may recall that Kochetkov and Khomutova [201] developed a method of synthesis based on the reaction of hydroxylamine with β-keto-acetals (ω-acylmethyldioxolanes). An oxime is formed as an intermediate in the reaction, which permits the selective synthesis of trisubstituted isoxazoles.

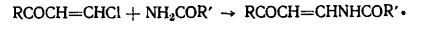
We may also recall the synthesis of certain nitrogenous six-membered heterocycles using guanidine, alkylamidines, urea, thiourea, α-aminopyridine, 2-aminopyridine, etc. Thus, on heating, β-chlorovinyl ketones [203,204] and β-halogenoacroleins [182,184,205] react with guanidines in a strongly acid medium with formation of 2-aminopyrimidine derivatives. However, in this case the site of the primary attack by the nucleophilic agent cannot be deduced, since the intermediate products were not isolated. The use of thiourea in this reaction leads to the formation of 2-mercaptopyrimidine [184].

A method of synthesis of heterocyclic cations containing an ammonium nitrogen atom in the bridge—dehydroquinolizinium salts and their 1-aza- and 1,9-diaza-analogues [compounds (XXVIII), (XXIX), and (XXX) respectively]—has been developed on the basis of β-chlorovinyl ketones and their derivatives—β-keto-acetals [206-209]:

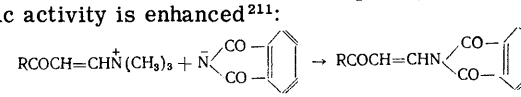


(XXVIII) (XXIX) (XXX)

The ketovinylation of carboxylic acid amides is difficult and requires heating to 180–200°C, the yields of products being low (8–22%): [210]

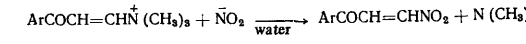


However, the anions of acid amides, for example, the phthalimide ion, are successfully ketovinylated when quaternary β-acylvinyltrimethylammonium salts are used. This reaction takes place at room temperature, and with β-aroylvinyltrimethylammonium salts aqueous solutions may be employed. On the other hand, with quaternary aliphatic ammonium salts [$AlkCOCH{=}CH\overset{+}{N}(CH_3)_3X^-$] the phthalimide ion is much too weak a nucleophilic agent in water and therefore the reaction must be carried out in a dipolar aprotic solvent—dimethylformamide (DMFA). [151] The anions are known to be much less solvated in solvents of this kind than in water and consequently their nucleophilic activity is enhanced [211]:



where R = Ar (solvent—water) or R = alkyl (solvent—dimethylformamide). The structure of the compounds obtained was demonstrated by hydrolysis to the corresponding β-aminovinyl ketones [151].

Carbonylvinylammonium salts proved to be completely irreplaceable in the synthesis of β-nitrovinyl ketones [66]. It is noteworthy that, despite all attempts, β-chlorovinyl ketones could not be made to react with the nitrite ion. The reaction of the quaternary salts with the nitrite ion was carried out in aqueous solution, potassium dihydrogen phosphate being added as a buffer. The buffer solution is necessary because the aryl β-nitrovinyl ketones formed are very sensitive to the action of hydroxide ions, the concentration of which increases as trimethylamine is eliminated. It was found that the yield of aryl β-nitrovinyl ketones falls as the electron-acceptor properties of the substituent in the phenyl ring become more pronounced:



Probably this is associated with the enhanced tendency of the resulting aryl β-nitrovinyl ketones to react further with the nucleophilic agents present in the reaction mixture. Thus the yield of β-nitrovinyl *p*-tolyl ketone is 45%, [212] while *p*-nitrophenyl β-nitrovinyl ketone was obtained in a yield of only 3%. [150]

The *N*-ketovinylation of the axide ion occupies a special position, since it led to possibilities of interest not only for syntheses but also for theory. Since these data were obtained in connection with the study of the stereochemistry of ketovinylation and the effect of groups eliminated on substitution, they will be discussed in detail in a later section (see section IV).

3. *S*-Ketovinylation

Methods for the *S*-ketovinylation have been developed comparatively little. Among these the ketovinylation of RS ions (R = alkyl or aryl), which are very powerful nucleophilic agents, has been investigated in greatest detail. It has been found that the reaction of thiophenoxides with β-halogenovinyl ketones yields β-phenylthiovinyl ketones[213]. Montanari and coworkers[214,215], who investigated the stereochemistry of this reaction, noted that the geometrical configuration of the initial ketone is retained on substitution. The reaction of course takes place more readily than with phenols. In some cases it was found that the halogen is very readily exchanged for an alkanethiolate ion even in benzene solution[216]:

$$RCOCH{=}CHCl + R'S^- \xrightarrow{H^+} RCOCH{=}CHSR' \xrightarrow{R'SH} RCOCH_2CH(SR')_2.$$

When an excess of mercaptans is used in the reaction, the latter does not stop at the β-alkylthiovinyl ketone stage, since a second mercaptan molecule adds to the double bond. This results in the formation of β-keto-mercaptals[217] (cf. the *O*-ketovinylation of OR^- in the presence of ROH):

$$RCOCH{=}CHCl + \bar{S}Alk \rightarrow RCO\bar{C}H{-}CH\!\!\begin{matrix}\diagup Cl\\ \diagdown SAlk\end{matrix} \rightarrow$$

$$\rightarrow RCOCH{=}CHSAlk \xrightarrow{\bar{S}Alk} RCO\bar{C}H{-}CH\!\!\begin{matrix}\diagup SAlk\\ \diagdown SAlk\end{matrix} \xrightarrow{H^+} RCOCH_2CH(SAlk)_2.$$

It was found that under these conditions the reaction with ethane-1,2-dithiol yields cyclic β-keto-mercaptals[217]. The corresponding β-ethylthiovinyl and β-phenylthiovinyl ketones were obtained also with ethynyl ketones as the ketovinylating agents in the presence of basic catalysts[125].

A brief communication has been published on the synthesis of mercaptals when mercaptans react with β-hydroxyvinyl ketones in an acid medium[218].

Phenylthio-derivatives are oxidised with hydrogen peroxide to the corresponding sulphoxides and sulphones[219]:

$$RCOCH{=}CHSC_6H_5 \xrightarrow{H_2O_2} RCOCH{=}CHSOC_6H_5 \xrightarrow{H_2O_2} RCOCH{=}CHSO_2C_6H_5.$$

The latter can also be obtained directly by the ketovinylation of the benzene sulphinate ion[219]:

$$C_6H_5COCH{=}CHCl + \bar{S}O_2C_6H_5 \rightarrow C_6H_5COCH{=}CHSO_2C_6H_5.$$

ββ-Dichlorovinyl methyl ketone reacts with sodium benzenesulphinate in a very unusual manner. Diphenylsulphonylmethane was obtained as the main product[65] together with a small amount of 1-chloro-1-phenylsulphonylbuten-3-one:

$$CH_3COCH{=}CCl_2 + C_6H_5\bar{S}O_2 \rightarrow CH_3COCH{=}C\!\!\begin{matrix}\diagup SO_2C_6H_5\\ \diagdown Cl\end{matrix} + CH_2\!\!\begin{matrix}\diagup SO_2C_6H_5\\ \diagdown SO_2C_6H_5\end{matrix}.$$

The formation of diphenylsulphonylmethane can be explained by the rapid hydrolysis of the intermediate 1,1-diphenylsulphonylbuten-3-one:

$$CH_3COCH{=}C\!\!\begin{matrix}\diagup SO_2C_6H_5\\ \diagdown SO_2C_6H_5\end{matrix} + \bar{O}H \rightarrow CH_3COCH(OH){-}\bar{C}\!\!\begin{matrix}\diagup SO_2C_6H_5\\ \diagdown SO_2C_6H_5\end{matrix} \rightleftarrows$$

$$\rightleftarrows CH_3{-}COCH(O){-}CH\!\!\begin{matrix}\diagup SO_2C_6H_5\\ \diagdown SO_2C_6H_5\end{matrix} \rightarrow \bar{C}H\!\!\begin{matrix}\diagup SO_2C_6H_5\\ \diagdown SO_2C_6H_5\end{matrix} + (?)\ CH_3COCH$$

$$\downarrow H^+$$

$$CH_2(SO_2C_6H_5)_2.$$

Another method of ketovinylation, using ethynyl ketones, may be successfully employed for the synthesis of β-keto-sulphones[125,200]. However, the most convenient ketovinylating agents for this purpose proved to be the quaternary ammonium salts $RCOCH{=}CH\overset{+}{N}(CH_3)_3Cl^-$. The reaction, carried out in an aqueous medium, results in a very rapid (literally on mixing the solutions!) formation of the sulphone with a high yield[221]. Ketovinylation with the aid of quaternary carbonylvinylammonium salts has the advantage that the product is obtained immediately in a pure form and does not contain the starting material as an impurity, as happens when aryl β-chlorovinyl ketones are employed. Since both the initial quaternary salts and the resulting sulphones have the *trans*-configuration, it was concluded that the configuration is retained on substitution of the $\overset{+}{N}(CH_3)_3$ group. However, the reaction was not investigated with *cis*-derivatives, since quaternary *cis*-β-acylvinyltrimethylammonium salts are so far unknown.

The ketovinylation of the sulphide ion has been demonstrated with the β-butyrylvinylammonium salt as an example[66]. The doubly charged sulphide ion is then ketovinylated twice and bis-(β-butyrylvinyl) sulphide was isolated in 88% yield:

$$2C_3H_7COCH{=}CH\overset{+}{N}(CH_3)_3 + S^{2-} \rightarrow (C_3H_7COCH{=}CH)_2S.$$

Despite the attempts made, this reaction could not be stopped at the mono-ketovinylation stage. This could not be done even when sodium hydrogen sulphide was employed[222]. Mono-ketovinylation could be achieved only by the reaction of β-chlorovinyl ketones with thioacetate salts. β-Acylethylenethiol is obtained after the hydrolysis of the reaction product[222]:

$$C_4H_9COCH{=}CHCl + CH_3COSNa \rightarrow C_4H_9COCH{=}CHSCOCH_3 \xrightarrow{NaSH} C_4H_9COCH{=}CHSH.$$

It is interesting to note that, according to the data of Nesmeyanov et al.[65], the analogous reaction with ββ-dichlorovinyl ketone yields a thioketen dimer after hydrolysis and elimination of hydrogen chloride:

$$CH_3COCH{=}CCl_2 + CH_3COSNa \rightarrow \left[CH_3COCH{=}C\!\!\begin{matrix}\diagup Cl\\ \diagdown SCOCH_3\end{matrix} \xrightarrow{H_2O} CH_3COCH{=}C\!\!\begin{matrix}\diagup Cl\\ \diagdown SH\end{matrix}\right] \xrightarrow{-HCl}$$

$$\rightarrow [CH_3COCH{=}C{=}S]_2.$$

In the synthesis of β-acylethylenesulphonates it was found that quaternary carbonylvinylammonium salts are the only possible ketovinylating agents, since in their reaction with the SO_3^{2-} ion in an aqueous medium they are sparingly soluble mixed salts of type (XXXI), which makes it possible to stop the reaction at the first stage. The mixed salts (XXXI) can be converted into alkali metal salts be subsequent treatment with KBF_4, KCN, or $NaNO_3$:[221]

$$RCOCH{=}CH\overset{+}{N}(CH_3)_3 + SO_3^{2-} \rightarrow RCOCH{=}CHSO_3^-\overset{+}{N}(CH_3)_3CH{=}CHCOR \xrightarrow{KBF_4}$$

$$\rightarrow RCOCH{=}CHSO_3K\ (soln.) + RCOCH{=}CH\overset{+}{N}(CH_3)_3B\bar{F}_4\ (ppt.).$$

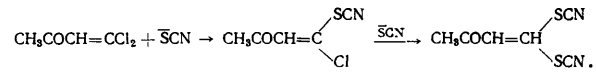
On the other hand, in the synthesis of hitherto unknown salts of phenylacylmethionic acids the fact that with β-chlorovinyl ketones the reaction proceeds further was employed[221,223]:

$$RCOCH{=}CHCl + Na_2SO_3 + NaHSO_3 \rightarrow RCOCH_2CH(SO_3Na)_2.$$

The interaction of β-chlorovinyl ketones with thiocyanate ions may be included among the *S*-ketovinylation reactions. This reaction was achieved for the first time by Panizzi[64] in only one case. It was developed further by Kochetkov[224], who employed a number of alkyl β-chlorovinyl ketones, and by the author of a patent[225], who described the use of ring-substituted aryl β-chlorovinyl ketones:

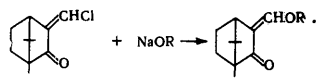
$$RCOCH{=}CHCl + \bar{S}CN \rightarrow RCOCH{=}CHSCN.$$

Nesmeyanov et al.[65] showed that ββ-dichlorovinyl ketones react with the thiocyanate ion, both chlorine atoms being substituted. Also it was possible to isolate the intermediate monosubstituted product:



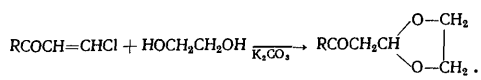
4. *O*-Ketovinylation

The first information about the ketovinylation of OR^- ions appeared in the patent literature in 1937[226-228]. The interaction of β-chlorovinyl ketones with alcohols in the presence of alkaline reagents was investigated in greater detail by Nesmeyanov et al.[229] and simultaneously by Price and Pappalardo[177]. These workers showed that the reaction with alkoxide ions in the corresponding alcohols does not as a rule stop at the substitution stage, the alcohol adding subsequently to the double bond of the intermediate β-alkoxyvinyl ketones. This results in the formation of β-keto-acetals in yields of 50–90%. Furthermore, it was found that β-keto-acetals are formed in low yields also when hydrogen chloride is employed as the catalyst[229]. The intermediate β-alkoxyvinyl ketone was isolated only in the case of the less reactive chloromethylenecamphor[230]:

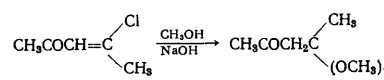


Therefore β-alkoxyvinyl ketones must be obtained by the elimination of the alcohol from the β-keto-acetals using various basic and acid catalysts[231-235].

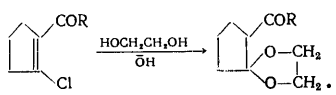
In recent years the synthesis of β-keto-acetals has been extended to higher aliphatic[230,236-239] and heterocyclic[239] homologues. The use of glycols in these reactions lead to the development of a method for the synthesis of stable dioxolane derivatives[233,240]:



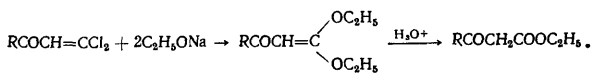
It is noteworthy that β-alkyl-substituted β-chlorovinyl ketones also react with alkoxides, albeit with difficulty, forming monoketals of β-diketones[139]:



Even the relatively unreactive cyclic β-chlorovinyl ketones with a fixed *cis*-configuration react with ethylene glycol in the presence of alkaline agents forming monoketals[188]:



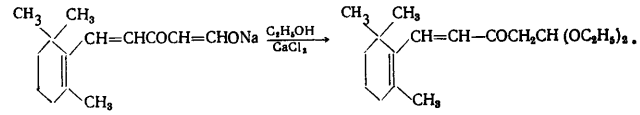
In ββ-dichlorovinyl ketones both chlorine atoms are exchanged for alkoxy-groups. In an anhydrous medium this results in the formation of β-dialkoxyvinyl ketones[65,139,163], which are readily hydrolysed to acylacetate esters[65]:



When alcoholic solutions of alkalis were allowed to react with ethynyl ketones, β-keto-acetals were also obtained[125].

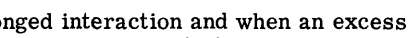
Hydroxymethylene ketones too can be used for the synthesis of β-keto-acetals, but in this case it is necessary to employ acid catalysts[241-247]. Royals and Brannok[248] made a detailed study of the reaction of the sodium salts of hydroxymethylene ketones with alcohols in the presence of hydrochloric acid and found that, depending on the structure of the initial ketones, acetals or β-alkoxyvinyl ketones are formed.

β-Keto-acetals with a fairly complex structure were obtained similarly[249]:



β-Keto-acetals have been used as intermediates for the synthesis of a wide variety of compounds. In particular, they have been employed for the preparation of certain heterocycles[9,250,251]: they are used very often for the synthesis of various derivatives formed by the reaction of the carbonyl group[252,253]. Higher members of the $RCOCH_2.CH(OR')_2$ series, where $R = C_9-C_{12}$, have the scent of oranges and therefore it is suggested that they be employed in cosmetics and in the manufacture of perfumed soap[254].

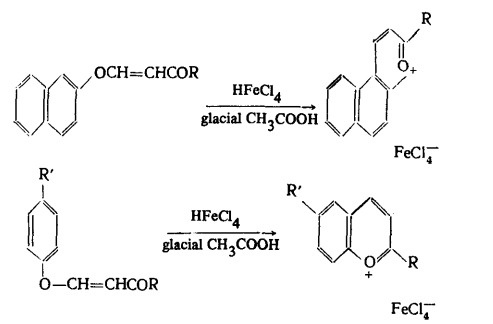
In contrast to alcohols, the reaction of β-chlorovinyl ketones with phenols may be stopped at the first stage, which leads to the formation of β-aryloxyvinyl ketones[62]. It has been shown for alkyl β-chlorovinyl ketones that this reaction is general and is catalysed by alkaline agents in various solvents (water, dioxan, excess of phenol):



During prolonged interaction and when an excess of phenol is used, the reaction proceeds further to some extent, yielding the acetals of β-keto-aldehydes[229] as in the case of alcohols.

The reaction of β-chlorovinyl ketones with sodium β-naphthoxide differs significantly from that described above. Both in aqueous alkali and in dioxan the products of *C*-ketovinylation at the α-carbon atom of the naphthalene ring were isolated[61] together with the *O*-ketovinylation products (see p. 436).

Nesmeyanov et al.[91] showed that the most interesting property of β-aryloxyvinyl ketones is their capacity to undergo a rearrangement analogous to the Fries rearrangement. It was found that, on treating solutions of β-phenoxyvinyl ketones in glacial acetic acid with a solution of iron(III) chloride in concentrated hydrochloric acid, the chloroferrates(III) of 2-substituted benzo- and naphthopyrylium cations are formed. The isomeric 4-substituted pyrylium salts are not produced. Thus it was shown that the products of the *O*-ketovinylation of phenols rearrange in an acid medium to *C*-ketovinylation products:

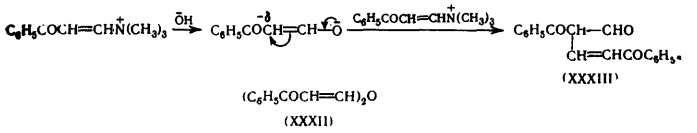


the rearrangement occurring not only in the *ortho*-position but also in the *para*-positions of the phenol ring, if the

latter is free. We may recall that the same pyrylium salts were obtained also by the direct condensation of β-chlorovinyl ketones with phenols and naphthol[88,89].

Finally, it should be noted that nucleophilic addition to ethynyl ketones has also been employed for the *O*-ketovinylation of phenols. Thus Bowden et al.[125] observed the nucleophilic addition of phenols to ethynyl ketones in the presence of bases.

The ketovinylation of the OH^- ion by any of the ketovinylating agents takes place in a complex manner and as a rule results in the formation of ketones (hydrolytic decomposition)[26]. β-Aroylvinyltrimethylammonium salts are an exception. They readily react with aqueous solutions of weak bases and even with water, which sometimes results in complications if the ketovinylation is carried out in an aqueous medium. This leads to products in which there are two carbonylvinyl residues per oxygen atom derived from water. This was noted for the first time by Kochetkov et al.[170] They found that β-benzoylvinyltrimethylammonium chloride undergoes "hydrolysis" in aqueous solution under the action of sodium bicarbonate with formation of a compound for which two alternative structures were proposed on the basis of elemental analysis and molecular weight measurements: either the structure of the β-benzoylvinyl ether (XXXII) or benzoyl(β-benzoylvinyl)acetaldehyde (XXXIII). According to infrared spectroscopic data, the latter is the most likely structure[151], but is complicated by the occurrence of ring–chain tautomerism. It is suggested that the decomposition of the quaternary salt with water is accompanied by successive *O*- and *C*-ketovinylation according to the mechanism

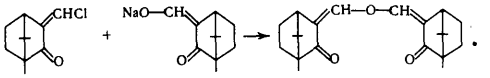


(XXXIII)

$(C_6H_5COCH{=}CH)_2O$

(XXXII)

It is interesting to note that, in contrast to β-aroylacetaldehyde, the enolates of hydroxymethylenecamphor are ketovinylated at the oxygen atom[63]:



The "hydrolysis" is particularly facilitated by the presence of electron-acceptor groups in the aryl ring. Thus β-aroylvinyltrimethylammonium chlorides containing halogen atoms in the *ortho*- or *para*-positions are "hydrolysed" even as a result of atmospheric moisture during storage and consequently these compounds cannot be stored in aqueous solutions. The mechanism of the "hydrolysis" changes sharply when one methyl group in the quaternary salts is replaced by the benzyl group[151]:

$$C_6H_5COCH{=}\overset{+}{N}H(CH_3)_2CH_2C_6H_5 \xrightarrow{H_2O} C_6H_5COCH{=}NH(CH_3)_2 + C_6H_5CH_2OH.$$

The weakly nucleophilic acetate ion could not be made to undergo the ketovinylation reaction for a long time. This became possible only when powerful ketovinylating agents such as β-acylvinyltrimethylammonium salts were employed. In order to avoid "hydrolytic" side processes, it is necessary to employ dry dipolar solvents such as dimethylformamide. In glacial acetic acid the process does not stop at the ketovinylation stage and acylals of β-ketoaldehydes are formed[151]:

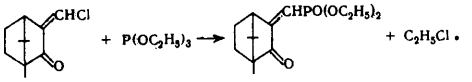
$$RCOCH{=}\overset{+}{N}H(CH_3)_2 + \overline{O}COCH_3 \rightarrow RCOCH{=}CHOCOCH_3 \xrightarrow{CH_3COOH} \rightarrow RCOCH_2CH(OCOCH_3)_2.$$

5. *P*-Ketovinylation

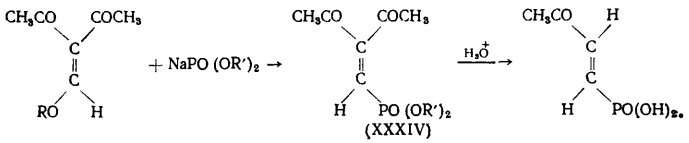
Ketovinylation of a phosphorus–carbonylvinyl group bond has been investigated extremely little and its possibility in principle has been demonstrated in only a few instances. In 1959 Kreutzkamp and Schindler[255] found that β-chlorovinyl methyl ketone undergoes the Michaelis–Arbuzov reaction with tributyl phosphite, forming dibutyl β-acetylvinylphosphonate:

$$CH_3COCH{=}CHCl + P(OC_4H_9)_3 \rightarrow CH_3COCH{=}CH{-}PO(OC_4H_9)_2 + C_4H_9Cl.$$

They showed further that chloromethylenecamphor[256] reacts likewise:



A similar phosphonic acid derivative (XXXIV) was obtained also with β-alkoxyvinyl diketone, subsequent treatment with the acid (XXXIV) leading to the formation of β-acetylvinylphosphonic acid[255,257]:



(XXXIV)

Nifant'ev et al.[258] suggested the reaction with triphenylphosphine for the identification of β-chlorovinyl methyl ketone. The structure of a phosphonium salt was attributed to the product of this reaction.

6. Ketovinylation at a Halogen Atom

The synthesis of β-chlorovinyl ketones from hydroxymethylene ketones under the action of thionyl chloride may be regarded formally as ketovinylation at a halogen atom. The chlorine atoms in β-chlorovinyl ketones are replaced by other halogens on reaction with iodide and fluoride ions. Since these ions are insufficiently nucleophilic in proton-containing media (particularly the fluoride ion!), the exchange of chlorine is carried out in aprotic dipolar solvents. Kochetkov showed[224] that the exchange with sodium iodide takes place fairly smoothly in acetone with formation of alkyl β-iodovinyl ketones. Subsequently it was shown by infrared and proton spin resonance spectroscopy that in this case the initial *trans*-configuration is retained[173]: *trans*-AlkCOCH=CHCl+I^- → AlkCOCH=CHI-*trans*. The exchange of chlorine for fluorine atoms has been recently achieved in α-methyl-substituted β-chlorovinyl phenyl ketone. Dimethylformamide was used as the solvent:

$$C_6H_5COC(CH_3){=}CHCl + F^- \xrightarrow{DMFA} C_6H_5CO(CH_3)C{=}CHF.$$

β-Bromovinyl ketones were not obtained by the exchange reaction, but their synthesis was achieved by another ketovinylation procedure—using ethynyl ketones[125,158,214]. Bowden et al.[125,158] obtained these compounds by the addition of hydrogen bromide to the triple bond of ethynyl ketones. β-Chlorovinyl ketones can be obtained similarly[215].

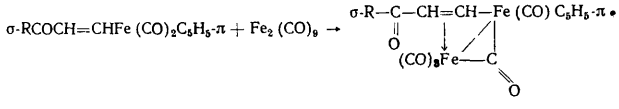
7. *Fe*-Ketovinylation

The ketovinylation of anions containing metals is of considerable interest. Complex anions of transition metals may be sufficiently nucleophilic among these.

In order to synthesise organoiron compounds containing the carbonylvinyl group linked by a σ bond to the iron atom, a study was made of the ketovinylation of the anion $[Fe(CO)_2C_5H_5\text{-}\pi]^-$.[259] Since according to Dessy's data[260] the nucleophilicity of this anion is close to that of the thiophenate ion, β-chlorovinyl ketones, which are known to react smoothly with thiophenate ions[213,214] were chosen as the ketovinylating agents:

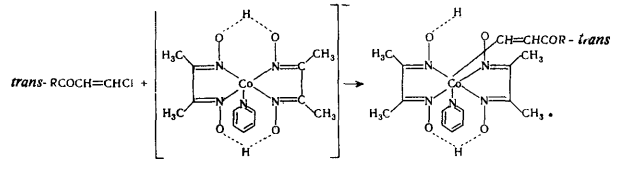
$$RCOCH{=}CHCl + Na^+[Fe(CO)_2C_5H_5]^- \rightarrow \sigma\text{-}RCOCH{=}CH{-}Fe(CO)_2C_5H_5\text{-}\pi .$$

The resulting complexes σ-RCOCH=CHFe=$(CO)_2C_5H_5$-π proved to be interesting objects for the investigation of the synthesis of mixed σ–π complexes with Fe–Fe bonds. The latter are formed when σ-RCOCH=CHFe$(CO)_2C_5H_5$-π reacts with iron nonacarbonyl[261]:



8. *Co*-Ketovinylation

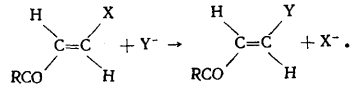
A complex anion of a fundamentally different type—pyridinatocobaloxime—was used to synthesise σ complexes with carbonylvinyl–cobalt bonds. Since the stability of this ion in water is evidence of its relatively low basicity, β-chlorovinyl ketones were chosen as ketovinylating agents[262]:



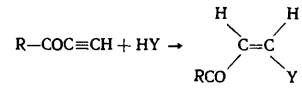
As for the ion $[Fe(CO)_2C_5H_5\text{-}\pi]^-$, it was found that the configuration is retained on substitution in the *trans*-series. It is interesting to note that the Co–CH=CHCOR bond in these complexes readily dissociates under the action of halogens. When the complexes are treated with iodine, *trans*-β-iodovinyl phenyl ketone and the corresponding complex with a Co–I bond are formed. Since the initial σ-(β-benzoylvinyl)pyridinatocobaloxime also had the *trans*-configuration, it was suggested that in this type of dissociation of the carbonylvinyl–cobalt bond the configuration is preserved.

III. CHOICE OF β-KETOVINYLATING AGENT

It follows from the studies reviewed that the correct choice of reagents is important for successful β-ketovinylation. The choice of the ketovinylating agent is determined mainly by the chemical and steric structure of the αβ-unsaturated ketone obtained, the nature of the attacking nucleophilic agent, and the possibility of a particular reaction mechanism. For example, in the synthesis of β-substituted vinyl ketones of the *trans*-series, the first β-ketovinylation method is used, i.e. the nucleophilic substitution reaction with the compounds *trans*-RCOCH=CHX, since it has been demonstrated in numerous instances[32,33,66,150,221,259] that the geometrical configuration is preserved on substitution:



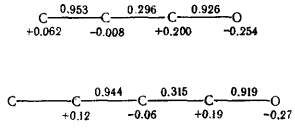
On the other hand in the synthesis of *cis*-isomers one uses as a rule nucleophilic addition to ethynyl ketones (second ketovinylation method), which leads to a *trans*-adduct[125,214,215]:



It is noteworthy that the first method is in principle suitable also for the synthesis of *cis*-isomers[211,215], but ketovinylating agents such as *cis*-β-chlorovinyl ketones are difficult to obtain and are usually synthesised by the addition of hydrogen halides to ethynyl ketones. Various β-substituted vinyl ketones, such as β-chloro- and β-amino-vinyl ketones and β-acylvinyltrialkylammonium salts, are most often used as ketovinylating agents, since nucleophilic addition to the triple bonds of ethynyl ketones does not allow the synthesis of, for example, compounds of the type RCOCR′=CHR″ or RCOCR′=CR″R‴. Furthermore, it is important to note that ethynyl ketones are themselves difficult to obtain.

In choosing the ketovinylating agent it is essential to take into account the selectivity of nucleophilic agents in relation to the particular electrophilic centre. In αβ-unsaturated carbonyl-containing compounds there are at least two electrophilic centres§: the carbonyl carbon atom and the β-carbon atom of the double bond, the electron density of the former being much lower than at the latter. Calculation of molecular diagrams of αβ-unsaturated ketones[265] by the LCAO MO method shows that the partial charge on the carbonyl carbon atom greatly exceeds the positive charge on the carbon atom of the double bond.

Molecular diagrams of the αβ-unsaturated oxo-compounds[265]

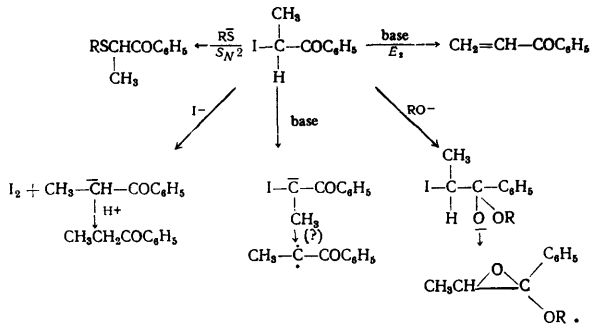


The numerals over the bonds indicate the bond orders and those over the atoms the charges. This calculation is evidently consistent with the empirical rule of vinylogy.

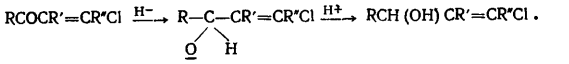
The study of nucleophilic reactivity has shown that nucleophilic agents are selective in relation to an electrophilic centre of a particular type and in the presence of several electrophilic centres in the same molecule various sites of nucleophilic attack are possible depending on the nature of the nucleophilic agent[266,267]. As an illustration,

§ It is also necessary to bear in mind a third possibility: the attack by the nucleophilic agent on the α-carbon atom. However, this probably occurs with much greater difficulty in the case of αβ-unsaturated ketones. For example, Kursanov and Parnes[263] showed that αβ-unsaturated ketones $ArCO\underset{\alpha}{C}H{=}\underset{\beta}{C}H{-}\underset{\gamma}{C}\lesssim$ without hydrogen atoms at the C_γ atom do not undergo hydrogen exchange under the action of bases. Miller and Lee[264] arrived at a similar conclusion concerning the derivatives of αβ-unsaturated carboxylic acids.

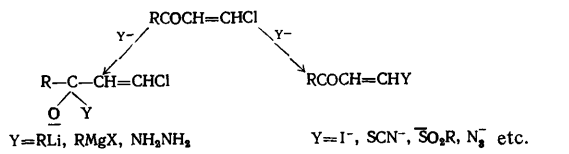
we may examine the interaction of α-halogeno-ketones with various nucleophilic agents[266]:



On the basis of numerous experimental facts, investigators concluded that nucleophilic agents which are at the same time strong bases tend to interact with electrophilic centres having a reduced electron density (for example the carbon atom of C=O group). On the other hand, large readily polarisable anions, which are as a rule weak bases, react preferentially with electrophilic centres having a higher electron density. Jencks and Carriuollo[268] found that, in relation to reactions with a carbonyl carbon atom, the reactivity series of nucleophilic agents is the same as their basicity series. On the other hand, for aliphatic and aromatic electrophilic centres, the reactivity series depends both on the polarisability and on the basicity of the nucleophilic agent and to a greater extent on the polarisability[269]¶. Consequently the presence of two electrophilic centres in the molecules of $\alpha\beta$-unsaturated ketones gives rise to problems of the choice of the ketovinylating agent as a function of the nature of the nucleophilic agent employed. Indeed, the review of all the experimental data concerning the ketovinylation reaction showed that, for example, in the case of β-chlorovinyl ketones there is a distinct tendency for all nucleophilic agents to be classified into two groups. Nucleophilic agents which are very strong bases (RLi, RMgX, NH_2NH_2) react mainly at the carbonyl group (1,2-addition). It is interesting to note that the hydride hydrogen from $LiAlH_4$, $NaBH_4$, and $Al(iso\text{-}OC_3H_7)_3$, which is a very powerful nucleophilic agent, also reacts at the carbonyl group with formation of the corresponding carbinols[163,185,270-272]:



Therefore, with rare exceptions, β-chlorovinyl ketones cannot be used for the ketovinylation of the hydride ion. On the other hand, nucleophilic agents such as the readily polarisable ions RS^-, I^-, SCN^-, N_3^-, $\bar{S}O_2R$, etc., which are weak bases, attack β-chlorovinyl ketones at the β-carbon atom of the double bond. This leads to substitution products (ketovinylation reaction). Hydroxylamine occupies an intermediate position between these two groups, since it reacts in both ways simultaneously:

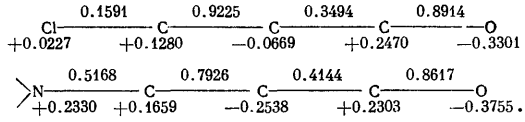


¶ The polarisability and basicity are known not to vary in parallel[269].

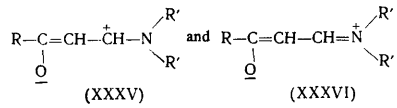
Instead of the sparingly water-soluble β-chlorovinyl ketones, it is very convenient to employ quaternary ammonium salts obtained from them for the ketovinylation of nucleophilic agents of the second type (SO_3^{2-}, CN^-, SO_2R, NO_2^-, CH_3COO^-, etc.). The high electrophilicity of the double bond and solubility in water make these ketovinylating agents very suitable for reactions with anions[34]. In addition, it is important to note that, when quaternary ammonium salts are used, it is possible to achieve the ketovinylation of CN^-,[66] NO_2^-,[150,212] SO_3^{2-},[22] and CH_3COO^-[151] ions, whereas β-chlorovinyl ketones proved to be altogether unsuitable in these cases.

The development of ketovinylation methods made possible the successful application of nucleophilic agents of the first type (RLi, RMgX, NH_2NH_2). It was found that β-dialkylaminovinyl ketones can be usefully employed in reactions with these nucleophilic agents. As a result of the replacement of the chlorine atom by the dimethylamino-group, only powerful nucleophilic agents react with β-dimethylaminovinyl ketones and only at the β-carbon atom of the double bond. In order to account for this sharp change in the properties of the molecule, the following arguments may be put forward. The unshared electron pair of the nitrogen atom very markedly suppresses the electrophilicity of the carbonyl carbon atom. The molecular diagram† of β-aminovinyl ketone shows that the positive charge on the nitrogen atom is larger than the charge on the carbonyl carbon atom.

Molecular diagrams of β-chloro- and β-amino-vinyl ketones

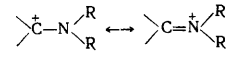


Furthermore, the carbon atom adjacent to the nitrogen also has a large positive charge. Thus structures (XXXV) and (XXXVI) make a considerable contribution to the resonance hybrid of β-aminovinyl ketone, i.e. the groups

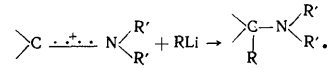


(XXXV) (XXXVI)

characteristic of immonium salts,



are present. In immonium salts the carbon atom adjacent to the nitrogen is attacked by the carbanions derived from RLi and RMgX:[275]



† The molecular diagrams of β-chloro- and β-aminovinyl ketones were calculated by N. P. Gambaryan and A. V. Tutkevich by the LCAO-MO method. The following parameters were used in the calculation: $\alpha_O = \alpha + 1.2\beta$, $\alpha_N = \alpha + \beta$, $\beta_{C=O} = 2\beta$, and $\beta_{CN} = 0.9\beta$;[273] $\alpha_{Cl} = \alpha + 2\beta$ and $\beta_{C-Cl} = 0.4\beta$.[274]

On the other hand, comparison of the molecular diagrams of β-amino- and β-chloro-vinyl ketones shows that the bond order in the C=O group in β-aminovinyl ketones is lower than in the carbonyl group of β-chlorovinyl ketones. Consequently the capacity of the C=O group to undergo addition reactions is much lower in the case of β-aminovinyl ketones. These considerations explain the mode of attack by nucleophilic agents.

It is also clear why β-aminovinyl ketones are passive in relation to weak nucleophilic agents. Indeed, the attack by the nucleophilic agent (Y^-) on the double bond of β-amino- and β-chloro-vinyl ketones leads to the formation of the carbanions RCOĈHCHXY [where X = Cl or $N(CH_3)_2$], in which the electron pairs of the hetero atom X are not conjugated. According to calculation, the gain in conjugation energy in the amino-derivative is higher by 0.42β than in β-chlorovinyl ketones.

Finally, in choosing the ketovinylating agent one should also take into account the possible reaction mechanism. In Section IV, the question of the possible ketovinylation mechanisms will be discussed separately.

IV. STEREOCHEMISTRY AND MECHANISM OF REACTION

The first systematic studies on and the interest in ketovinylation reactions arose in connection with the attempt by Nesmeyanov and coworkers to elucidate nucleophilic substitution at the olefin carbon atom after Nesmeyanov and Borisov[276-278] formulated the rule concerning the retention of configuration in electrophilic and homolytic substitution at an unsaturated reaction centre.

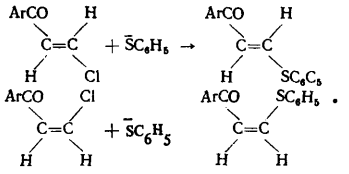
However, the difficulties encountered in the attempt to isolate pure *cis*- and *trans*-isomers of β-substituted vinyl ketones and at the same time the lack of reliable methods for the determination of their configuration directed these studies into the synthetic field.

The mechanism of ketovinylation reactions has so far been little investigated. It has been established in a number of instances that these reactions are bimolecular. Kudryavtseva et al.[279,280] found that the reactions of *trans*-β-chlorovinyl ketones with sodium ethoxide in alcohol are of the second order. However, the stereochemistry of ketovinylation could not be investigated in this model reaction, since the process does not stop at the first stage, a further alcohol molecule adding to the double bond. The kinetics of the reaction of nitrovinyl phenyl ketone with methanol have been studied: one of the pathways in this reaction constitutes ketovinylation[28].

Marchetti and Passalacque[282] found that the reaction of *trans*-β-arylaminovinyl phenyl ketones with pyrrolidine is also a second-order process. It was noted that the configuration is retained during ketovinylation, but this study is likewise restricted to the *trans*-series only.

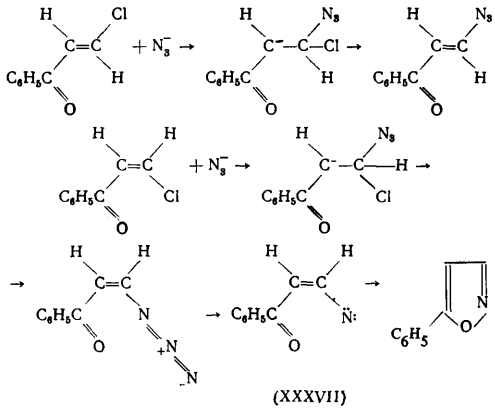
The conclusion that the configuration is retained on substitution in the *trans*-series was based on numerous examples of ketovinylation of nucleophilic agents such as, for example, ferrocenyl-lithium, sodium cyclopentadienide, alkali metal cyanides, potassium phthalimide, sodium nitrite, sulphite, sulphide, and benzenesulphinate, salts containing the complex anions $[Fe(CO)_2C_5H_5\text{-}\pi]^-$ or pyridinatocobaloxime, etc.

However, the stereochemical result of the reaction in the case of both *cis*- and *trans*-isomers has in fact been studied only in two instances—the ketovinylation of thiophenoxide and azide ions. Landini and Montanary showed in a brief communication[215] that aryl *cis*- and *trans*-β-chlorovinyl ketones react with the thiophenoxide ion, the geometrical configuration being mainly retained:



The stereochemistry of the ketovinylation of the azide ion was studied in greater detail. Nesmeyanov and Rybinskaya found that the stereochemical result of the reaction with the azide ion depends on the nature of the substituent X in the compound $C_6H_5COCH{=}CHX$. Thus *trans*-β-chlorovinyl phenyl ketone reacts with sodium azide in aqueous alcohol with formation of *trans*-β-azidovinyl phenyl ketones[283,284]. Other aryl *trans*-β-chlorovinyl ketones and *trans*-β-acylvinyltrimethylammonium quaternary salts react similarly[283]. In the reaction of *cis*-β-chlorovinyl phenyl ketone with sodium azide, 5-phenylisoxazole was isolated as the main product instead of the expected β-azidovinyl phenyl ketone. The formation of this product is regarded as the result of the spontaneous decomposition of the intermediate *cis*-β-azidovinyl phenyl ketone, which, probably as the result of the nearness of the carbonyl and azide groups, is probably converted with evolution of nitrogen into the nitrene species (XXXVII) having the *cis*-configuration. This species is most likely to be stabilised by the reaction of the nucleophilic oxygen atom of the carbonyl group with the electrophilic centre—the nitrene nitrogen:

Scheme 1



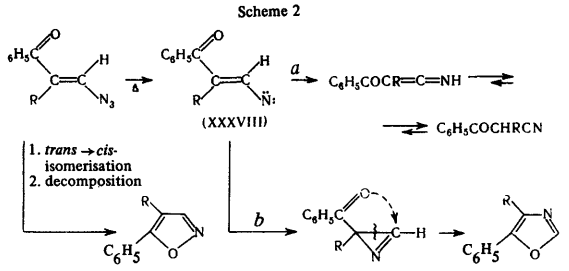
(XXXVII)

In this connection it is interesting to note that benzoisoxazole was obtained from 2-azidobenzophenone, which is known to be a "*cis*-compound"[285].

The configuration of *trans*-β-azidovinyl phenyl ketone was confirmed by spectroscopic and chemical correlation methods[284]. It was found that, when this compound is decomposed by heating in DPA solution, the product is mainly benzoylacetonitrile, 5-phenyloxazole also being isolated in a low yield. Its isomer, 5-phenylisoxazole, was detected only in trace amounts[286]. It may be supposed that the decomposition of *trans*-β-azidovinyl phenyl ketone involves

the formation of the nitrene species (XXXVIII), which has the *trans*-configuration, in contrast to (XXXVII):

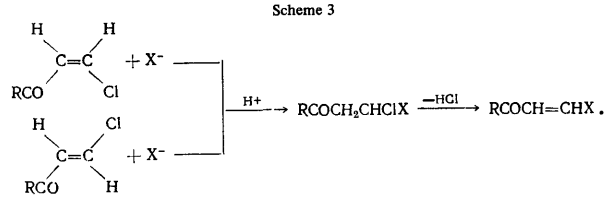
Scheme 2



This species may be stabilised either by rearrangement to the imine of benzoylketen, which is a tautomeric form of benzoylacetonitrile (branch *a* of Scheme 2) or by the formation of the azirine ring, which is known to form readily in the thermolysis of certain vinyl azides[287,288]. The subsequent dissociation of the bond (previously the double bond) with ring closure, as shown in Scheme 2 (branch *b*), leads to the corresponding oxazole. The traces of 5-phenylisoxazole are probably formed as the result of a possible *trans*-*cis*-isomerisation (branch *c*). Consequently the products of the decomposition and subsequent rearrangement differ significantly for *cis*- and *trans*-β-azidovinyl phenyl ketones, which makes it possible to establish the configuration of the products of the ketovinylation of the azide ion. Investigation showed that the ketovinylation of the azide ion with *cis*- and *trans*-β-chlorovinyl phenyl ketones takes place mainly with the retention of the initial geometrical configuration, although it should be noted that in the case of the *cis*-isomer an admixture of *trans*-β-azidovinyl phenyl ketone was isolated as an impurity together with the main product—5-phenylisoxazole.

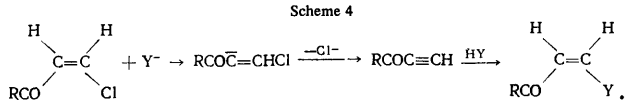
The observed stereochemical results are most consistent with the direct nucleophilic substitution mechanism shown in Scheme 1. The alternative addition—elimination mechanism (Scheme 3), in which the stereochemical result of the reaction should be independent of the configuration of the initial ethylenes, must be rejected on the basis of these results.

Scheme 3

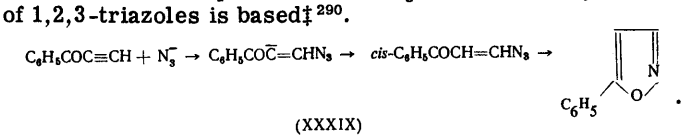


However, it is known that the preferential retention of the initial geometrical configuration in the reaction of the *cis*-isomer is not by itself evidence of the direct nucleophilic substitution mechanism being the only one possible, since the same stereochemical results may be obtained also in the elimination–addition mechanism (Scheme 4).

Scheme 4

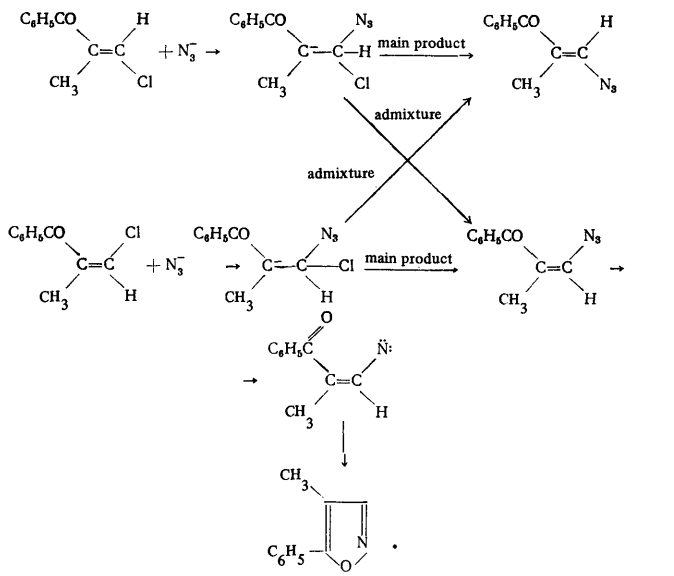


Indeed, on addition of HN_3 to ethynyl ketones at low pH in aqueous solution, 5-phenylisoxazole was obtained[289]. In this connection it is interesting to note that the behaviour of ethynyl ketones in relation to HN_3 differs from the usual reactions of the triple bond with HN_3 on which the synthesis of 1,2,3-triazoles is based‡[290].

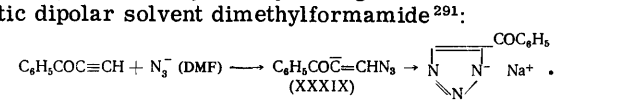


(XXXIX)

In order to exclude the possibility of the elimination–addition mechanism, the stereochemistry of the ketovinylation of the azide ions with both *cis*- and *trans*-α-methyl-substituted β-chlorovinyl phenyl ketones was studied. Since such compounds are much less reactive than the β-chlorovinyl ketones unsubstituted at the carbon atoms of the double bond, dimethylformamide, the nucleophilicity of anions in which is greatly enhanced, was employed as the solvent. Then *trans*-β-chloro-α-methylvinyl phenyl ketone reacted with the N_3^- ion very readily and *trans*-β-azido-α-methylvinyl phenyl ketone was isolated from the nitrogen-containing products. 4-Methyl-5-phenylisoxazole was isolated as an impurity. At the same time, the *cis*-isomer reacted more slowly under the same conditions and 4-methyl-5-phenylisoxazole was isolated from the reaction mixture as the main product; *trans*-β-azido-α-methylvinyl phenyl ketone was isolated as an impurity. Thus, although the elimination–addition mechanism is impossible in such cases (α-hydrogen atoms are absent from the starting materials), substitution products were obtained from both isomers and mainly with retention of the geometrical configuration.



‡ The synthesis of 4-acyl-1,2,3-triazoles on the basis of ethynyl ketones and sodium azide was developed by Nesmeyanov and Rybinskaya using as the medium the aprotic dipolar solvent dimethylformamide[291]:



The sharp difference in the behaviour of ethynyl ketones in relation to azide ions in a proton-containing medium and in dimethylformamide was attributed to different conditions of the stabilisation of the intermediate carbanion (XXXIX), which is very rapidly protonated in the first case with formation of *cis*-β-azidovinyl phenyl ketone (subsequently converted into 5-phenylisoxazole). In dimethylformamide this carbanion can be stabilised only by dipolar cyclisation, which leads to the formation of the stable anion of 4-acyl-1,2,3-triazole.

This shows that in the case considered the direct nucleophilic substitution mechanism probably operates. Recent kinetic data[300] also confirmed this mechanism.

It is interesting to note that, in contrast to unsubstituted *trans*-β-azidovinyl phenyl ketone, the *trans*-β-azido-α-methylvinyl phenyl ketone obtained decomposes on heating with formation of 4-methyl-5-phenyloxazole as the main product and the corresponding benzoylacetonitrile is obtained as an impurity (Scheme 2, branch *b*)[286]. Probably the stabilisation of the nitrene species is influenced not only by stereochemical factors but also by electronic factors. The appearance of the electron-donor CH_3 group adjacent to the double bond facilitates the interaction of the electrophilic nitrene nitrogen atom with the carbon atom of the ethylene bond, which results in the formation of the azirine ring. The conversion of acylazirines into oxazole rings has already been discussed (see p. 449).

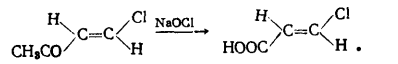
It was found that the stereochemical result of the nucleophilic substitution at the double bond depends on the nature of the group eliminated[292]. In relation to the ketovinylation of the azide ion in proton containing media, the compounds $C_6H_5COCH{=}CHX$ can be divided into several groups.

Compounds of group I, where X = Cl§, Br, $\overset{+}{N}(CH_3)_2$, or NO_2, react with formation of a substitution product, the initial geometrical configuration being largely retained. Compounds where X = $SO_2C_6H_5$ (intermediate group) react with azide ions also forming a substitution product, but in this case the same mixture of substitution products, containing mainly the thermodynamically more stable *trans*-isomer, was obtained regardless of the initial configuration of the substrate. Finally, the reaction of compounds having X = CN or SO_3^- (group II) with the N_3^- ion yielded 4-benzoyl-1,2,3-triazole instead of the substitution product regardless of the initial configuration. As the compounds of both groups contain both powerful [NH_2 and $(CH_3)_3N^+$ in group I and CN in group II] and weak (Cl and Br in group I and SO_3^- in group II) electron acceptors, these observations could not be explained by any electronic effects in the initial molecules. The reasons for the differences in the behaviour of the compounds $C_6H_5COCH{=}CHX$ may be due to the different rates of heterolysis of the C–X bond in the intermediate carbanion $C_6H_5\bar{C}OCH{-}CHXN_3$. If the heterolysis of the C–X bond in this carbanion is fast (group I), or is almost simultaneous with the formation of a new C–N_3 bond, a substitution product with retention on the initial configuration is formed. If the heterolysis of the C–X bond is slower (the intermediate case with X = $SO_2C_6H_5$), the lifetime of such a carbanion is longer and consequently there appears the possibility of free rotation about the single bond in the carbanion. Then of course the thermodynamically more stable substitution product, i.e. *trans*-β-azidovinyl phenyl ketone, is formed with both the *cis*- and *trans*-isomers. Finally, if the heterolysis of the C–X bond is altogether slow, the lifetime of the intermediate carbanion is fairly long and, as a result, there is sufficient time for dipolar cyclisation to occur, i.e. substitution is complicated by cyclisation. This leads to the formation of the triazoline anion, which is converted into the stable heterocyclic 1,2,3-triazole system with elimination of the X^- anion. This classification of eliminated groups in terms of the rate of heterolysis of the C–X bond in the intermediate carbanion into readily and slowly eliminated is supported by the following experimental data. In fact, the chloro- and nitro-groups in β-chloro- or β-nitro-vinyl ketones are substituted by the methoxide anion¶ so fast that it is possible to isolate only the substitution product, while in the case of β-cyanovinyl phenyl ketone the isolation of the addition product $C_6H_5COCH_2CHCN(OCH_3)$ presents no difficulty[294].

V. SYNTHESIS OF GEOMETRICAL ISOMERS OF β-CHLOROVINYL KETONES AND DETERMINATION OF THEIR CONFIGURATION AND CONFORMATION

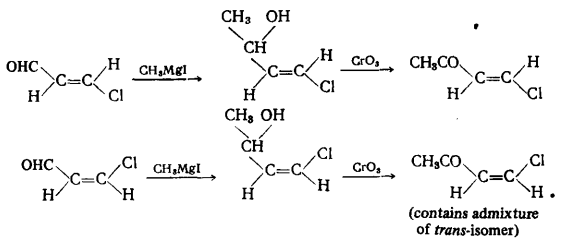
The principal information about the mechanism of nucleophilic substitution at the double bond comes from stereochemical studies. Such data can of course be reliable only if the geometrical configuration of the starting materials and reaction products has been correctly established.

Depending on the method of synthesis, β-chlorovinyl ketones with a definite configuration are obtained as a rule. These methods have been discussed in detail in reviews[1,5-8] and here we shall consider only some of them. The problem of the configuration of β-chlorovinyl ketones obtained by the addition of acid chlorides to acetylene in the presence of aluminium chloride was considered for the first time by Kochetkov et al.[295] It was found that the compounds thus obtained belong to the *trans*-series, since the oxidation of β-chlorovinyl methyl ketone with sodium hypochlorite yielded *trans*-β-chloroacrylic acid:



A detailed study of the infrared[10,173], ultraviolet[173], and nuclear magnetic resonance[173] spectra showed that all β-chlorovinyl ketones obtained in this way belong to the *trans*-series.

Skoldinov et al.[17] developed another version of the synthesis of β-chlorovinyl ketones, whereby both *trans*- and *cis*-isomers can be prepared:



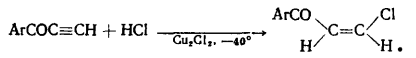
The configuration of the reaction products was established very convincingly by infrared and nuclear magnetic resonance spectroscopy[17,296] and by chemical correlations. However, it was impossible to obtain pure *cis*-β-chlorovinyl methyl ketone by this procedure. According to NMR spectra, the reaction product in this case contained about 30% of the *trans*-isomer[296].

The determination of the configuration of alkyl β-chlorovinyl ketones usually does not present special difficulties. The most important information in these cases was obtained with the aid of infrared and NMR spectra and by chemical correlations. However, Nesmeyanov et al.[259] showed that NMR spectra of aryl β-chlorovinyl ketones of the *trans*-series, susceptible to interpretation, could be

§ Reactions of both *cis*- and *trans*-isomers were investigated with X = Cl.

¶ Both carbon atoms of the ethylene bond in β-nitrovinyl ketones react with $\bar{O}CH_3$. Here we are considering only the attack by $\bar{O}CH_3$ on the β-carbon atom. The problem of the mode of addition of nucleophilic agents to the system XCH=CHY was examined by Nesmeyanov et al.[293]

obtained only with a 100 MHz instrument, since the characteristic AB quartet of the protons at the double bond is partially overlapped by signals due to the protons of the aromatic ring. Aryl *cis*-β-chlorovinyl ketones were obtained by the addition of hydrogen chlorides to aryl ethynyl ketones in the presence of copper(I) chloride[215]:



Their configuration was established by the absence of absorption in their spectra at 930–940 cm^{-1} and on the basis of NMR spectra[284]. In this case the interpretation of the NMR spectrum was extremely simple.

The study of the properties of the *cis*- and *trans*-isomers of aryl β-chlorovinyl ketones[215,284] showed that the *trans*-form is thermodynamically more stable, while the *cis*-isomers are extremely labile and are readily converted into *trans*-isomers under the action of hydrogen chloride even at room temperature. Therefore in their synthesis from ethynyl ketones and hydrogen chloride it is necessary to employ an exactly calculated amount of hydrogen chloride and the reaction temperature should not exceed −40°C. It is noteworthy that *cis*-β-chlorovinyl methyl ketone also proved to be less stable than the *trans*-isomer[17]. The lower stability of the *cis*-isomers can probably be accounted for by the steric interaction between the RCO and Cl groups located close together, in which dipole–dipole repulsion may play a major role[17]. *trans*-β-Chloro-α-methylvinyl phenyl ketone was synthesised using the Claisen method by the formulation of propiophenone with subsequent treatment of the intermediate β-hydroxy-α-methylvinyl phenyl ketone with thionyl chloride in benzene[284].

According to thin-layer chromatographic and NMR spectroscopic data, the product of this reaction contained an insignificant amount (about 5%) of the *cis*-isomer. The content of the *cis*-isomer may be increased by keeping an ethereal solution of *trans*-β-chloro-α-methylvinyl phenyl ketone in diffuse sunlight. The pure *cis*-isomer was isolated from the mixture by means of preparative thin-layer chromatography. However, the most convenient method for the separation of the isomer proved to be a chemical procedure based on the fact that the *trans*-isomer reacts with sodium sulphite in dimethylformamide much faster than the *cis*-isomer[34]. The configuration of α-methyl-substituted β-chlorovinyl phenyl ketones was established on the basis of NMR spectroscopic data and chemical correlations[284], since neither infrared nor ultraviolet spectra provided adequate information.

Conformational analysis of β-chlorovinyl ketones has been carried in a very limited number of cases. For a simpler model, for example acrolein, it has been shown that the transoid conformation is more stable by approximately 2 kcal $mole^{-1}$ than the cisoid conformation[297]. However, in other αβ-unsaturated carbonyl compounds the relative stabilities of S-*cis*- and S-*trans*-forms are strongly influenced by the dimensions and nature of the substituents. The solvent probably also plays a significant role. One may suppose *a priori* that resonance stabilisation with participation of canonical structures of the type $\overset{+}{Cl}=C-C=C-\bar{O}$ plays an appreciable role in β-chlorovinyl ketones[298]. Benson and Pohland[173], who investigated the infrared and ultraviolet spectra of alkyl *trans*-β-chlorovinyl ketones, attributed the transoid conformation to these compounds. In the study of the infrared and quadrupole resonance spectra of *trans*-β-chlorovinyl methyl ketone and its deuterated derivatives on instruments with a high resolving power, Dabrowski and Terpiński[299] concluded that *trans*-β-chlorovinyl methyl ketone exists in both conformations, S-*cis* and S-*trans*, and that the equilibrium S-*cis* ⇌ S-*trans* is displaced to the right in more polar solvents (CH_3CN, CH_3OH) and conversely to the left in non-polar solvents (carbon tetrachloride, hydrocarbons). This problem has also been discussed by Shapet'ko et al.[296] In the conformational analysis of the *cis*- and *trans*-isomers of β-chloroacrolein and β-chlorovinyl methyl ketone they used the nuclear magnetic resonance spectra of carbon tetrachloride solutions. For comparison, a study was made of the spectra of malonic and methylmalonic dialdehydes, which form cyclic enolic forms and consequently have the cisoid conformation. Analysis of the changes in the chemical shifts of the individual protons in the isomeric transition from the *cis*- to the *trans*-configuration is evidence, according to the authors[296], in favour of the cisoid conformation of both isomers of β-chlorovinyl methyl ketone. Unfortunately, in this case the effect of solvents on conformation was not studied specially, so that the data obtained cannot be fully compared with those of Dybrowski and Terpiński[299], but it should be noted that both groups of investigators concluded that the conformation of *trans*-β-chlorovinyl methyl ketone in carbon tetrachloride solution is predominantly cisoid. This is probably because in a non-polar solvent there is a possibility of direct interaction in the molecule (via the field) of oxygen and chlorine atoms which have opposite charges.

In conclusion, we may mention the investigation of the conformation of ββ-dichlorovinyl ketones carried out recently by American workers[298].

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