MECHANISMS OF THE DARZENS AND RELATED CONDENSATIONS

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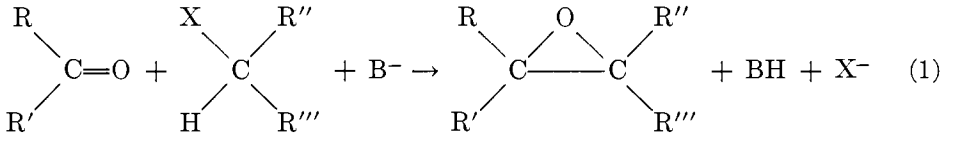
I. INTRODUCTION

A general review on the Darzens condensation has been contributed by Newman and Magerlein (66). This review presents a survey of the facts that are of mechanistic significance, as well as their interpretation in the light of current ideas.

II. OUTSTANDING FEATURES OF THE CONDENSATION

At present, a rather general definition of the Darzens condensation is accepted, including *all the base-catalyzed condensations of carbonyl compounds with halogenomethylene substances yielding, with the separation of halide ion, compounds having oxirane rings formed by the carbonyl and the halogenomethylene carbon atoms*, i.e.:



(1)

The base is used up by the reaction and acts therefore as a third reactant; nevertheless it is also the catalyst for the condensation.

The conditions under which this condensation has been carried out vary considerably. The selected reaction temperatures have been from many degrees

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below zero up to the boiling point of the solvent employed, depending on the nature of the reactants and catalyst. The solvent has been in many cases of the aprotic non-polar type, like anhydrous benzene or anhydrous ethyl ether, but ethyl alcohol and even aqueous dioxane have been used. The selection of the solvent has been determined in many cases by the nature of the condensing agent. For example, when sodium amide is used, anhydrous solvents of the inert type must be employed.

Using the terminology generally accepted for formally similar condensations (see Section III), the carbonyl and the halogenomethylene parts will also be called the A and B components, respectively, of the condensation (35).

As a general rule, the condensation can occur only when the B component has an "activated" hydrogen atom attached to the halogenomethylene carbon atom. Accordingly, besides esters of α-halogeno acids, the condensation can be carried out with amides of these acids (16), with α-halogeno ketones (89), with halogenomethylsulfones (3), and even with some aryl-substituted methyl halides (11, 34). If activation of the hydrogen atom on the halogenated carbon does not occur, the condensation does not take place. Thus, in the reaction of esters of β-halogeno acids with enolizable ketones alkylation reactions occurred, giving esters of δ-keto acids (30, 31).

At least in the condensation with enolizable A components with which a competing alkylation reaction is possible, the most favorable halogen for the B component is chlorine. In fact, in certain conditions, while the esters of the α-chloro acids yield glycidic esters, those of α-iodo acids—and also those of α-bromo acids, although to a lesser extent—give esters of γ-keto acids (30, 31). These results may be ascribed to the greater ease with which bromine or iodine is displaced by an S_N2 mechanism.

It has been shown that a *p*-toluenesulfonate group may be substituted for a halogen atom in the B component (65).

The A component may be an aldehyde or a ketone, the former being, as usual, more active than the latter. Some of the ketones reported to react sluggishly or to be inactive in other carbonyl reactions failed to give the Darzens condensation.

Unsuccessful attempts have been made to perform condensations with Michler's thioketone as an A component. In the cases reported the ethylene corresponding to the expected thiirane was isolated, being formed probably through the latter (11). This result is not surprising in view of the well-known oxidizing character of some epoxides, especially those which may be prepared by a Darzens condensation (14, 22).

As far as the condensing agent is concerned, sodium has been used in addition to sodium ethoxide or sodium amide (see Section V). In the condensations with arylmethyl halides potassium carbonate has been preferred (11), and in those with phenacyl halides sodium hydroxide has been used with excellent results (1, 2, 3). It has been recently reported that sodium *tert*-butoxide gives good results in the condensations with esters of α-halogeno acids (52).

The base employed has been either soluble in the medium, and the reaction

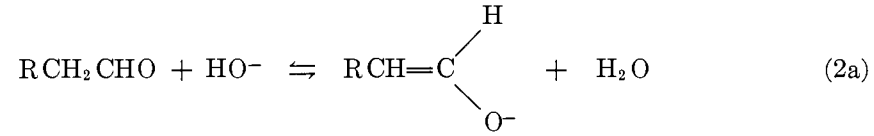
carried out therefore under homogeneous conditions, or insoluble in it, as in the condensations with sodium amide.

III. GENERAL CONSIDERATIONS OF THE MECHANISM

A. Preliminary physical-organic considerations

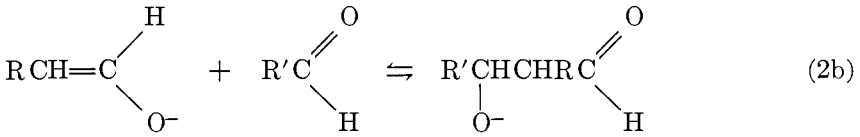
It is generally agreed that aldol and related condensations, like the Perkin, Knoevenagel, or Claisen condensation, proceed by formation of the enolate ion of the B component as a first step (33). The B component has a hydrogen atom (bonded to a carbon atom) whose removal as a proton is favored to a varying extent by structural features such as a carbonyl group in the α-position. The separation of that proton is essential as far as the enolization is concerned.

The anion resulting from the attack of the base on the B component is provided with a strong nucleophilic character, and therefore is much more reactive towards the A component (carbonyl component) than the B component itself. The accepted general mechanism is the following:



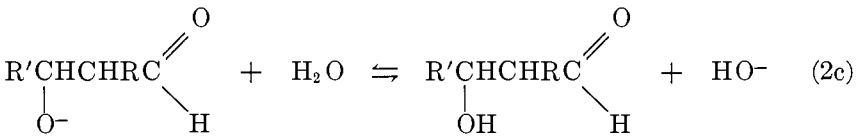
(2a)

B component Enolate ion



(2b)

A component



(2c)

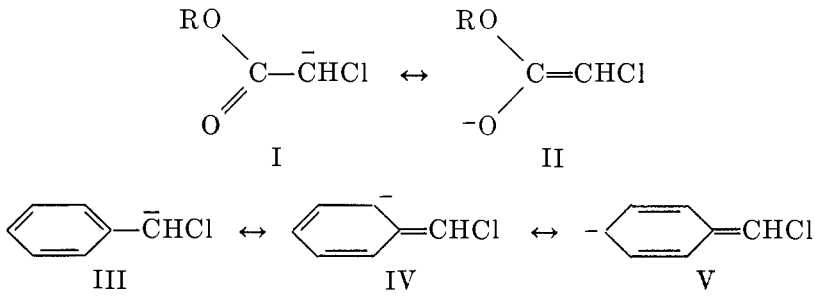
Aldol

The alternative assumption suggested by some authors (20, 86) of a preliminary addition of the base to the A component seems not to be adequate, for it would imply that the reaction takes place between two molecular species of comparatively reduced mutual affinity (48).

All the preceding considerations are fully applicable to the Darzens condensation. It is therefore reasonable to assume that the basic catalyst activates the B component, i.e., the halogenomethylene compound. Besides, the inductive effect of its halogen atom, as has been shown in the haloform reaction (5, 7) and in the halogenation of ketones (9), must facilitate the separation of the proton. Furthermore, it is well known that some of the most remarkable reactions of the α-halogeno ketones (halogenation, the Favorskiĭ reaction, self-condensation) are

base-catalyzed, and so it shows the probability of the preliminary reaction of these halogenomethylene compounds with the base in their condensation reactions.

The anion formed from the B component will presumably owe part of its stability to resonance:



(3)

In the case of phenylmethyl halides the contribution of electronic structures such as IV and V to the resonance will be increased with ring-substitution by electron-attracting groups in the places where the negative charge is located, i.e., in the ortho or para position. Accordingly, in such condensations *p*-nitrobenzyl chloride has been the preferred B component (11). It is doubtful whether the unsubstituted benzyl chloride is able to undergo condensation (55).

It is reasonable to assume that the halogen atom in the anion is more disposed to separate as halide ion than in the unionized B component from which it comes. Therefore, the possibility exists that the anion would reorganize itself with halide-ion separation. This is equivalent to elimination of a molecule of hydrogen halide, both atoms coming from the same carbon, i.e., what has been referred to by Ingold and Jessop as 1,1-elimination (49). Consequently, a so-called "bivalent radical" would be formed. Such radicals were used liberally by Nef in the interpretation of organic reactions around the end of the last century (64), but the disproof of such mechanisms in some cases has led to bivalent radicals falling into general disfavor.

In spite of that, Hine has recently proposed that the singular kinetics of the hydrolysis of chloroform may be ascribed to the formation of a transient bivalent radical, CCl_2, formed through the sequence outlined above (36):

$$Cl_3CH + HO^- \underset{}{\overset{\text{rapid}}{\rightleftharpoons}} Cl_3C^- + H_2O$$

$$Cl_3C^- \xrightarrow{\text{slow}} Cl_2C + Cl^- \qquad (4)$$

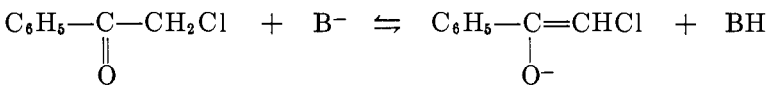
It has been shown that chloroform has a hydrogen atom which can be exchanged with deuterium at a greater rate than that of its hydrolysis (37, 74), consistent with Hine's mechanism. Work still in progress in this laboratory also points out strongly the existence of the carbon dichloride radical. Also, Hughes has recently indicated the existence of both "bivalent carbon" and "enolate ion" sequences in the base-catalyzed reactions of α-halogeno ketones (44, 45).

Therefore, two paths for the Darzens condensation are *a priori* possible. One

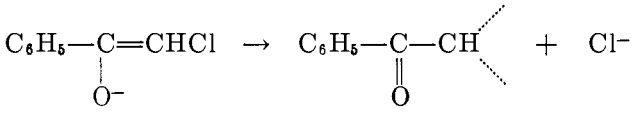
would lead to what may be called the "enolate ion" mechanism and the other to the "bivalent radical" mechanism.

B. The "bivalent radical" mechanism

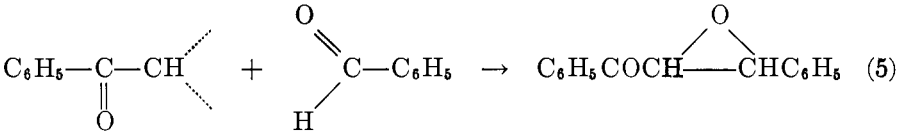
The following sequence is an example of the "bivalent radical" mechanism:



B component Chloroenolate ion

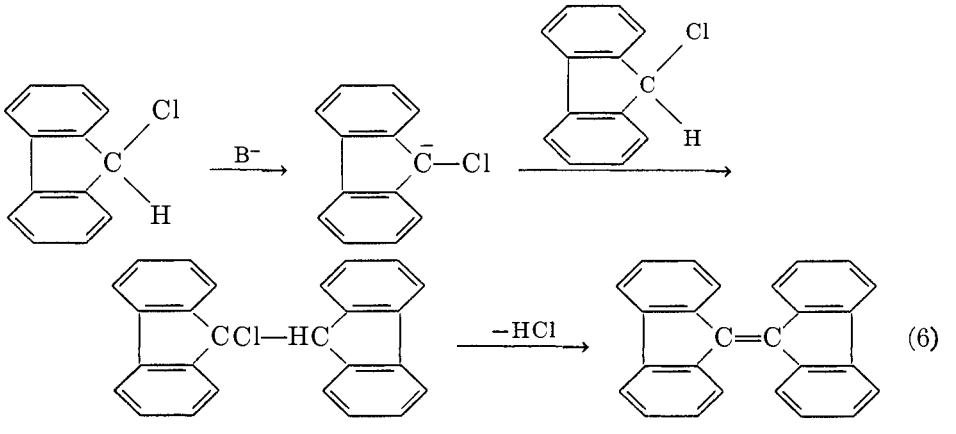


Bivalent radical

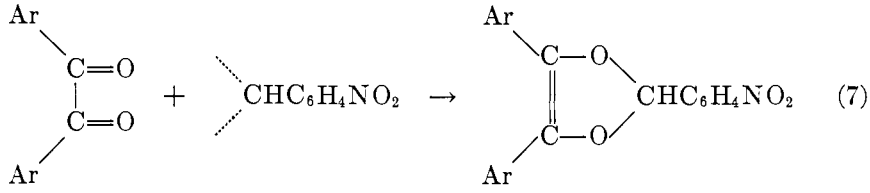


A component Oxirane compound

An essentially identical mechanism had been considered by Bodforss (15) for the condensations of carbonyl compounds with phenacyl halides and was proposed by Bergmann and Hervey (11) for the condensations with arylmethyl halides. According to the latter, these bivalent radicals would be "captured" by the carbonyl compound before having the chance to react with one another to yield symmetrical ethylenes. The formation of such ethylenes, along with the oxirane compound or in the absence of a carbonyl compound, was considered as strong evidence supporting the idea of bivalent radicals. However, as Kleuker pointed out (55), the presence of ethylenes can be explained without resorting to the assumption of such radicals. A substitution reaction followed by elimination of hydrogen halide could account for the facts:

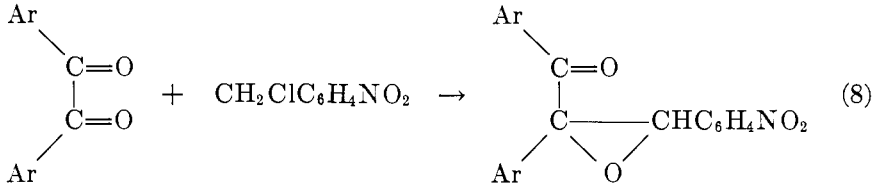


Another piece of evidence for a "bivalent radical" mechanism was afforded by Bergmann and Hervey. The reaction of benzil or phenanthrenequinone with *p*-nitrobenzyl chloride, which occurs, according to these authors, in the following way,



(7)

was shown to be incorrect, for the condensation products were actually keto epoxides, as they should be in a normal Darzens condensation of one molecule of *p*-nitrobenzyl chloride with one molecule of an α-diketone (29):



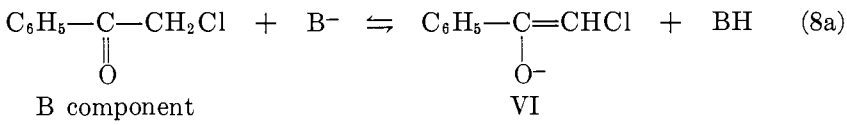
(8)

What happens then in the condensation of a carbonyl compound with chloroform, in which the capacity to yield bivalent radicals upon the attack of a base seems well established? There exists a considerable amount of work on this particular condensation. In all cases, chloroform—and bromoform as well—reacts with aldehydes or ketones to give trichloromethylcarbinols (10, 21, 23, 28, 38, 39, 40, 50, 56, 57, 58, 72, 77, 87, 90), but not to give oxiranes, i.e., as in an aldol condensation. Although these results do not support the "bivalent radical" mechanism they do not rule it out, for there is in this particular case the possibility that the trichloromethyl anion might react with the carbonyl component before undergoing significant decomposition into CCl_2.

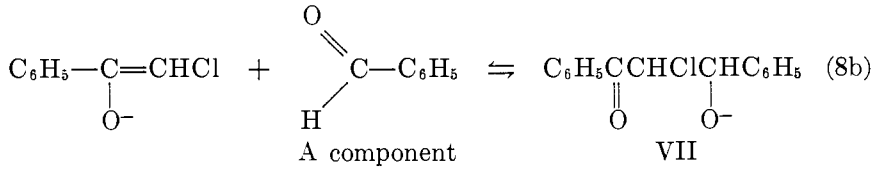
The kinetic data, however (Section IV), do not seem to agree with this mechanism.

C. The "enolate ion" mechanism

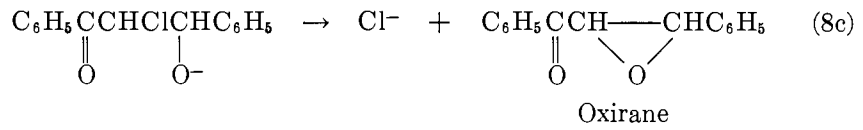
The "enolate ion" mechanism could be written as follows:



B component VI (8a)



A component VII (8b)



(8c)

Oxirane

In the third step (8c) the halogenohydrin anion (VII) would undergo an intramolecular substitution reaction, giving the oxirane compound.

The above sequence is consistent with the current assumption of a halogenohydrin anion as an intermediate in the formation of oxiranes from halogenohydrins (91).

The stereochemical course of oxirane-ring closure from a halogenohydrin shows that Walden inversion takes place at the carbon atom bearing the halogen atom (6). Inversion of configuration is one of the most outstanding characteristics of the reactions taking place through an S_N2 mechanism. The Darzens condensation might therefore be expected to fail to proceed beyond step 8b in cases in which an S_N2 displacement of that halogen would be unfavorable. In fact, in the following cases in which all other requirements for a Darzens condensation to occur are fulfilled, the condensation yields α-halogenohydrins or their metal derivatives.

The condensation of halogenonitromethanes with aldehydes gives 2-halogeno-2-nitroethanols (59). This result should be related to the deactivation observed in substitution reactions of halogen which is attached to a carbon atom bearing a nitro group (69).

Another case is the already mentioned condensation of chloroform with carbonyl compounds. It has been established that accumulation of halogen atoms on a carbon atom leads also to increasing difficulty attending their displacement. For example, methyl chloride is much more easily hydrolyzed than methylene chloride or carbon tetrachloride (36, 42). Chloroform, as Hine has shown (36), is a quite different case, for the removal of a hydrogen atom is the essential first step of its hydrolysis. The mechanism available for the hydrolysis of carbon tetrachloride is not a simple displacement reaction (44).

The deactivation by the nitro group as well as that by halogen atoms has been attributed to the shielding of the backside of the carbon atom on which the substitution takes place (41, 70). However, in the case of the nitro group it could alternatively be explained by assuming an increased difficulty for the separation of halide ion with the pair of electrons of the carbon–halogen bond. The strong "positive" character of the halogen in such halogenonitro compounds is well illustrated by the reaction of the sodium derivative of a malonic ester with 2-bromo-2-nitropropane. The nature of the reaction products can be reasonably explained only by assuming an unusual cleavage of the carbon–bromine bond to yield a carbanion and a bromine cation (83).

α-Halogeno sulfones are known to be rather inert towards S_N2 displacement of halogen (18, 82, 92). Nevertheless, it has been found that chloromethyl *p*-tolyl sulfone condenses easily with benzaldehyde to a very good yield of epoxysulfone (3). This is an example of the fact that reactions often occur intra-

molecularly which would be greatly hindered if they had to occur between two molecules. A study of such internal nucleophilic displacements might throw some light on the nature of the unfavorable influence of some groups in S_N2 reactions.

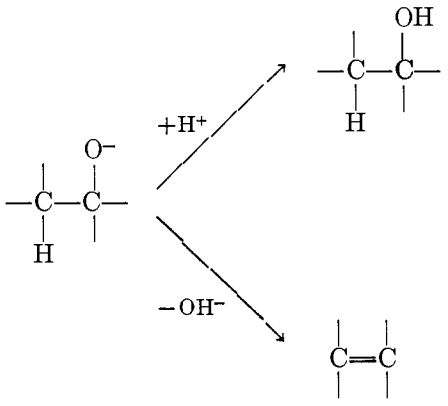
The internal displacement could also be made difficult by partial neutralization of the free negative charge on the oxygen of the intermediate halogenohydrin anion, making it, consequently, less nucleophilic. It has been reported lately that when diisopropylaminomagnesium bromide was used as a condensing agent in the condensation of benzaldehyde with ethyl chloroacetate (or with ethyl α-chloropropionate), a product believed to be $C_6H_5CH(OMgBr)CHCl\text{-}COOC_2H_5$ was obtained (63). This product, upon acid treatment, gave a small yield of the corresponding chlorohydrin. Accordingly, this result has been ascribed to the high covalent character of the oxygen–magnesium bond (63).

When the halogenomethylene group is attached to an aryl, carbethoxyl, or carbonyl group there is no reason to expect difficulty in the formation of the oxirane ring, for it is well known that arylmethyl halides, esters of α-halogeno acids, or α-halogeno ketones have a halogen which is more easily displaced in nucleophilic substitution reactions than is the halogen of alkyl halides (32, 43). However, while aliphatic ketones, such as chloroacetone, react with benzaldehyde to give oxiranes (79, 80, 81), chloroacetone, under rather different but perhaps not too far from equivalent conditions, reacts with formaldehyde to yield only α-chlorohydrins (46).

Therefore, there exists very strong evidence pointing to a mechanism involving a halogenohydrin anion as an intermediate in the Darzens condensation.

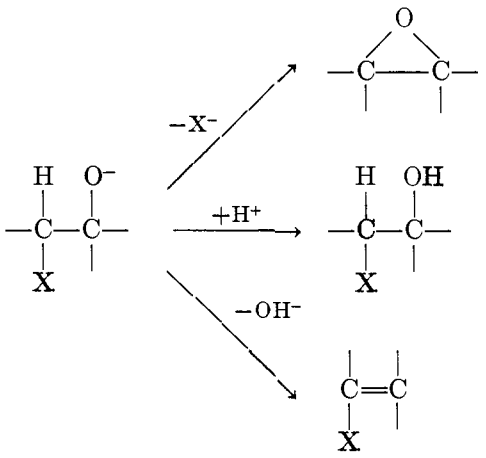
It is assumed that the first two steps (8a and 8b) of the Darzens condensation are fundamentally identical with those of an aldol condensation, i.e., 2a and 2b. As in the aldol condensation the intermediate halogenohydrin anion (VII) may pick up a proton from the medium and give the halogenohydrin. To complete this analogy another reaction, occurring also in the aldol condensation, i.e., elimination of hydroxyl ion from the intermediate (VII) and consequent formation of an ethylene compound, actually occurs in some cases:

Aldol condensation:



(9)

Darzens condensation:



For example, it has been reported that the condensation of benzaldehyde with chloroacetylmesitylene gives 1-chloro-1-mesitoyl-2-phenylethylene as the only identifiable reaction product (51). Also, in the Darzens condensation with esters of α-halogeno acids, halogenoethylenes have been reported as by-products. Thus, Claisen isolated some ethyl α-chlorocinnamate in the condensation of benzaldehyde with ethyl chloroacetate (19). In the light of the "enolate ion" mechanism this would mean of course that in such cases the rate of elimination of hydroxyl ion from VII is comparable with that of formation of the oxirane ring from the same intermediate.

The possibility exists that these halogenoethylenes and the oxiranes were not formed through the same intermediate; nevertheless, considering the evidence given, it appears extremely probable that both the aldol and the Darzens condensation are not only formally but also essentially similar.

IV. THE KINETIC RESULTS

A. The order of the reaction

A desirable feature that a reaction must fulfill to be suitable for a kinetic study is a high yield in the sole reaction product. Unfortunately, such yields are uncommon in the Darzens condensation. Consequently, for that purpose it was necessary to find a homogeneous high-yield reaction. The hydroxyl-ion-catalyzed condensations of phenacyl chloride with benzaldehyde and of *p*-methoxyphenacyl chloride with *p*-nitrobenzaldehyde, in aqueous dioxane, give yields close to the theoretical values. However, the rates of such condensations are usually too high under easily controllable conditions to be measured. The rate of the latter condensation could not be measured at all (1), and the former could be followed at 0°C. only when the initial concentrations of the reactants were around or below 10^{-3} molar (4).

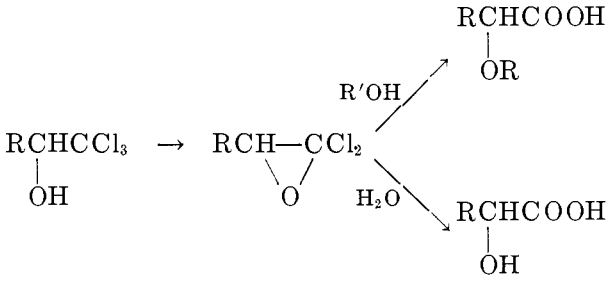
It was found that the condensation of benzaldehyde with phenacyl chloride

is of first order with respect to each of the three reactants—phenacyl chloride, benzaldehyde, and hydroxyl ion—and therefore of third order overall (4).

The kinetic results are consistent with the "enolate ion" mechanism, although two such mechanisms leading to the observed data can alternatively be given. One assumes step 8c to be rate-determining and the other postulates step 8b as rate-determining.

B. The rate-determining step

Although intramolecular changes of transient intermediates like VII may be assumed to occur very rapidly, it must be kept in mind that (*1*) step 8b, analogous to step 2b of an aldol condensation, is essentially reversible, and (*2*), as has been stressed in Section III, the reaction occasionally stops with formation of the halogenohydrin. Only by increasing the severity of the conditions are products obtained which appear to have been formed through a labile oxirane compound. Thus, Weizmann, Sulzbacher, and Bergmann have performed alkaline hydrolyses of a number of trichloromethylcarbinols, prepared by condensation with chloroform, in the presence of aliphatic alcohols yielding substituted α-alkoxyacetic acids (88):

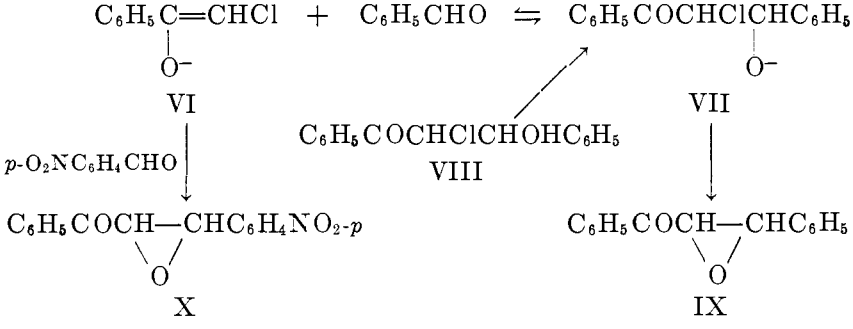


(10)

In 1897 Jocick had already written an oxirane of this type to explain the formation of some chlorophenylacetic acid in the alkaline hydrolysis of trichloromethylphenylcarbinol (50). Therefore, step 8c can, at least in some cases, be very slow.

It was, therefore, desirable to establish specific experimental evidence to decide between those two possibilities concerning the rate-determining step.

Upon the addition of hydroxide ion to a solution of chlorohydrin (VIII) and *p*-nitrobenzaldehyde the following changes in the system might take place:



(11)

If step 8c were rate-determining, and therefore step 8b a rapid equilibrium, virtually every chlorohydrin anion (VII) formed by the attack of the base on VIII would split into benzaldehyde and the chloroenolate anion (VI). Consequently, since *p*-nitrobenzaldehyde is kinetically much more active than benzaldehyde—as has been shown in a competitive experiment—from every VI formed, a molecule of X should be obtained. The experiment has been performed, the keto epoxide (IX) being obtained in 97.5 per cent yield and no amount of X being detected (2). Therefore, step 8c is much faster than the reverse of 8b and, consequently, than 8b. It must be concluded therefore that reaction 8b is the rate-determining step.

In some aldol condensations, such as self-condensation of acetaldehyde (8) and the condensation of glyceraldehyde with itself (17) or with dihydroxyacetone (84), step 2a, i.e., enolization, is rate-determining. The α-chloro atom in the B component, as has been shown by Bartlett (5, 7) and by Bell and Lidwell (9), strongly accelerates the base-catalyzed enolization; it should reduce also the nucleophilic character of the chloroenolate anion with respect to that of the unhalogenated B component. Consequently, step 8b should be essentially slower. It is reasonable therefore to expect, in view of the fact that the condensation of benzaldehyde with acetophenone involves the former in the rate-determining step (20), that the condensation of benzaldehyde with phenacyl chloride would afford no example of rate-determining enolization (4).

C. The influence of the substituents

The only data available concerning the effect of the substituents on the rate of the Darzens condensation are also obtained from the study of condensations involving phenacyl halides.

It has been already stated that a *p*-nitro group in benzaldehyde accelerates the condensation with phenacyl chloride. It can be generally said—as seems to be the case in the aldol condensation (20)—that electron-attracting substituents in benzaldehyde enhance the reaction rate.

By the action of a basic agent phenacyl halides may undergo self-condensation, giving an isomeric mixture of the so-called "α- and β-halogenodiphenacyls" (27, 67, 68). It has been recently shown that such self-condensation is actually a Darzens condensation in which one molecule of phenacyl halide acts as an A component and another as a B component (12, 85):

$$\begin{array}{l} C_6H_5C{=}O \\ \quad | \\ \quad CH_2Cl \end{array} + CH_2ClCOC_6H_5 \rightarrow \begin{array}{l} \quad\quad O \\ \quad\quad /\ \backslash \\ C_6H_5C{-}CHClCOC_6H_5 \\ \quad | \\ \quad CH_2Cl \end{array} \qquad (12)$$

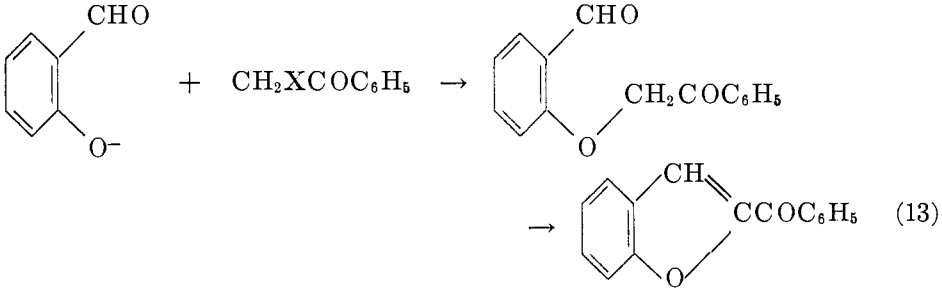
cis and *trans*

As Bodforss showed (15), the activity in the kinetic sense of phenacyl bromide as an A component is sufficiently close to that of benzaldehyde to make it possible to divide the substituted benzaldehydes and other aldehydes into two groups: those which are about as active as benzaldehyde or more so, and those which are less active than benzaldehyde. In the reaction of phenacyl bromide in

the presence of an A component less active than benzaldehyde, self-condensation of the former must preferentially occur. Such has been the case with *p*-tolualdehyde, anisaldehyde, piperonal, and cinnamaldehyde, which in their intended condensation with phenacyl bromide gave only the mixture of α- and β-bromodiphenacyls. However, *o*-, *m*-, and *p*-nitrobenzaldehyde, *p*-chlorobenzaldehyde, terephthaldehyde, and isopropylbenzaldehyde condense with phenacyl bromide to yield the expected epoxyketones. Furthermore, the introduction of an electron-attracting substituent, such as a bromine atom or a nitro group, into anisaldehyde, piperonal, or cinnamaldehyde may restore the ability to act effectively as an A component. This shows that electron-attracting substituents speed up the rate of the condensation, and also that electron-releasing substituents have an opposite effect.

The effect of the substituents on the rate of the condensation is due to their influence on the amount of nucleophilic character of the carbonyl group of the A component. It can be expected, therefore, that an electron-releasing group will diminish the activity of the phenacyl halides as A components, e.g., the rate of self-condensation. In fact, *p*-methoxyphenacyl chloride has been reported to be unusually resistant to self-condensation, and thus its condensation with comparatively deactivated benzaldehydes is made possible (15). Conversely, the presence of an electron-attracting group like the nitro group in phenacyl halides has a very unfavorable influence (47, 51).

A components having hydroxyl groups in the ortho position with respect to the halogenoacetyl group do not give a Darzens condensation but yield aroylcoumarones (71). In view of the influence of electron-releasing substituents in benzaldehyde on the condensation with phenacyl halides it could therefore be expected that no intermediate formation of halogenohydrin anion would be involved in the intramolecular ring-closure in the condensation of salicylaldehyde. It is known that phenacyl halides may react under basic conditions with phenols, giving ω-hydroxyacetophenone phenol ethers (27, 60). The formation of aroylcoumarones probably involves therefore a preliminary substitution reaction followed by an intramolecular aldol condensation:



(13)

As far as the effect of substituents in the B component on the rate of the reaction is concerned, no experimental evidence has been reported, although it would be expected to parallel that of the aldol condensation, i.e., an increase in the rate for electron-attracting substituents and a decrease for electron-releasing substituents (20).

It seems general that the Darzens condensation proceeds faster than the aldol condensation of the corresponding unhalogenated B component. Thus, from the reported data, taking into account the differences in the reaction conditions, it is evident that the condensation of benzaldehyde with phenacyl chloride (4) is much faster than that of benzaldehyde with acetophenone (20). It is significant also that the condensation of benzaldehyde with chloroacetone, as well as with each of the two isomeric α-chlorobutanones, occurs with the formation of over a 50 per cent yield of epoxyketone (81). Furthermore, the condensation of formaldehyde with chloroacetone occurs also on the chloromethyl group (46).

The above considerations seem to indicate that the reaction rate in such condensations parallels the acidity of the B component and not the nucleophilic character of its enolate ion.

D. The catalyst

The third-order kinetics of the reaction of benzaldehyde with phenacyl chloride shows that the first step, involving the base, must be a rapid equilibrium. No general base catalysis can therefore be expected. Accordingly, no acetate-ion catalysis could be detected in conditions likely to reveal its existence. Reaction in buffer mixtures, such as trichlorophenol–trichlorophenoxide or *p*-chlorophenol–*p*-chlorophenoxide, leads to complicating predominant side-reactions, such as halogen substitution (3). Spontaneous or "water" reaction as well as acid catalysis was absent (4).

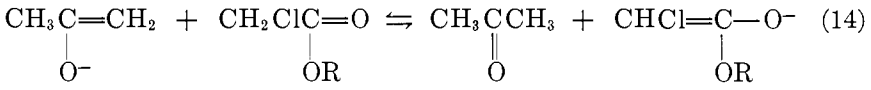
V. OTHER PROPOSED MECHANISMS

The mechanisms suggested for the Darzens condensation may be classified into three groups: (*a*) those assuming the activation of the A component by the base; (*b*) the "enolate ion" mechanisms; (*c*) the mechanisms of the radical type.

Erlenmeyer was the first author to propose a mechanism for the condensation of benzaldehyde with ethyl chloroacetate by means of sodium and a "drop of alcohol." It was assumed that the alcohol attacked the sodium, giving sodium alcoholate which added to the benzaldehyde, and that the resulting complex gave the intermediate chlorohydrin and alcohol, which resumed the attack on the sodium (25). Claisen, who carried out this and other condensations but used sodium amide instead of sodium, assumed also a preliminary addition of the condensing agent to the A component (19). Bodforss proposed a fundamentally analogous mechanism to explain the condensation of aldehydes with phenacyl halides (15). However, in Section III the reasons for discarding such mechanisms have already been considered. In spite of that, it is worthwhile to mention the experiments and ideas of Rutowski and Dajew (73), which have led to interesting polemics.

Rutowski and Dajew considered that in the Darzens condensation the basic catalyst is not simply added to the A component but forms an enolate with it, which next reacts with the B component. In accord with this, a number of condensations using the enolate of the A component as a starting material were performed. Furthermore, it was pointed out that the sodium derivative of ethyl chloroacetate does not react with benzaldehyde, as it should if the reaction happened by means of an "enolate ion" mechanism of the type considered.

Scheibleg and Tutundzitsch affirmed (75) that the possibility of carrying out condensations with an enolate of the A component can be reconciled with the "enolate ion" mechanism, for an equilibrium is established leading to the formation of the enolate of the B component:



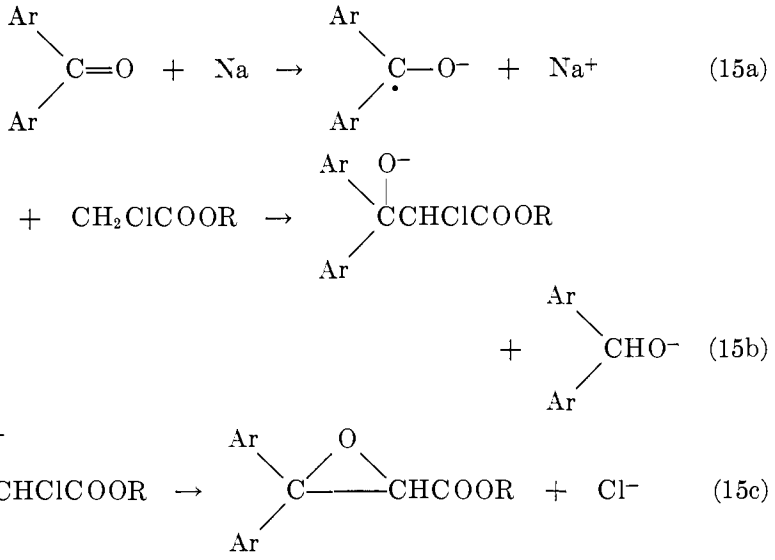
(14)

Moreover, the correctness of Rutowski and Dajew's experiments concerning the unreactivity of the enolate of ethyl chloroacetate *versus* benzaldehyde was denied, and earlier results (24) were cited to show that very probably what those authors called sodium chloroenolate was actually something else.

Concerning the "enolate ion" mechanism, Scheibler and Tutundzitsch were the first authors to propose a mechanism fundamentally identical with that already considered (75).

The radical mechanisms can be subdivided into "bivalent radical" and "trivalent carbon" sequences. In Section III the evidence concerning the "bivalent radical" mechanism has already been considered.

Rutowski and Dajew also proposed a "trivalent carbon" mechanism to explain why the condensation could alternatively be carried out with non-enolizable, aromatic A components (73). Sodium dissolves slowly in such A components, giving colored solutions shown to contain trivalent carbon (ketyl) radicals (13, 76, 78). Reasoning from this fact those authors proposed the following mechanism:



(15a)

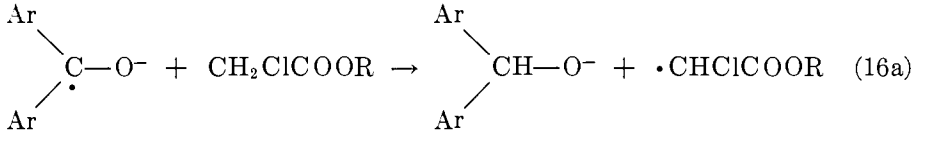
(15b)

(15c)

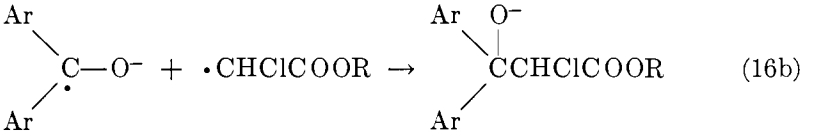
Accordingly, a glycidic ester condensation of ethyl chloroacetate with benzaldehyde sodium ketyl and with benzophenone sodium ketyl could be realized. Also, the results show that the corresponding alcohols—benzyl alcohol and benzhydrol, respectively—should be formed in a molar yield similar to that for the

condensation products. Consequently, only slight evolution of hydrogen was observed. Rutowski and Dajew confessed, however, that this mechanism does not harmonize with the lack of benzyl alcohol in the condensation with benzaldehyde reported by Erlenmeyer (25).

The chief failure of the preceding mechanism is its inability to explain why condensations with non-enolizable A components can be performed using non-radical inducers, like sodium amide or sodium ethoxide, as condensing agents. In spite of this, the previous experimental results seem to point strongly, when operating under very special conditions, to an alternative free-radical mechanism. Step 15b may be interpreted as occurring in two stages:



(16a)



(16b)

The existence of the radical •CHClCOOR, as well as its formation from ethyl chloroacetate upon a radical attack, is strongly supported by the experiments of Kharasch, Jensen, and Urry concerning the decomposition of diacetyl peroxide in methyl chloroacetate (54). Among various reaction products, a mixture of the meso and racemic forms of methyl α,α'-dichlorosuccinate was isolated, which was presumably formed by dimerization of that radical. Such a type of radical owes its stability to resonance between the following structures (53):

$$\bullet CHClC(OR)=O \leftrightarrow CHCl=C(OR)O\bullet \qquad (17)$$

In ordinary conditions, like those employed by Erlenmeyer for example, the presence of small amounts of substances—impurities or added alcohol—containing hydrogen readily displaceable by sodium probably prevents the formation of sodium ketyls and makes the "enolate ion" mechanism available. This would explain why Erlenmeyer did not report any aromatic alcohol as a by-product.

Finally, the attempt of Fourneau and Billeter to refine further the ketyl mechanism must be mentioned (26). From the fact that the hydrolysis of benzophenone sodium ketyl can give benzopinacol, it was concluded that the condensation occurred through sodium benzopinacolate as an intermediate. It was further assumed that two simultaneous mechanisms occurred, one taking care of the benzhydrol formation and the other of the evolution of hydrogen:

$$(C_6H_5)_2C(ONa)C(ONa)(C_6H_5)_2 + CH_2ClCOOR \rightarrow (C_6H_5)_2CHONa + (C_6H_5)_2C(ONa)CHClCOOR \qquad (18a)$$

$$(C_6H_5)_2C(ONa)C(ONa)(C_6H_5)_2 + 2CH_2ClCOOR \rightarrow H_2 + 2(C_6H_5)_2C(ONa)CHClCOOR \qquad (18b)$$

In fact, it has been shown that metallic pinacolates exist in equilibrium with ketyl radicals (61, 62).

$$(C_6H_5)_2C(ONa)C(ONa)(C_6H_5)_2 \rightleftharpoons 2(C_6H_5)_2\dot{C}ONa \qquad (19)$$

However, the assumption that such pinacolates are more reactive in a reaction involving their symmetrical cleavage than the corresponding free radicals themselves is indeed a most unusual one.

VI. REFERENCES

(1) BALLESTER, M.: Anales real soc. españ. fís. y quím. (Madrid) **50B**, 475 (1954).
(2) BALLESTER, M.: Anales real soc. españ. fís. y quím. (Madrid) **50B**, 759 (1954).
(3) BALLESTER, M.: Unpublished experiments.
(4) BALLESTER, M., AND BARTLETT, P. D.: J. Am. Chem. Soc. **75**, 2042 (1953).
(5) BARTLETT, P. D.: J. Am. Chem. Soc. **56**, 967 (1934).
(6) BARTLETT, P. D.: J. Am. Chem. Soc. **57**, 224 (1935).
(7) BARTLETT, P. D., AND VINCENT, J. R.: J. Am. Chem. Soc. **57**, 1596 (1935).
(8) BELL, R. P.: J. Chem. Soc. **1937**, 1637.
(9) BELL, R. P., AND LIDWELL, O. M.: Proc. Roy. Soc. (London) **A176**, 88 (1940).
(10) BERGMANN, E. D., GINSBURG, D., AND LAVIE, D.: J. Am. Chem. Soc. **72**, 5012 (1950).
(11) BERGMANN, E., AND HERVEY, J.: Ber. **62**, 893 (1929).
(12) BERSON, J. A.: J. Am. Chem. Soc. **74**, 5175 (1952).
(13) BLICKE, F. F.: J. Am. Chem. Soc. **46**, 2560 (1924).
(14) BODFORSS, S.: Ber. **49**, 2795 (1916).
(15) BODFORSS, S.: Ber. **51**, 192 (1918).
(16) BODFORSS, S.: Ber. **52**, 142 (1919).
(17) BONHOEFFER, K. F., AND WALTERS, W. D.: Z. physik. Chem. **A181**, 441 (1938).
(18) BORDWELL, F. G., AND COOPER, G. D.: J. Am. Chem. Soc. **73**, 5184 (1951).
(19) CLAISEN, L.: Ber. **38**, 693 (1905).
(20) COOMBS, E., AND EVANS, D. P.: J. Chem. Soc. **1940**, 1295.
(21) CRISTOL, S. J., AND HARMS, D. L.: J. Am. Chem. Soc. **71**, 2875 (1949).
(22) DARZENS, G.: Compt. rend. **150**, 1243 (1910).
(23) EKELEY, J. B., AND KLEMME, C. J.: J. Am. Chem. Soc. **46**, 1252 (1924).
(24) ERLENBACH, A.: Ann. **269**, 14 (1892).
(25) ERLENMEYER, E., JR.: Ann. **271**, 161 (1892).
(26) FOURNEAU, E., AND BILLETER, J. R.: Bull. soc. chim. France [5] **6**, 1616 (1939).
(27) FRITZ, Z.: Ber. **28**, 3028 (1895).
(28) GARLAND, C. E., AND WELCH, W. A.: J. Am. Chem. Soc. **53**, 2414 (1931).
(29) HAHN, G.: Ber. **62**, 2485 (1929).
(30) HALLER, A.: Bull. soc. chim. France [4] **31**, 1093–4 (1922).
(31) HALLER, A., AND BAUER, E.: Compt. rend. **153**, 145 (1911).
(32) HAMMETT, L. P.: *Physical Organic Chemistry*, pp. 153–5, 208. McGraw-Hill Book Company, Inc., New York (1940).
(33) Reference 32, p. 343.
(34) HATZIG, H.: Inaugural dissertation, Strassburg, 1909.
(35) HAUSER, C. R.: J. Am. Chem. Soc. **60**, 1957 (1938).
(36) HINE, J.: J. Am. Chem. Soc. **72**, 2438 (1950).
(37) HORIUTI, Z., AND SAKAMOTO, Y.: Bull. Chem. Soc. Japan **11**, 627 (1936); Chem. Abstracts **31**, 4189 (1937).
(38) HOWARD, J. W.: J. Am. Chem. Soc. **47**, 455 (1925).
(39) HOWARD, J. W.: J. Am. Chem. Soc. **57**, 2317 (1935).

(40) HOWARD, J. W., AND CASTLES, I.: J. Am. Chem. Soc. **57**, 376 (1935).
(41) HÜCKEL, W.: Ann. **540**, 274 (1939).
(42) HUGHES, E. D.: Trans. Faraday Soc. **37**, 625 (1941).
(43) HUGHES, E. D.: Trans. Faraday Soc. **37**, 626, 627 (1941).
(44) HUGHES, E. D.: Quart. Revs. (London) **5**, 245 (1951).
(45) HUGHES, E. D.: Private communication.
(46) HURD, C. D., MCPHEE, W. D., AND MOREY, G. H.: J. Am. Chem. Soc. **70**, 329 (1948).
(47) HUTCHINS, W. A., MOTWANI, D. C., MUDBHATKAL, K. D., AND WHEELER, T. S.: J. Chem. Soc. **1938**, 1882.
(48) INGOLD, C. K.: Trans. Faraday Soc. **37**, 718 (1941).
(49) INGOLD, C. K., AND JESSOP, J. A.: J. Chem. Soc. **1929**, 2357.
(50) JOCICZ, J.: Chem. Zentr. **68, I**, 1013 (1897).
(51) JÖRLANDER, H.: Ber. **50**, 1457 (1917).
(52) JOHNSON, W. S., BELEW, J. S., CHINN, L. J., AND HUNT, R. H.: J. Am. Chem. Soc. **75**, 4995 (1953).
(53) KHARASCH, M. S., AND GLADSTONE, M. T.: J. Am. Chem. Soc. **65**, 15 (1943).
(54) KHARASCH, M. S., JENSEN, E. V., AND URRY, W. H.: J. Org. Chem. **10**, 386 (1945).
(55) KLEUCKER, E.: Ber. **62**, 2587 (1929).
(56) LEVEDEV, S.: Chem. Zentr. **71, II**, 326 (1900).
(57) LOMBARD, R., AND BOESCH, R.: Bull. soc. chim. France **1953**, 733.
(58) LEUTHOLD, W. VON: French patent 791,172 (1935); Chem. Abstracts **30**, 3157 (1936).
(59) MAAS, J.: Chem. Zentr. **70, I**, 179 (1899).
(60) MÖHLAU, R.: Ber. **15**, 2497 (1882).
(61) MÜLLER, E., AND JANKE, W.: Z. Elektrochem. **45**, 380 (1939).
(62) MÜLLER, E., AND WIESEMANN, W.: Ann. **537**, 86 (1938).
(63) MUNCH-PETERSEN, J.: Acta Chem. Scand. **7**, 1041 (1953).
(64) NEF, J. U.: Ann. **298**, 202–374 (1897).
(65) NEWMAN, M. S., AND MAGERLEIN, B. J.: J. Am. Chem. Soc. **69**, 469 (1947).
(66) NEWMAN, M. S., AND MAGERLEIN, B. J.: In *Organic Reactions*, edited by R. Adams, Vol. V, pp. 413–40. John Wiley and Sons, Inc., New York (1949).
(67) PAAL, C., AND SCHULZE, H.: Ber. **36**, 2405 (1903).
(68) PAAL, C., AND STERN, H.: Ber. **32**, 530 (1899).
(69) PEARSON, R. G.: Private communication.
(70) PEARSON, R. G., LANGER, S. H., WILLIAMS, F. V., AND MCGUIRE, W. J.: J. Am. Chem. Soc. **74**, 5130 (1952).
(71) RAP, E.: Gazz. chim. ital. **25, II**, 285 (1895); Ber. **29**, 290 (1896) (Referate).
(72) RAPSON, W. S., SAUNDER, D. H., AND STEWART, E. T.: J. Chem. Soc. **1944**, 74.
(73) RUTOWSKI, B. N., AND DAJEW, N. A.: Ber. **64**, 693 (1931).
(74) SAKAMOTO, Y.: J. Chem. Soc. Japan **57**, 1169 (1936); Chem. Abstracts **31**, 931 (1937).
(75) SCHEIBLER, H., AND TUTUNDZITSCH, P. S.: Ber. **64**, 2916 (1931).
(76) SCHLENK, W., AND WEICKEL, T.: Ber. **44**, 1182 (1911).
(77) SCHWYZER, J.: *Die Fabrikation pharmazeutischer und chemischtechnischer Produkte*, p. 150. Julius Springer, Berlin (1931).
(78) SUGDEN, S.: Trans. Faraday Soc. **30**, 18 (1934).
(79) TEMNIKOVA, T. I., AND KROPACHEV, V. A.: J. Gen. Chem. (U.S.S.R.) **18**, 692 (1948); Chem. Abstracts **43**, 139 (1949).
(80) TEMNIKOVA, T. I., AND KROPACHEV, V. A.: J. Gen. Chem. (U.S.S.R.) **21**, 501 (1951); Chem. Abstracts **45**, 8447 (1951).
(81) TEMNIKOVA, T. I., AND MARTYNOV, V. F.: J. Gen. Chem. (U.S.S.R.) **15**, 499 (1945); Chem. Abstracts **40**, 4694 (1946).
(82) THOMSON, T., AND STEVENS, T. S.: J. Chem. Soc. **1932**, 69.
(83) VAN TAMELEN, E. E., AND ZYL, G. V.: J. Am. Chem. Soc. **71**, 835 (1949).

(84) WALTERS, W. D., AND BONHOEFFER, K. F.: Z. physik. Chem. **A182**, 265 (1938).
(85) WASSERMAN, H. H., AUBREY, N. E., AND ZIMMERMAN, H. E.: J. Am. Chem. Soc. **75**, 96 (1953).
(86) WATSON, H. B.: Trans. Faraday Soc. **37**, 707 (1941).
(87) WEIZMANN, C., BERGMANN, E., AND SULZBACHER, M.: J. Am. Chem. Soc. **70**, 1189 (1948).
(88) WEIZMANN, C., SULZBACHER, M., AND BERGMANN, E.: J. Am. Chem. Soc. **70**, 1153 (1948).
(89) WIDMAN, O.: Ber. **49**, 477 (1916).
(90) WILLGERODT, C.: Ber. **14**, 2451 (1881).
(91) WINSTEIN, S., AND LUCAS, H. J.: J. Am. Chem. Soc. **61**, 1576 (1939).
(92) ZIEGLER, W. M., AND CONNOR, R.: J. Am. Chem. Soc. **62**, 2596 (1940).