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Advances in the Chemistry of Aliphatic Diazoketones

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The review deals with the methods of synthesis of aliphatic diazoketones and gives a systematic account of the extensive literature data on their chemistry. The work on the physical properties, structures, and ultraviolet, infrared, and NMR spectra of diazoketones is summarised in a separate section where problems of $p-\pi$ conjugation and rotational isomerism are also discussed. The concluding section deals with the hitherto few but interesting data on the biological activity of diazoketones.
The bibliography includes 295 references.

CONTENTS

I. Introduction	371
II. Methods of synthesis	371
III. Spectra and structure	374
IV. Chemical properties	378
V. Some aspects of practical applications.	385

INTRODUCTION

The remarkable part which aliphatic diazoketones have played in the development of organic chemistry is well known. Numerous original papers, reviews, and monographs have been devoted to these compounds[1-10].

The aim of the present review is to give a systematic account of the literature data for the methods of synthesis, spectra, structure, and chemical properties of diazoketones. Earlier such attempts were not made, although they merit special consideration in view of some of their characteristics.

The earlier reviews emphasise primarily the fact that aliphatic diazo-compounds have common properties. Therefore these reviews and the present review are not mutually exclusive but complement one another. The inevitable repetition may be justified in each case by the novelty of approach to the analysis of literature data and by the authors' wish to give a complete presentation of the available information.

In recent years interesting data were obtained on the structure of diazoketones, which, in contrast to diazoalkanes, have many structural characteristics and show an unusual chemical behaviour owing to the presence of the α-carbonyl group. $p-\pi$ conjugation, which involves a chain of five atoms in the $COCH_2N_2$ fragment, leads to the appearance of partial bonds. As a result, free rotation about the C–C bond is hindered and *cis–trans* conformers are produced. In the discussion of the structure of diazoketones, ultraviolet, infrared, and NMR spectroscopic data, dipole moments, and also calculations by the molecular orbital method are invoked.

The present review gives a brief account of the methods of synthesis of diazoketones. In order to demonstrate the large number and great variety of procedures, we have described both well known methods developed long ago as well as methods which have appeared recently. In the discussion of chemical reactions, certain reactions of diazoketones have been omitted. In particular the large series of studies on the addition of diazoketones to double bonds is not dealt with, since many excellent reviews have been devoted to this reaction[8,9]. On the other hand, we considered the reactions which have not as yet been developed adequately but have undoubted interest for the further development of the chemistry of diazo-compounds.

The last section of the review deals with data on the biological activity of diazocarbonyl compounds. The fact that certain diazoketones inhibit the growth of malignant tumours is noteworthy.

II. METHODS OF SYNTHESIS

The methods of preparation of diazoketones may be divided into seven principal groups: (1) *C*-acylation of aliphatic diazo-compounds; (2) reaction of organic azides with active methylene compounds; (3) oxidation of monohydrazones of α-aldehydoketones and α-diketones; (4) diazotisation of primary amines containing a carbonyl group; (5) diazotisation of ketoximes; (6) alkaline cleavage of *N*-acyl-*N*-nitrosamines; (7) alkaline cleavage of tosylhydrazones of α-carbonyl compounds. Within the limits of the scope of the present review, each of the above methods is discussed below.

1. *C*-Acylation of Aliphatic Diazo-compounds

The method consists of the direct acylation of diazo-derivatives by carboxylic acid halides and anhydrides. The nature of the product formed depends considerably on the reaction conditions and on the structure of the diazo-compounds and acylating agents. For example, acetyl chloride reacts with diazoacetic ester according to the mechanism[11]

$$ClCOCH_3 + N_2CHCOOC_2H_5 \longrightarrow C_2H_5COOCN_2COCH_3.$$

The reaction of carboxylic acid chlorides with diazo-compounds without an activated α-hydrogen atom takes place differently[11]:

$$R{-}COCl + N_2C(C_6H_5)_2 \rightarrow R{-}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{Cl}{|}}{C}(C_6H_5)_2 + N_2 .$$

The reaction of aromatic acid chlorides with diazomethane at room temperature using equimolar amounts of the reactants leads to the formation of aryl chloromethyl ketones[12-15]:

$$C_6H_5COCl+CH_2N_2\longrightarrow C_6H_5COCH_2Cl+N_2\,.$$

C-Acylation of diazoalkanes takes place in the presence of an excess of the latter at a reduced temperature (0–5°C) and may be described by the following mechanism[16-19]:

$$R-COCl+2CH_2N_2\longrightarrow R-COCHN_2+HCl,$$
$$HCl+CH_2N_2\longrightarrow CH_3Cl+N_2\,.$$

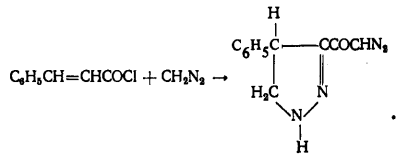
In the presence of a deficiency of diazoalkane, a side reaction leading to the formation of a chloromethyl ketone is possible:

$$HCl+R-COCHN_2\longrightarrow R-COCH_2Cl+N_2\,.$$

Triethylamine may be used to combine with hydrogen chloride[20]. An excess of diazoalkane promotes the formation of an azine[21,22].

The method of *C*-acylation of diazo-compounds (the Arndt–Eistert method) has been developed in fair detail and is widely used to synthesise not only primary but also secondary diazoketones[23]. It constitutes the basis of the synthesis of mono-, bis-, and tris-diazoketones[24,25]. Thus 1,3,5-tridiazoacetylbenzene has been obtained by treating trimesoyl chloride with an excess of diazomethane[25].

The reaction of diazomethane with unsaturated acid chlorides results in its 1,3-cycloaddition to the double bond simultaneously with *C*-acylation[26-28]:



Many different diazoketones, including derivatives with heterocyclic and perfluoroalkyl substituents[29-32] and also with heteroatoms in the chain, have been obtained by the Arndt–Eistert method[33,34]:

$$ClCOCH_2N(NO_2)CH_2COCl+CH_2N_2\rightarrow N_2CHCOCH_2N(NO_2)CH_2COCHN_2\,.$$

A systematic account of all past studies on the Arndt–Eistert reaction is given in a review by Bachmann and Struve[1].

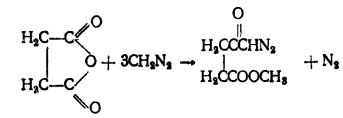
While *C*-acylation of diazo-compounds by carboxylic acid chlorides and bromides has been investigated in fair detail, acid fluorides are rarely used for this purpose. The synthesis of diazoacetaldehydes may serve as an example[35]:

$$HC(=O)F+CH_2N_2\rightarrow HC(=O)CHN_2\,.$$

There are also only a few examples of the *C*-acylation of diazo-compounds by carboxylic acid anhydrides[5,36-40]. Benzoic acid anhydride reacts with diazomethane to form diazoacetophenone[36]. Trifluorodiazoacetone is formed in the reaction between diazomethane and the mixed anhydride of acetic and trifluoroacetic acids[5]:

$$F_3CC(=O)-O-C(=O)CH_3+2CH_2N_2\rightarrow F_3CC(=O)CHN_2+CH_3COOCH_3+N_2\,.$$

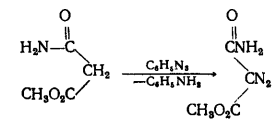
Anhydrides of dibasic acids are converted into monodiazoketones[37]:



The mechanism of the *C*-acylation of diazoalkanes has been frequently discussed in the literature and therefore we do not consider it here[2-4].

2. Reactions of Organic Azides with Active Methylene Compounds

The reaction involving the introduction of diazo-groups into an active methylene group with the aid of phenyl azide was discovered in 1910 by Dimroth[41]:



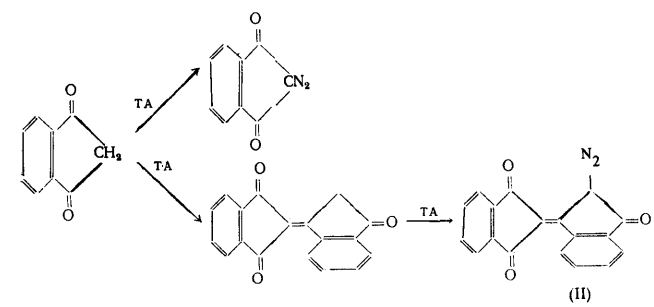
Later it was shown that *p*-tosyl azide can also be used to transfer the diazo-group[42]. However, at the time this interesting method of preparing diazo-compounds did not attract attention and its detailed development began as late as 1953[43-50]. The method proved to be suitable for the synthesis of cyclic diazo-compounds[44-48], including diazoketones[49,50]. The reaction is carried out in ethanol in the presence of potassium ethoxide, triethylamine[51,52], or potassium hydroxide[53] and also in methanol in the presence of sodium methoxide[54].

Diazoketones are not always obtained in a pure form owing to the formation of secondary reaction products. Thus, in the reaction of *p*-tosyl azide with benzoyl-(*p*-nitrobenzoyl)methane in methylene chloride in the presence of pyridine, the process does not stop at the stage involving the formation of product (I):

$$C_6H_5COCH_2C_6H_4NO_2\text{-}p\longrightarrow C_6H_5COCN_2C_6H_4NO_2\text{-}p\,.$$
(I)

The product is partly cleaved into benzoyl diazomethane and *p*-nitrobenzoyldiazomethane. The separation of the mixture of diazo-derivatives is difficult[55]. Pure diazoketone (I) may be obtained when the reaction is carried out in ethanol with added catalytic amounts of triethylamine[53,55].

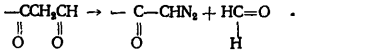
The formation of a mixture of diazo-compounds was also noted in the synthesis of 2-diazoindan-1,3-dione. The principal reaction product is 2-diazo-1′,3,3′-trioxo-1,2′-bisindanylidene (II), which arises as a result of the self-condensation of indan-1,3-dione under the influence of a base. The self-condensation product reacts further with tosyl azide (TA)[51]:



(II)

Carbonyl compounds of the type $-CH_2C(=O)-$ react with sulphonyl azides to form diazo-derivatives when the C–H group is sufficiently activated[56-61].

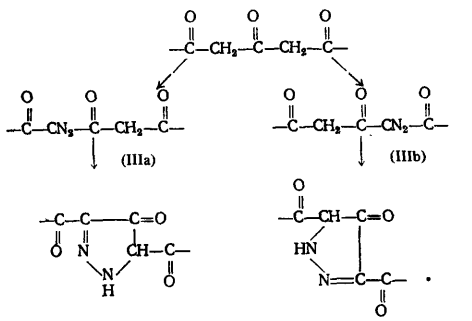
β-Oxoaldehydes are convenient acceptors of the diazo-group. Ketones, which are unsuitable for the direct introduction of the diazo-group, are converted by the Claisen condensation into β-oxocarbonyl compounds. The latter are smoothly converted into diazoketones, with elimination of the formyl group[62,63]:



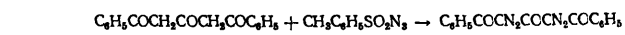
α-Formylcycloalkanones are also readily converted into diazocycloalkanones[62-65]:



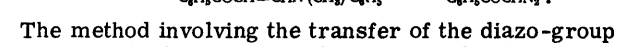
In the reaction of 1,3,5-triketones with tosyl azide, pyrazolones were isolated in high yields, instead of the expected bisdiazoketones. The formation of the pyrazolones is due to an intramolecular reaction of the intermediate diazoketone (IIIa,b)[66]:



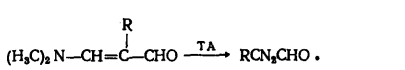
However, when the reactants are mixed slowly, the reaction can be driven towards the formation of bisdiazoketones[67]:



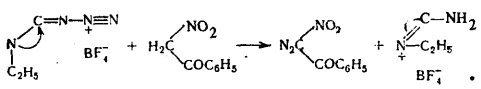
Diazoketones are formed in the reaction of enamines with arenesulphonyl azides[68,69]:



The method involving the transfer of the diazo-group to active methylene compounds has proved suitable for the synthesis of diazoaldehydes[68] and other diazo-compounds: diazosulphones[54,70], α-diazophosphinoketones, and α-diazophosphinoethers[71,72]. For example, diazoaldehydes are formed according to the mechanism:

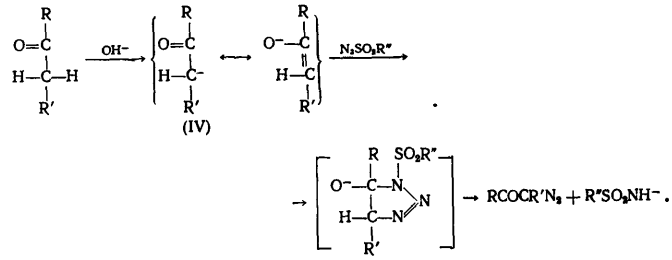


Attempts to extend this method to the synthesis of nitrodiazoketones have been described. Azidinium salts were used as donors of the diazo-group. The reaction takes place in methanol at room temperature in the presence of sodium acetate[73]:



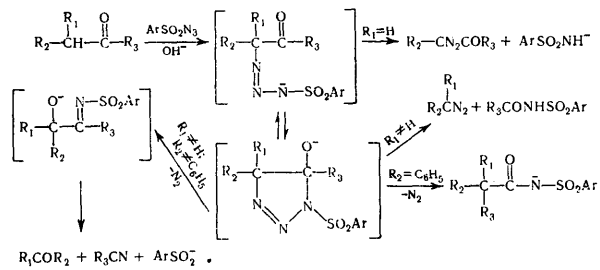
Various mechanisms for the reaction of organic azides with active methylene compounds have been proposed[56,58,74].

The cyclic mechanism is the most probable. In the first stage the diazo-group acceptor is converted under the influence of the base into a carbanion in which a double bond may be formed. The subsequent addition of the sulphonyl azide to the anion (IV) leads to the formation of a triazoline which dissociates into a diazo-compound and a sulphonamide[56,58]:



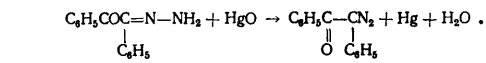
Some workers believe that the formation of a cyclic intermediate product is possible only when the activated methylene group contains one hydrogen atom[74].

A general mechanism has been proposed for the transfer of the diazo-group, which can explain the formation of diazoketones, amides, ketones, cyano-derivatives, and sulphonate salts[74]:



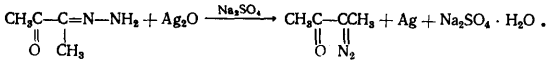
3. Oxidation of Monohydrazones of α-Aldehydoketones and α-Diketones

In 1889 Curtius obtained benzoylphenyldiazomethane by oxidising benzilhydrazone with yellow mercury(II) oxide in cold benzene solution[75]:



Subsequently mercury(II) oxide was used for this purpose also by other investigators[76-86].

Other metal oxides are also widely used for the synthesis of diazoketones. The oxidation of diacetyl monohydrazone with silver oxide in the presence of anhydrous sodium sulphate has been described[87]:



As a rule, in the presence of drying agents such as sodium or magnesium sulphate silver oxide is used only in those cases where other oxidants (HgO, CuO, PbO) are ineffective[88].

A mixture of sodium hydroxide and calcium hypochlorite in aqueous methanol has been used to synthesise 3-diazo-D-camphor[89]. Recently activated manganese dioxide has been suggested as an oxidant. The reaction was carried

out in chloroform at room temperature, diazoketones being formed in quantitative yields[89-91]:

$$RCOCH=N-NH_2+MnO_2\longrightarrow RCOCHN_2 .$$

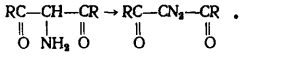
It is noteworthy that the oxidation of hydrazones by metal oxides is used mainly for the preparation of acyclic monodiazoketones and aryl-substituted diazomethanes[92].

4. Diazotisation of Primary Amines

This method has been used to synthesise diazoacetophenone[93]:

$$C_6H_5COCH_2NH_2\cdot HCl+NaNO_2\longrightarrow C_6H_5COCHN_2 .$$

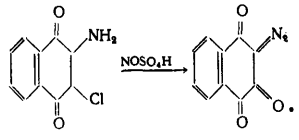
Later the method was employed to synthesise many cyclic diazoketones[93-97]. Diazotisation of an amino-group located between two carbonyl groups leads to the formation of the corresponding diazoketones[98-101]:



Intermediates obtained by the reduction of nitration, nitrosation, or azo-coupling products and not the pure amines are as a rule employed in the reaction[5]. The diazotisation takes place via a diazohydroxide, which, depending on the mobility of the α-atom, is converted either into a diazo-compound or an alcohol is formed with evolution of nitrogen[3]. In the case of α-aminoketones and α-aminoacid esters, an activated methylene group removes a proton with formation of diazoketones or diazoesters:

$$RCOCH_2NH_2\cdot HCl+NaNO_2\xrightarrow{H^+}RCOCH_2NH{-}NO\rightarrow RCON{=}NOH\rightarrow RCOCHN_2+H_2O.$$

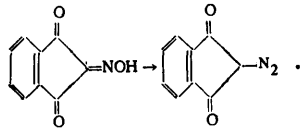
The use of nitrosylsulphuric acid as a nitrosating agent has been described[102,103]. The diazotisation of 2-amino-3-chloro-1,4-naphthoquinone with this reagent is accompanied by oxidation, which leads to the formation of 2-diazo-1,3,4-trioxotetralin[102]:



Similarly 2,5-diamino-3,6-dichlorobenzoquinone forms 1,4-bisdiazotetraoxocyclohexane[102].

5. Diazotisation of Oximes

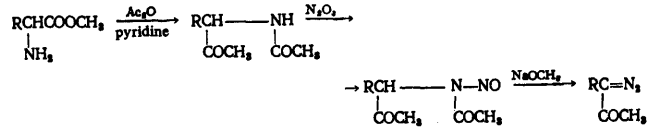
Several examples of the conversion of cyclic ketoximes into α-diazoketones under the influence of chloramine via the familiar Forster reaction[104] have been described:



The reaction is carried out in a cooled alkaline medium. The method is used to synthesise a wide variety of cyclic diazoketones[105-108]. The synthesis of condensed polycyclic bisdiazoketones was described recently[109].

6. Alkaline Cleavage of *N*-Acyl-*N*-nitrosamines

Diazoketones with the structure $H_3CCOCN_2CH_2R$ may be obtained via the mechanism[110]



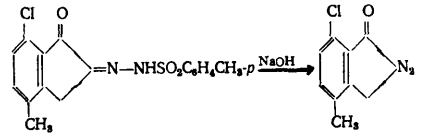
The conversion of aminoacids into *N*-acylaminoketones has been investigated in detail[111]. *N*-Nitroso-derivatives are formed in the nitrosation of *N*-acylaminoketones with N_2O_3 in glacial acetic acid. They are subsequently decomposed to diazoketones with sodium methoxide[110]. Benzoylphenyldiazomethane with a labelled carbonyl carbon atom was obtained by the above mechanism[111].

Alkaline cleavage of nitrosourethanes containing the sulphone group makes it possible to obtain diazosulphones[112]:

$$H_3CCOC_6H_4SO_2CH_2NHCOOC_2H_5\xrightarrow{KOH}H_3CCOC_6H_4SO_2CHN_2 .$$

7. Alkaline Cleavage of Tosylhydrazones of α-Carbonyl Compounds

The method was first used to synthesise 7-chloro-2-diazo-4-methylindan-1-one[105]:



The reaction proved convenient for the synthesis of cyclic diazoketones. It takes place in pentane, ether, and methylene chloride at a low temperature in the presence of sodium hydroxide or basic alumina. A series of papers dealing with detailed studies of this reaction have been published[25,113-118].

Other methods of synthesising diazocarbonyl compounds are also known. For example, the synthesis of *N*-acetyldiazoacetamide by the reduction of *N*-acetyl-3-benzylsydnoneamine in methanol in the presence of palladised charcoal has been described[119].

In choosing the method of synthesis of diazoketones, it is of course necessary to take into account the specific features of the method and the characteristics of the structure of the diazo-derivatives. The Arndt–Eistert method and the reactions of organic azides with active methylene compounds are the most common and universal.

III. SPECTRA AND STRUCTURE

1. General Characteristics

The lowest representatives of the diazoketone series are liquids. For example, diazoacetone is a mobile pale-yellow liquid with b.p. 46–47°/13 mm and d_4^{20} = 1.0864.[120] 1-Diazo-2,3-dimethylbutan-2-one is a brick-red liquid with b.p. 69°/15 mm, d_4^{25} = 0.9630, and n_D^{25} = 1.4709.[121] The higher diazoketones are crystalline substances. Depending on the substituents, their colour

varies from lemon-yellow to white. As a rule, diazoketones are readily soluble in organic solvents. The accumulation of electronegative substituents in the diazoketone molecule, for example of carbonyl and nitro-groups, leads to an increase of the melting point, a "lightening" of the colour, and an increase of chemical stability.

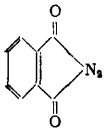
Certain diazoketones have a specific odour, for example diazoacetophenone and diazoacetone.

In contrast to diazoalkanes, diazoketones can be stored for a long time in the dark at 0–20°C; they decompose under the influence of sunlight. The liquid compounds may decompose on coming into contact with a rough surface. Special care is necessary in the distillation of diazoketones: rapid heating (at about 100°C) leads to explosion[5].

2. Spectra and Structure

The ultraviolet spectra of diazoketones have two absorption bands: in the range 240–270 nm and in the range 270–301 nm.[122–125] Table 1 shows the dependence of the electronic spectra on solvents. In protic solvents, the intensity of the first band diminishes relative to that of the second[126].

Table 1. Ultraviolet spectra of certain diazoketones[51,122].

Diazoketone	λ_{max}, nm		ϵ_{max}*, litre mole^{-1} cm^{-1}	Solvent
$N_2CHCO(CH_2)_4COCHN_2$	247		24 800	Dioxan
	248	273	21 200	Chloroform
	248	270	19 100	Ethanol
			16 700	
$(CH_2)_3COCHN_2$	251		6 840	Methylene chloride
	250	270	6 990	Ethanol
	247	275	6 600	Water
			4 600	
	244		4 550	Methanol

* $\epsilon max = (1/bc)\ lg_{10}(I_0/I)$.

The absorption spectra of 1,8-bisdiazo-octane-2,7-dione recorded in an acetonitrile–water solvent mixture intersect at an isosbestic point[122]. It would appear that this can be readily accounted for by iso–diazo (1) or diazoketo–diazoenol (2) tautomerism:

$$R{-}CO\overline{C}H{-}\overset{+}{\overline{N}}{\equiv}N \rightleftarrows R{-}CO{-}\overline{C}{=}\overset{+}{\overline{N}}{=}NH, \quad (1)$$

$$R{-}CO\overline{C}H{-}\overset{+}{\overline{N}}{\equiv}N \rightleftarrows R{-}C(OH){=}\overline{C}{=}\overset{+}{\overline{N}}{=}\overline{N}. \quad (2)$$

However, the ultraviolet spectra of benzoyldiazoacetic ester and dimethyl $\alpha\alpha'$-bisdiazo-$\beta\beta'$-dioxoadipate, which show no tendency towards tautomeric conversion, also have an isosbestic point[125]. Fahr rejected the possibility of an intramolecular rearrangement and explained the presence of the isosbestic point by the reaction of the diazocarbonyl compound with the hydroxyl-containing solvent[125].

Special studies on the ultraviolet spectra of diazoketones in hydroxyl-containing solvents showed that Fahr's hypothesis of an intermolecular reaction between the diazoketone and the solvent cannot account for the spectra. The shift of the absorption band from 250 to 300 nm cannot be explained solely by an intermolecular reaction between the diazoketone and the solvent, since the energy difference between the two bands is fairly large (11.0 kcal mole^{-1}). It is most probable that in this case the band splits owing to a conformational equilibrium[127].

The spectra of diazoacetone in hydroxyl-containing solvents also have an isosbestic point. It could be accounted for by the presence of the *cis*- and *trans*-isomers of the diazoketone owing to the different $\pi \rightarrow \pi^*$ transitions for each isomer. However, similar effects of the solvent were observed for 2-diazocyclohexanone, 3-diazonorcamphor, and 3-diazocamphor, for which the existence of *trans*-isomers is impossible. Consequently, the effect of the solvent on the spectra of acyclic diazoketones cannot be accounted for by the occurrence of conformational isomerism[128].

In a study of the ultraviolet spectra of *para*- and *meta*-substituted derivatives of diazoacetophenone, a linear relation was observed between the shift of the 250 nm band in hexane for different *para*-substituted (F, Cl, Br, CH_3, NO_2, CH_3O, and C_2H_5O) derivatives relative to the unsubstituted compound and the activity constant σ_S for the corresponding substituent[126].

Thus, in the interpretation of the ultraviolet spectra of diazoketones, it is necessary to bear in mind that they may be significantly influenced not only by the structure of the diazo-derivatives but also by the experimental conditions. At the present time there is no unique hypothesis which would account for the above characteristics of the ultraviolet spectra of diazocarbonyl compounds. Nevertheless, on the basis of data derived from electronic absorption spectra, one may conclude that, depending on the compound investigated, the absorption bands of diazoketones correspond either to $\pi \rightarrow \pi^*$ or $\pi \rightarrow \sigma^*$ transitions or to their combination. Since α-diazoketones exhibit *s*-isomerism, the absorption bands represent the sum of the superimposed spectra of the *s-cis*- and *s-trans*-isomers[128].

The study of the electronic spectrum of diazoacetone and quantum-mechanical calculations for this compound make it possible to illustrate the $\pi \rightarrow \pi^*$ and $\pi \rightarrow \sigma^*$ transitions with the aid of the orbital energy levels. The diazoacetone molecule may be excited by ultraviolet irradiation in four ways, two of which (Figs. 1 and 2) occur in the region observed.

Fig. 1 presents the principal spectroscopic orbital energy levels and transitions for *s-cis*-diazoacetone[128]. Fig. 2 shows the predicted transition energies for *s-cis*- and *s-trans*-diazoacetones. The low and high vertical lines represent respectively the allowed and the overlap forbidden transitions[128].

In α-diazoketones with different substituents, the number of ways in which the molecule may be excited increases and the electronic spectra are more complex.

The diazo-group gives rise to a distinct band in the infrared spectra of diazoketones in the region 2058–2170 cm^{-1}, which is characteristic of the stretching vibrations of the N–N bond[125,129]. This confirms the linear structure of the diazoketones, otherwise the N–N stretching vibration would give rise to absorption in the region of 1636 cm^{-1}.[129] Moreover, in the spectra of diazoketones and diazoesters an intense absorption is observed in the region 1429–1335 cm^{-1}.[130] This band was assigned to the symmetrical stretching vibrations of the diazo-group, which are markedly displaced owing to conjugation and interaction with skeletal vibrations.

The infrared spectra of diazoacetone, diazoacetophenone, and benzoylphenyldiazomethane have been investigated in carbon tetrachloride and butanol. A change of solvent almost does not affect the position of the maximum of the band due to the N–N bond in the infrared spectrum and has little effect on its integral intensity. However, the peak intensity of this band in butanol is much lower than in carbon tetrachloride and its half-width is greater in butanol. Since this effect is observed not only for diazoacetone and diazoacetophenone but also for benzoylphenyldiazomethane which has no mobile hydrogen, it cannot be due to tautomerism but must be caused by hydrogen bonding, dipole–dipole interaction, and rotational isomerism. The formation of hydrogen bonds between the above diazoketones on the one hand and phenol and pyrrole on the other has been observed on the basis of the shift of the OH and NH absorption bands. The appearance of new absorption bands due to the carbonyl group in the low-frequency region in the spectra of diazoketones in the presence of butanol or phenol is associated with the rotational isomerism of these compounds[127].

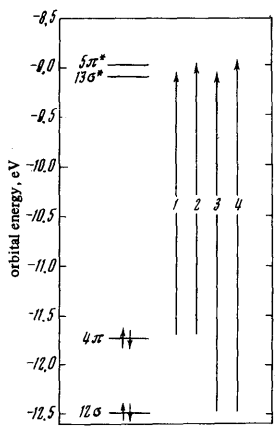


Figure 1.

Using the infrared spectroscopic data for the N–N stretching vibrations, it is possible to assess unambiguously the multiplicity of the bonds between the nitrogen atoms in the diazo-group. If the bond multiplicity is close to 3, the diazo-group absorbs at high frequencies but if the multiplicity is less than 3 the absorption shifts towards lower frequencies. This agrees well with calculations on the distribution of π-electron density in the C–N–N fragment in diazo-compounds (Table 2).

In diazomethane the π-electron cloud is appreciably displaced towards the extreme nitrogen atom and the multiplicity of the bond between the nitrogen atoms is a minimum. If the diazo-compound has substituents with –I and –C effects at the α-carbon atom, the p-electrons at this atom are delocalised over the orbitals of the atoms of the substituents, which leads to a shift of electron density from the orbital of the extreme nitrogen atom. The introduction of a carbonyl group into aliphatic diazo-compounds in the α-position relative to the diazo-group, causes a shift of the absorption bands of the diazo-group towards higher wave-numbers, on average by 40 cm^{-1}. For example, the diazo-group in diazomethane absorbs in the region of 2088 cm^{-1} and in acetyldiazomethane in the region of 2107 cm^{-1}. The introduction of a chlorine atom into the methyl group of diazoacetone promotes, owing to its inductive effect, an even greater shift of the absorption bands due to the diazo-group towards higher wave-numbers (2114 cm^{-1})[132]. The diazo-group in benzoylphenyldiazomethane absorbs in the region of 2072 cm^{-1}, which is evidence that the phenyl group at the carbon atom linked to the diazo-group behaves as an electron donor and reduces the multiplicity of the N–N bond[133]. The diazo-group in diazoacetophenone absorbs in the region of 2108 cm^{-1}.[134] The multiplicity of the bond between the nitrogen atoms increases. An example of the limiting shift of electron density in the diazo-fragment is provided by aromatic diazo-compounds.

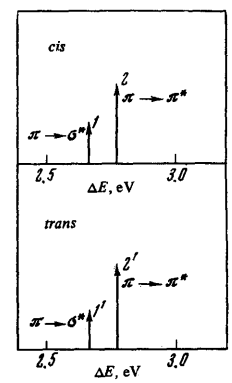


Figure 2.

Table 2. Distribution of π-electron density in the diazo-fragment[131,140].

Diazo-compound	Distribution of π-electron density in C–N–N diazo-fragment	Multiplicity of N–N bond (Ref.140)	Wave-number cm^{-1}
Diazomethane	−0.4995 +0.8418 −0.3423	2.7441	2088
Diazoacetone	−0.4214 +0.8679 −0.2095	2.8194	2103
Diazomalonic ester	−0.3869 +0.8779 −0.1486	2.8543	2188
Phenyldiazonium	+0.0062 +0.8800 +0.0772	2.9284	2304—2237

The introduction of a nitro-group in the α-position relative to the diazo-group has a considerable effect on the position of the band due to its stretching vibrations. Thus $\Delta\nu$ for diazomethane and its nitro-derivatives is 27 cm^{-1},[135] while for diazoacetophenone and its nitro-derivatives $\Delta\nu$ increases to 47 cm^{-1}.[73] A similar behaviour is observed also with N-nitraminodiazoketones[136].

The carbonyl group in diazoketones gives rise to two absorption bands in the region 1755–1620 cm^{-1}. The shift of the bands towards lower wave-numbers (1652–1620 cm^{-1}) is associated with a decrease of the multiplicity of the C=O bond[129,137], which is caused by a shift of electron density to the carbonyl oxygen atom.

The carbonyl absorption band in the spectra of diazoketones has undergone significant changes relative to the spectra of unsubstituted ketones. Thus in the spectrum of diazoacetone it is displaced towards lower wave-numbers by 60 cm^{-1}, which is due to the effect of the $p-\pi$ conjugation in the $COCHN_2$ fragment[137]. A similar shift is observed also in diazoacetophenone relative to acetophenone[134,138]. The phenyl group in diazoacetophenone increases the electron density at the oxygen atom in the carbonyl group owing to its conjugation with the ring and the carbonyl absorption band in the spectrum of diazoacetophenone is displaced towards lower wave-numbers by 26 cm^{-1} compared with diazoacetone. A negative inductive effect of substituents in diazoketones promotes a shift of the absorption bands of the carbonyl group towards higher wave-numbers. Thus, for diazoacetone and trichlorodiazoacetone, this shift is 20 cm^{-1}.[132]

The presence of two carbonyl absorption bands and several absorption bands of different intensities due to the diazo-group in the region of higher wave-numbers is due to the existence of the *s*-isomers in diazoketones[128,137].

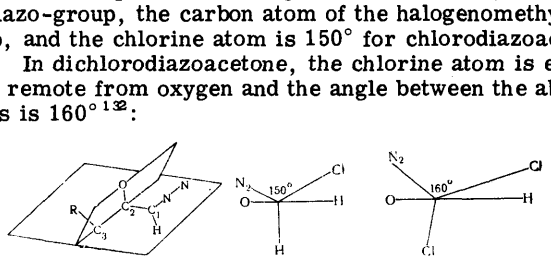
Important evidence in support of the *s*-isomerism of diazoketones was obtained in a study of NMR spectra. Kaplan and Meloy demonstrated that the NMR spectrum of diazoacetone varies with temperature, which indicates the existence of *cis*- and *trans*-isomers[139]. The NMR spectra of other diazocarbonyl compounds, recorded in the temperature range between 71° and −40°C, also confirmed the occurrence of conformational isomerism. In the temperature range investigated, the ratio of the *cis*- and *trans*-isomers of diazoacetaldehyde varied from 9 : 1 to 7 : 3.

The dipole moments of diazoketones agree with the rigid planar structure of the $COCHN_2$ fragment, where CO and CN_2 can be either in the *cis*- or the *trans*-configuration[132] (Table 3).

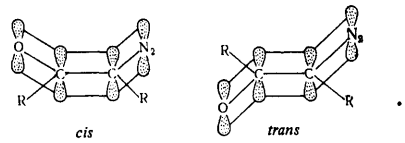
Table 3. Dipole moments of diazoketones[132].

Diazoketone	Dipole moment, debyes
CH_3COCHN_2	3.37
$ClCH_2COCHN_2$	2.80
$Cl_2CHCOCHN_2$	2.65
$Cl_3CCOCHN_2$	2.46

In diazoacetone an equilibrium is observed between the *cis*- and *trans*-conformers, while chloro-derivatives of diazoacetone are mainly in the *cis*-form. Free rotation of the halogenomethyl group about the R–CO bond is hindered by steric and electrostatic effects. The optimum angles between the planes in which the diazo-fragment is located and the plane containing the carbon atom joined to the diazo-group, the carbon atom of the halogenomethyl group, and the chlorine atom is 150° for chlorodiazoacetone. In dichlorodiazoacetone, the chlorine atom is even more remote from oxygen and the angle between the above planes is 160°[132]:



s-Isomerism in diazoketones is the result of the limited free rotation about the central carbon–carbon bond, which is caused by the interaction of the electron pair of the α-carbon with the π-electron-system of the carbonyl group:



cis *trans*

The barrier to free rotation in diazoketones about the carbon–carbon bonds is between 9 and 18 kcal $mole^{-1}$. For diazoacetone and diazopropanone, it amounts to 15.5 and 16.1 kcal $mole^{-1}$ respectively[35].

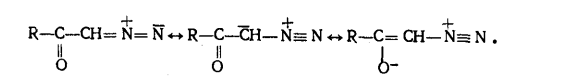
Table 4. Multiplicity of the bonds in the $COCHN_2$ fragment[132,149].

C–O	C–C	C–N	N–N
1.80	1.50	1.54	2.81
—	—	1.70	2.77

$p-\pi$ Conjugation in the $COCHN_2$ system leads to the appearance of fractional bond orders. Table 4 lists the calculated bond multiplicities in the $COCHN_2$ fragment.

Recently the molecular orbital method was used to demonstrate the occurrence of *cis–trans* isomerism in the diazoketone series. The calculations were made for diazoacetone and diazoacetophenone. The author succeeded in demonstrating convincingly the occurrence of rotational isomerism in these compounds. The geometrical configuration of diazoacetone used in the calculation is presented in Fig. 3†, which also gives the results of the calculation of the distribution of charges and dipole moments in the *s-cis* and *s-trans* diazoacetone isomers[128].

Studies in recent years have made it possible to describe the structure of diazoketones in the following way. The $COCHN_2$ ($OC^2-C^1-N^2-N^1$) fragment is coplanar, the C^1 atom is sp^2-hybridised, the C^1-N^2 bond is formed as a result of the withdrawal of the lone electron pair of the nitrogen atom to the sp^2 orbital of the carbon atom (singlet), and the lone electron pair in the p orbital of the C^1 carbon atom is conjugated with the π orbitals of the carbonyl and diazo-groups. This results in a conjugation chain involving five atoms. The above effect is illustrated in Fig. 2. It can also be described by the canonical structures‡



The structures of diazoacetone and diazoacetophenone have been discussed from the standpoint of the molecular

† The *Z* axis is not shown in Fig. 3; it is perpendicular to the plane and demonstrates the planarity of the molecule.

‡ Another interpretation of the bond types is possible. In particular, the C^1-N^2 bond is regarded as covalent and conjugation in the CNN fragment arises owing to the p electron of the carbon atom, the two p electrons of the middle nitrogen atom, and the p electron of the extreme nitrogen atom[132].

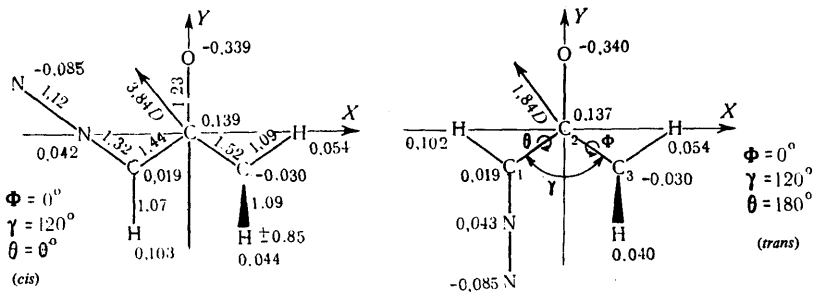


Figure 3.

orbital theory[128]. In the diazoacetone molecule there are 28 molecular orbitals: 21 of these are σ orbitals and 7 are π orbitals. Six π orbitals are formed from the $2p_Z$ orbitals of the nitrogen, carbon, and oxygen atoms. The seventh π orbital is formed from the orbitals linking in the methyl group the two hydrogen atoms located above and below the plane in which the diazoketone is located (the pseudo-π-orbital). Of the seven π orbitals, four are populated and three are vacant. The π orbital with the lowest energy (1π) embraces the π bond of the carbonyl group. A higher π orbital (2π) embraces the CNN fragment and has no vertical nodal plane between the three atoms. The third π orbital constitutes a pseudo-π-bond. The fourth π orbital has the highest energy, is also linked to the CNN bond, and has no nodal plane between the nitrogen atoms. The first antibonding π^* orbital (the $5\pi^*$ molecular orbital) embraces the entire diazoketone and has nodal planes between O and C, C and N, and N and N bonds. Of the 21 σ molecular orbitals, the first 12 are populated and the remaining 9 are vacant.

In the study of the mass spectra of diazoacetone, chlorodiazoacetone, trichlorodiazoacetone, and diazoacetophenone, the ionisation potentials of the compounds were determined as 9.40 ± 0.03, 9.92 ± 0.1, 9.95 ± 0.06, and 9.22 ± 0.04 eV respectively. From the ionisation potentials and the appearance potentials of the fragment ions, the bond dissociation energies in the above diazoketones were obtained: 3.3 eV for diazoacetone, 2.9 eV for chlorodiazoacetone, and 2.2 eV for trichlorodiazoacetone[141].

The above characteristics of the structure of diazoketones are responsible for their high chemical reactivity.

IV. CHEMICAL PROPERTIES

An intense investigation of the chemical reactions of diazoketones was begun in 1928, when Arndt and Amende discovered the reaction in which diazoalkanes are acylated by carboxylic acid halides[17]. Since then diazoketones have become readily available. They undergo reactions of the following characteristic types: (1) reactions with evolution of nitrogen; (2) reactions involving the nitrogen atoms of the diazo-group; (3) reactions in which the mobile α-hydrogen atom is substituted. Examples of these reactions are given below.

1. Reactions involving the Formation of Carbonium Ions

This group of reactions includes the reactions of diazoketone with water, alcohols, acids, halogens, *N*-halogeno-derivatives, and nitrogen oxides. Under the usual conditions, diazoketones are as a rule inert with respect to water. However, a few drops of acid (usually inorganic) are sufficient for the evolution of nitrogen to begin and an α-hydroxyketone to form. Sometimes the reaction takes place on heating. For example, an acetylmethanol may be obtained in this way from diazoacetone[94]. The hydrolysis of higher diazoketones with water is usually carried out in dioxan in the presence of catalytic amounts of inorganic acids.

Despite the fact that the decomposition of diazoketones in water has been known for a long time, the mechanism of this reaction remained controversial until recently. Wolff[94] and Bredig and Frankel[142] described the decomposition of diazoketones in an acid medium by the following process:

$$RCOCHN_2+H^++H_2O\longrightarrow RCOCH_2OH+N_2+H^+.$$

In other studies a different reaction mechanism was proposed by analogy with the hydrolysis of diazoalkanes, which has an *A*-S$_E$2 mechanism[143–145]:

$$RCOCHN_2+H^+\longrightarrow RCOCH_2N_2^+, \quad (a)$$

$$RCOCH_2N_2^+ + H_2O \rightarrow RCOCH_2OH + H^+ + N_2. \quad (b)$$

The rate of hydrolysis is determined by stage (a). The role of catalytic amounts of acid reduces to the protonation of the diazoketone.

Ingold suggested a mechanism including the protonation of the diazoketone (c) in the pre-equilibrium stage[146] with a subsequent slow stage (d) involving its decomposition—an *A* – S$_E$1 mechanism:

$$RCOCHN_2 + H^+ \rightleftharpoons RCOCH_2N_2^+, \quad (c)$$

$$RCOCH_2N_2^+ \rightleftharpoons RCOCH_2^+ + N_2, \quad (d)$$

$$RCOCH_2^+ + H_2O \rightarrow RCOCH_2OH + H^+. \quad (e)$$

However, he did not reject the possibility that diazoketones may be converted into hydroxyketones via the bimolecular mechanism involving reaction (a) and (b).

Whereas previously it was believed that the role of acid reduces to the protonation of the diazoketone, in recent studies it has been suggested that the catalyst protonates water[147,148]. The hydronium ion reacts with primary diazoketones via the mechanism

$$RCOCHN_2 + H_3O^+ \rightleftharpoons RCOCH_2N_2^+ + H_2O. \qquad (f)$$

Subsequently the diazonium ion is converted into a hydroxyketone via mechanism (b) (an A – SE2 mechanism)[149-152].

In contrast to primary diazoketones, secondary diazoketones are protonated irreversibly [stage (g)]. This stage is rate-determining. The hydroxyketone is formed from the diazonium ion via mechanisms (d) and (e):

$$RCOC(R)N_2 + H_3O^+ \rightarrow RCOCH(R)N_2^+ + H_2O. \qquad (g)$$

This reaction mechanism has been demonstrated for arylbenzoyldiazomethanes[153,154] and cyclic diazoketones[155,156].

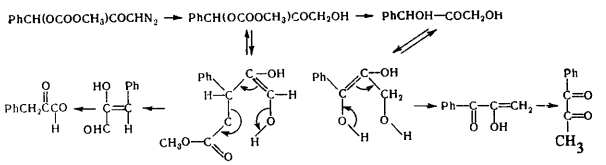
Acid hydrolysis of primary diazoketones does not result in the formation of α-hydroxymethylketones only. In the decomposition of 3-diazo-1-methoxycarbonyl-1-phenylpropan-2-one by dilute sulphuric acid, Bradley and Eaton isolated benzylglyoxal in 12% yield, the formation of which they believe may be due to an anionotropic migration of the phenyl group and the elimination of the second substituent[157]. Weygand et al. repeated this reaction with the diazoketone containing labelled carbon atoms and isolated benzylglyoxal in 6% yield[158]. On the basis of the measurements of the radioactivity of the products, they established that the phenyl residue does not migrate:

$$C_6H_5{}^{14}CH(OCOOCH_3)COCHN_2 \rightarrow C_6H_5{}^{14}CH_2COCHO.$$

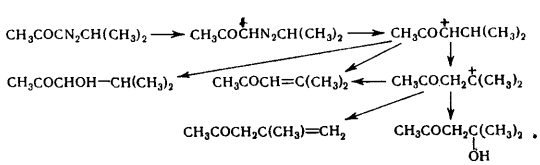
This reaction was investigated in greater detail by Dahn et al.,[159] who employed 10% phosphoric acid for the hydrolysis and obtained benzylglyoxal in 44% yield. In addition to the aldehyde, benzoylacetyl was also isolated. Hydrolysis of the diazoketones in which the carbon atom linked to the diazo-group was labelled confirmed that the phenyl group does not migrate from the first to the third atom, since the benzoic acid thus obtained is not radioactive:

$$\begin{matrix} C_6H_5 \\ | \\ CH{-}CO{-}{}^*CHN_2 \\ | \\ OCOOCH_3 \end{matrix} \rightarrow C_6H_5CH_2CO{-}{}^*CHO \rightarrow C_6H_5COOH + CO_2 + {}^*CO_2.$$

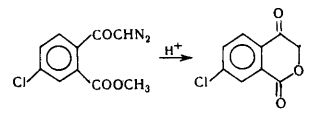
The authors explain the formation of benzylglyoxal and benzoylacetyl by the intermediate formation of a hydroxyketone and a diol:



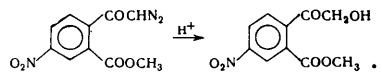
Unsaturated ketones were isolated in the acid hydrolysis of 3-diazo-1-methylpentan-2-one together with hydroxymethyl ketones[160]:



In the acid hydrolysis of diazoketones, the stabilisation of the carbonium ion depends both on the nature of the substituents and on their distribution relative to the diazo-group. For example, p-chloro-ω-diazo-o-methoxycarbonylacetophenone gives 7-chloro-1,4-dioxoisochroman on treatment with 3% sulphuric acid[161]:

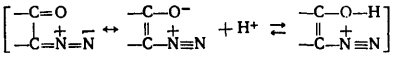


ω-Diazo-o-methoxycarbonylacetophenone undergoes a similar reaction[162]; under the hydrolysis conditions, ω-diazo-o-methoxycarbonyl-p-nitroacetophenone is converted into ω-hydroxy-o-methoxycarbonyl-p-nitroacetophenone[163]:



The acidity of alcohols is insufficient for the decomposition of diazoketones. Therefore the reaction with alcohols is as a rule carried out in the presence of catalysts. Inorganic acids, boron trifluoride, and metallic copper are employed for this purpose[153,164-166]. The reaction results in the formation of alkoxy-derivatives of α-hydroxyketones.

In contrast to diazoalkanes, diazoketones are more stable in relation to electrophilic agents. Many of them do not react with organic acids such as benzoic and cold acetic acids. Bisdiazoketones in which the diazo-group is between two carbonyl groups are not decomposed by concentrated nitric acid[137]. The authors explain this unusual behaviour of bisdiazoketones by the fact that the proton attacking the nucleophilic α-carbon atom is captured by the oxygen of the carbonyl group[137]:

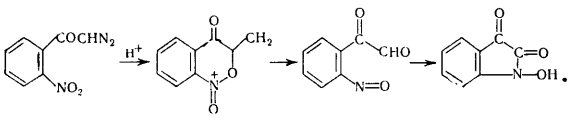


The inertness of diazoketones with respect to cold acetic acid makes it possible to carry out certain reactions in it[167].

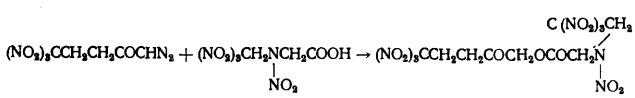
On heating with acetic acid, diazoketones form ketoesters[168-171]:

$$RCOCHN_2 + CH_3COOH \rightarrow RCOCH_2OCOCH_3.$$

An analogous synthesis was carried out using copper dioxide as a catalyst[172]. After refluxing 1-diazo-3-(*o*-nitrophenyl)acetone in glacial acetic acid, N-hydroxyisatin was isolated. The authors suggest that the initial reaction stage is cyclisation of the intermediate carbonium ion with formation of a six-membered ring followed by its deprotonation and cleavage to o-nitrosophenylglyoxal. Cyclisation of the latter leads to the formation of N-hydroxyisatin[173]:



Strong organic acids decompose diazoketones at room temperature[5]. ω-Nitrodiazoketones react with polynitrocarboxylic acids when the reactants are fused together[174]:



Platter and Heusser[175] achieved an interesting reaction of diazoketones. Starting with diazoketones and bromoacetic acid, they obtained butenolides:

$$RCOCHN_2+BrCH_2COOH\longrightarrow RCOCH_2OCOCH_2Br\longrightarrow \text{butenolides}\ .$$

Thiocarboxylic acids also decompose diazoketones with formation of the corresponding hydroxyketone esters[176].

The reaction of diazoketones with aliphatic and aromatic mono- and di-sulphonic acids led to the isolation of sulphonates derived from the α-hydroxyketones. The reaction is carried out in dioxan in the presence of a catalyst ($CuCl_2$) at 60–70°C[177] in polar solvents or acetic anhydride[34,178,179]. In the latter case the sulphonates are isolated after the hydrolysis of acetic anhydride with water. p-Toluenesulphonates derived from α-hydroxyketones are formed in high yield, readily crystallise, have distinct melting points, and may be used for the identification of diazoketones[178,179,180]:

$$RCOCHN_2+CH_3C_6H_4SO_2OH\longrightarrow RCOCH_2OSO_2C_6H_4CH_3+N_2\ .$$

Diazoketones undergo unusually interesting reactions with inorganic acids. However, only isolated examples of such reactions have been described. The reaction with nitric acid results in the formation of the corresponding nitric acid esters[34,138,167,181]:

$$RCOCHN_2+HNO_3\longrightarrow RCOCH_2ONO_2+N_2\ .$$

The reaction of diazoketones with sulphuric acid leading to the formation of sulphates derived from α-hydroxyketones has been described[34,153,182]:

$$2RCOCHN_2+H_2SO_4\longrightarrow (RCOCH_2O)_2SO_2+N_2\ .$$

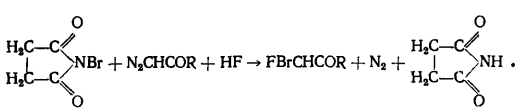
The reaction of diazoketones with phosphoric acid also yields the corresponding hydroxyketone esters[183].

In the reaction with inorganic acids, diazosulphones behave analogously to diazoketones. The synthesis of perchloric acid esters involving the mechanism

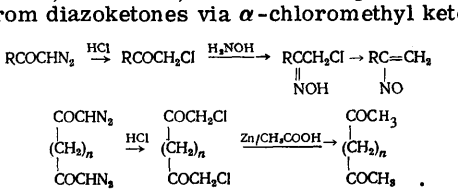
$$H_3CC_6H_4SO_2CHN_2+HClO_4\longrightarrow H_3CC_6H_4SO_2CH_2OClO_3+N_2$$

was described recently[184].

Hydrogen halides, except hydrogen fluoride, readily decompose diazoketones. Interesting experiments have been performed on the decomposition of diazoketones in hydrofluoric acid in the presence of N-bromosuccinimide[185]:



When diazoketones are treated with dry hydrogen chloride, α-chloromethyl ketones, which are starting materials for various syntheses, are obtained[5]. For example, nitroso-olefins, diketones, and other compounds have been obtained from diazoketones via α-chloromethyl ketones:



α-Bromomethyl ketones, formed in the reaction between diazoketones and hydrogen bromide, are also important starting materials for the synthesis of polyfunctional compounds[186]:

$$C_6H_5COCHN_2\xrightarrow{HBr}C_6H_5COCH_2Br\xrightarrow[CH_3CN]{AgNO_3}C_6H_5COCH_2ONO_2\rightarrow C_6H_5COCHO\ .$$

Hydriodic acid causes a far-reaching transformation of diazoketones leading to the formation of methyl ketones[187]. The conversion of the diazomethyl into the methyl group was first achieved by Wolfrom and Brown[187] for 1-diazoglucoheptulose[187]:

$$AcOCH_2(CHOAc)_4COCHN_2\xrightarrow{HI}AcOCH_2(CHOAc)_4COCH_3+N_2\ .$$

α-Iodomethyl ketones are formed according to the mechanism[138]

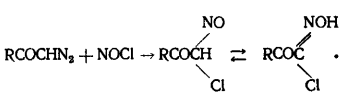
$$RCOCHN_2+HCl\rightarrow RCOCH_2Cl\xrightarrow{NaI}RCOCH_2I\ .$$

When diazoketones are decomposed in the presence of an excess thiocyanate, nitrate, and chloride anions in the reaction mixture, α-thiocyanato-, α-nitroxy-, and α-chloro-methyl ketones respectively are readily formed[138,188].

Treatment of diazoketones with chlorine, bromine, or iodine in inert solvents leads to the formation of $\alpha\alpha$-dihalogenomethyl ketones[187]. Iodobenzene dichloride may be employed as the chlorinating agent[189]:

$$ClCH=\underset{Cl}{C}COCHN_2+C_6H_5ICl_2\rightarrow ClCH=\underset{Cl}{C}COCHCl_2+C_6H_5I+N_2\ .$$

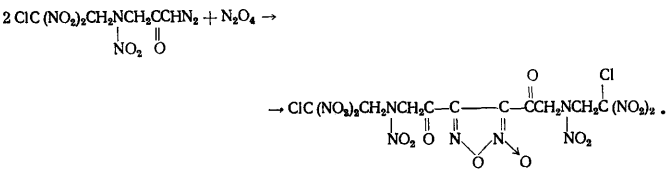
The reaction of a number of diazoketones with nitrosyl chloride has been investigated[190]. The resulting chloronitrosoketones are in tautomeric equilibrium with hydroxamic acid chlorides:



Benzoylphenyldiazomethane reacts with nitrogen tetroxide to form phenyldinitromethane[191]:

$$C_6H_5COCN_2C_6H_5+N_2O_4\longrightarrow HC(NO_2)_2C_6H_5\ .$$

It was established recently that ω-nitrodiazoketones are converted under the influence of nitrogen tetroxide into furoxans[192]:



In the series of diazoketones only a few examples of this interesting reaction have been carried out and it undoubtedly requires further study.

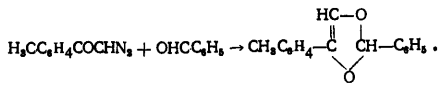
2. Reaction of Diazoketones with Carbonyl Compounds

This group of reactions includes those of diazoketones with aldehydes and ketones. The reaction of diazoketones with aldehydes was investigated for the first time by Diels and Ilberg[193]. On mixing 2-diazo-3-butanone with formaldehyde, they observed a vigorous evolution of nitrogen and heat. The reaction resulted in the isolation of o-hydroxy-2-methylbut-2-en-3-one:

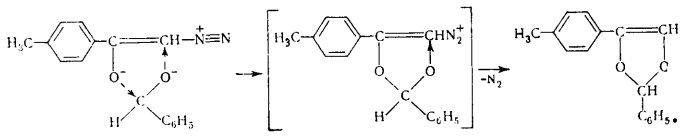
$$CH_3COCN_2CH_3+O=CH_2\rightarrow CH_3\underset{CH_3}{C}OC=CHOH+N_2\ .$$

The reaction of diazoketones with higher aldehydes occurs under more severe conditions. Thus on heating

with benzaldehyde in xylene for 18 h, *p*-methylbenzoyldiazomethane was converted in 39% yield into 2-phenyl-5-tolyl-1,3-dioxole[194]:

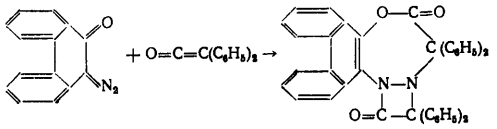


According to the authors, the condition governing the formation of dioxoles is the addition of the electrophilic carbon of the aldehyde group to the carbonyl oxygen of the diazoketone before the elimination of the diazo-group; otherwise the Wolff–Schroeter rearrangement is possible:

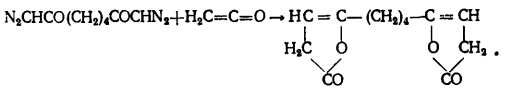


It is noteworthy that the reaction takes place smoothly only with *p*-methyl- and *p*-methoxy-benzoyldiazomethane. Benzoyldiazomethane having substituents with a +*C* effect either does not undergo the reaction or the reaction leads to the formation of diacylethylenes in high yields[194].

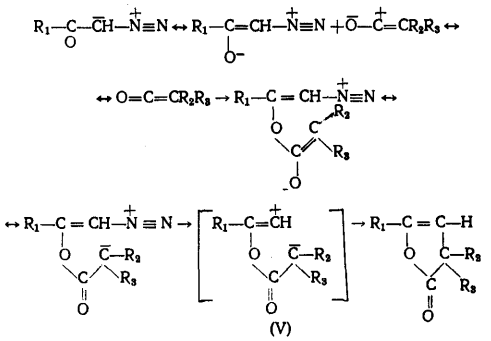
Diazoketones readily react with ketens. After allowing azibenzil to react with diphenylketen, Staudinger and Reber isolated a nitrogen-containing crystalline adduct[195]. Ried and Dietrich made a detailed study of the reaction of *o*-quinone diazides with ketens and showed that it results in the formation of polycyclic nitrogen-containing systems[196,197]:



Primary diazoketones react with ketens with evolution of nitrogen. This leads to the formation of βγ-butenolides, which split off a lactone and are converted into keto-acids[198]. The reaction of bisdiazoketones with ketens leads to the formation of bisbutenolides[198]:



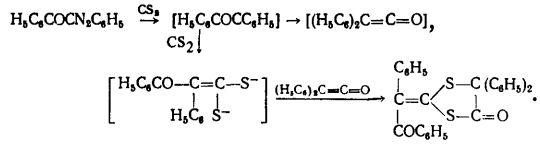
The reaction proceeds via the intermediate formation of a dipolar ion (V), which readily cyclises to a lactone[198]:



(V)

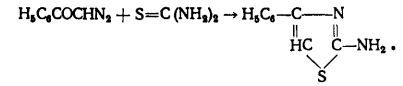
3. Reaction of Diazoketones with Sulphur-containing Compounds

In a study of the reaction of hydrogen sulphide with azibenzil, Meyer isolated 5-oxo-2-(2-oxo-1,2-diphenylethylidene)-4,4-diphenyl-1,3-dithiolane in 90% yield. Evidently, after the evolution of nitrogen, this reaction involves the formation of a carbene, part of which adds to the hydrogen sulphide and another part undergoes the Wolff–Schroeter rearrangement and adds to both sulphur atoms of the intermediate adduct[199]:

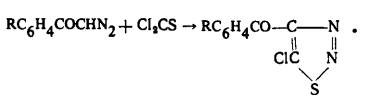


Analogous syntheses have been carried out by other investigators[200,201].

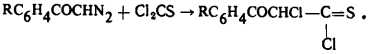
Benzoyldiazomethane reacts with thiourea to form a heterocyclic compound according to the mechanism[202]



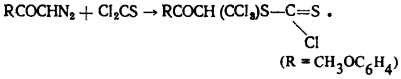
Depending on the position and nature of the substituent, ring-substituted benzoyldiazomethane derivatives can react with thiophosgene to form 1,2,3-thiadiazoles, substituted thiopropionic acid chlorides, and trichloroethanethiol derivatives. Thus *p*-nitro-, *p*-chloro-, and *p*-methyl-benzoyldiazomethane and *m*-nitrobenzoyldiazomethane react with thiophosgene to form 1,2,3-thiadiazoles[203]:



m-Methyl- and *m*-methoxy-benzoyldiazomethanes form β-aryl-α-chloro-β-oxothiopropionic acid chlorides:

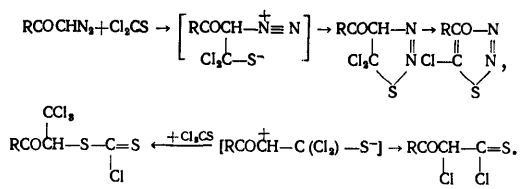


In the presence of an excess of thiophosgene, chlorothiocarbonic acid esters are formed:



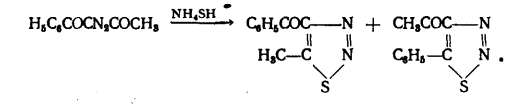
Azibenzil reacts with thiophosgene to form a thiafuran derivative via a thi-iran.

The authors suggest that the products enumerated above are obtained by the following mechanism:

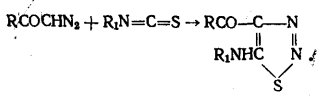


When secondary diazoketones react with hydrogen sulphide, thiadiazole derivatives are formed[92,204]. Thus treatment of azibenzil with hydrogen sulphide in ethanol in the presence of a small amount of ammonia leads to the

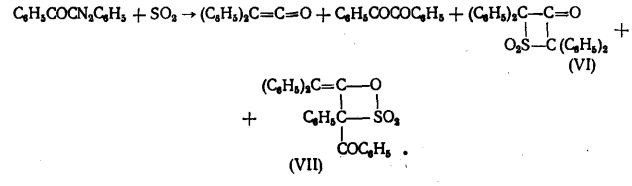
formation of 4,5-diphenyl-1,2,3-thiadiazole[205,206]. The reaction of asymetric 2-diazo-1,3-diketones with hydrogen sulphide in the presence of ammonia yields two isomeric 1,2,3-thiadiazolyl ketones: 4-benzoyl-5-methyl-1,2,3-thiadiazole and 4-acetyl-5-phenyl-1,2,3-thiadiazole[95]:



Ried and Beck obtained 1,2,3-thiadiazole by the reaction of primary diazoketones with mustard oils[207]:



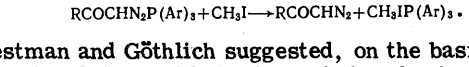
Thermolysis of azibenzil in benzene in the presence of sulphur dioxide yielded cyclic sulphones (VI, VII), benzil, and diphenylketen. Photolytic decomposition of azibenzil in the presence of sulphur dioxide at temperatures between −5° and −20°C leads to the formation of the above sulphones and benzil[208]:



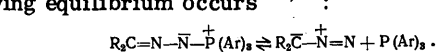
4. Reaction with Phosphines and Organophosphorus Compounds

The reaction of diazo-compounds with tertiary phosphines, in particular with triphenylphosphines, which was discovered by Staudinger, has been described in a number of publications[209-211]. It was investigated in detail by Bestman's school[143,212]. It results in the formation of triphenylphosphazines[212]. α-Ketoaldehydes[213], ketoesters[214], methyl ketones[212], and heterocyclic compounds[25,143,184,215,216] may be obtained via the phosphazines.

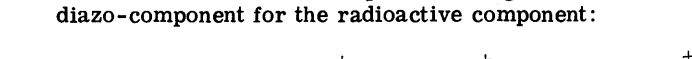
It is striking that very pure diazoketones may be obtained by the cleavage of phosphazines with methyl iodide[212,217]:



Bestman and Göthlich suggested, on the basis of the chemical and thermal behaviour of phosphazines, that the following equilibrium occurs[211,212]:

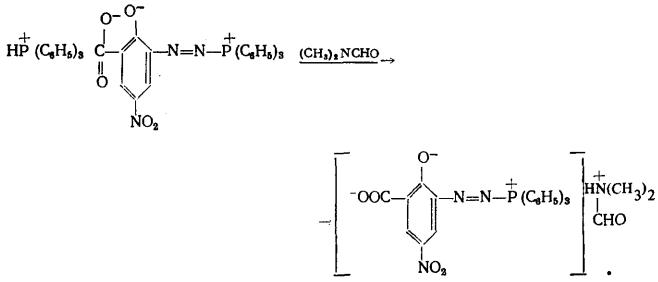


The accumulation of electronegative substituents in the diazoketone promotes a shift of the equilibrium to the right. To demonstrate the occurrence of the equilibrium, the authors carried out an exchange between the diazo-component of the phosphazine and a diazoketone containing a labelled carbon atom and isolated a radioactive phosphazine. This involved a complete exchange of the inactive diazo-component for the radioactive component:



Infrared spectroscopic data also confirmed this conclusion. The phosphazine spectra, recorded using potassium bromide discs, do not have absorption bands characteristic of the diazo-group, while in chloroform solution the band does appear[218].

Quinone diazides (*o*- and *p*-derivatives) react with triphenylphosphine to form the corresponding phosphazines[217,219]. *o*-Quinone diazides with electronegative substituents in the 4- and 6-positions of the ring behave anomalously[184,217]. In some cases it proved possible to isolate stable yellow adducts with the composition *o*-quinone diazide: $P(Ar)_3 = 1:2$. The diadducts are salt-like. This was confirmed by the finding that the triphenylphosphine molecule in the diadduct, which is linked by an anionic bond, is readily substituted by a dimethylformamide molecule:

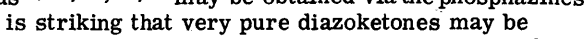


Apart from triphenylphosphine, the more nucleophilic triaminophosphines may be employed as the second component in the formation of phosphazines. In this case the reaction takes place instantaneously[220].

Phosphazines are synthesised in ether[211,212], acetonitrile[106], isopropyl ether[216], ethyl acetate[55], or in a mixture of benzene and ether[221]. Sometimes anhydrous zinc chloride is employed as a catalyst[213].

5. Electrophilic Substitution of α-Hydrogen in Diazoketones

Diazoketones are known to undergo a reaction in which electrophilic substitution of the hydrogen at the carbon atom linked to the diazo-group takes place. The reaction was first discovered by Buchner[221] when he allowed diazoacetic ester to react with yellow mercury(II) oxide:



The reaction has now been described in connection with the synthesis of mercury derivatives of 2,4,6-trimethylbenzoyldiazomethane, diazoacetone, and 4-methyldiazopentan-2-one[130,222]. The synthesis was carried out in anhydrous ether or petroleum ether using equimolar amounts of the reactants.

Silver oxide can also be employed as a deprotonating agent for diazoketones. The reaction is performed in tetrahydrofuran (THF) at temperatures between −15° and 0°C. Silver derivatives of diazoketones are excellent alkylating agents and serve as intermediates for the synthesis of unsaturated diazoketones[223]:

Organotin derivatives of diazoacetic ester, formed in the reaction of the latter with organotin derivatives of alkylamines, have been recently described[224].

An interesting example of this range of reactions of diazo-derivatives was recently discovered by Schollkopf and coworkers[225,226]. They succeeded in synthesising α-nitrodiazo-compounds. Thus nitrodiazoacetic ester was obtained by nitrating diazoacetic ester with nitrogen pentoxide[225]. Benzoyldiazomethane reacts with nitrogen

pentoxide in carbon tetrachloride at −30°C to form benzoylnitrodiazomethane[226]:

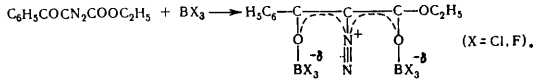
$$C_6H_5COCHN_2+N_2O_5\longrightarrow C_6H_5COC(NO_2)N_2\ .$$

By nitrating nitrodiazomethane[135] with nitrogen pentoxide, it proved possible to isolate a most interesting α-nitrodiazoalkane: dinitrodiazomethane[227].

We believe that a more detailed study of the above reactions and subsequent transformations of the resulting products should lead to a further development of this interesting field in the chemistry of diazo-compounds.

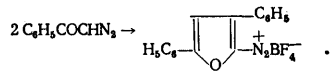
6. The Complex-forming Capacity of Diazoketones

The synthesis of internal diazonium complexes of diazocarbonyl compounds was first reported by Fahr[228], who found that benzoyldiazoacetic ester reacts with boron trifluoride or trichloride to form colourless, stable, but moisture-sensitive compounds. The following structure was attributed to them:

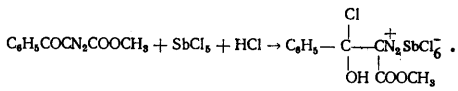


(X = Cl, F).

Benzoyldiazomethane reacts with boron trifluoride-ether in toluene at 60–70°C with evolution of nitrogen and the formation of 2,4-diphenyl-furan-5-diazonium fluoroborate, the first example of compounds with a diazonium group at the furan ring[229–231]:



Benzoyldiazoacetic ester reacts with antimony pentachloride in methylene chloride in the presence of hydrogen chloride, forming a diazonium salt[232]:



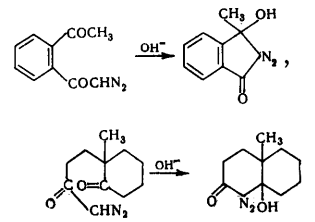
A complex of diazobarbituric acid with di(trinitromethyl)mercury was described recently. It is interesting that the reaction of 9-diazofluorene and diphenyldiazomethane with di(trinitrophenyl)mercury led to the isolation of 1-biphenylene-2,2-dinitroethylene and 2,2-dinitro-1,1-diphenylethylene[233].

7. Reactions of Diazoketones under the Influence of Bases

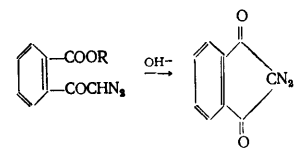
The reactions of diazoketones with bases have been inadequately investigated, evidently owing to their complexity. The reaction takes place unambiguously in the case of the amide of diazoacetic ester[234] and 2-diazo-3-pentanone[235]. In the first case the product is 5-oxo-1,2,3-triazole and in the second 1-(3,3-dimethyl-2-oxobutyl)-5-(2,2-dimethyl-1-oxopropyl)tetrazole. The reaction of ω-diazoacetophenone with sodium hydroxide or sodium methoxide in dioxan and ether leads to the formation of benzoic acid, 4-phenylbenzoylpyrazole, 3-benzoyl-5-hydroxy-4-phenylpyrazole, acetophenone, hydrogen cyanide and hydroxylamine. In concentrated sodium methoxide solutions the products are 3-benzoyl-4-hydroxy-5-phenylpyrazole and 5-benzoyltetrazole[236]. The reaction of diazoacetophenone with potassium t-butoxide yields a dimer of diazoacetophenone, 5-benzoyl-1-phenyltetrazole, and 5-benzoyl-2-phenylacyltetrazole. 1-Phenylacyltetrazole is obtained in ether in the presence of ammonium chloride[237].

On treatment with bases, diazodicarbonyl compounds decompose into diazomonocarbonyl derivatives[238]. No hypotheses have been put forward concerning the mechanism of the reaction of diazoketones with bases. A detailed study of the process is necessary in order to elucidate the causes of the formation of such a large number of reaction products.

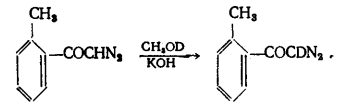
It was found recently that diazoketones undergo intramolecular condensation on treatment with alkalies[239]



Under the influence of bases, alkoxycarbonyldiazoketones undergo the Dieckmann condensation:



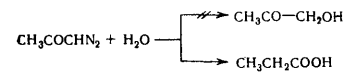
Diazoketones which are incapable of undergoing the above condensations, readily exchange their α-hydrogen atom for deuterium in an alkaline medium, which indicates an anionic mechanism of the above condensation[239]:



8. Reactions of Diazoketones via Ketocarbenes

A characteristic reaction of diazoketones is decomposition via ketocarbenes on irradiation and under the influence of heat and light. The intermediate species with an incomplete octet at the α-carbon atom, formed after the elimination of nitrogen, can be stabilised in different ways.

Wolff, who studied the reaction of diazoacetone and diazoacetophenone with water in the presence of silver oxide, isolated, instead of the expected α-hydroxyketones, propionic and phenylacetic acids[94,120].



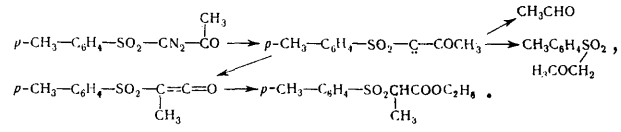
Somewhat later and independently of Wolff, Schroeter studied a similar reaction of phenylbenzoyldiazomethane and isolated diphenylacetic acid. By thermolysing azibenzil, he succeeded in obtaining diphenylketen—an intermediate in the formation of diphenylacetic acid[240,241]:

$$C_6H_5COCN_2C_6H_5\rightarrow C_6H_5\ddot{C}OCC_6H_5\rightarrow(C_6H_5)_2C{=}C{=}O\ .$$

Subsequently the conversion of α-diazoketones into acids or their derivatives, which takes place on heating under the influence of catalysts or on irradiation with

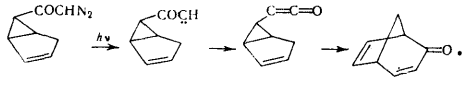
ultraviolet light in the presence of water, alcohols, ammonia, amines, etc. was called the Wolff–Schroeter rearrangement (more often this reaction is referred to as the Wolff rearrangement). Excellent reviews dealing with various reactions of diazo-compounds describe in detail both the theoretical and experimental aspects of this rearrangement[6,8,242–251]. A systematic account of work published recently is given below.

The catalysis of *p*-tosyl(acetyl)diazomethane in ethanol leads to the formation of ethyl α-methyl-α-tosylacetate, acetaldehyde, and tosylacetone[252]:



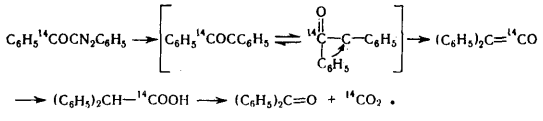
The reaction proceeds via the intermediate formation of a ketocarbene.

Recently the Wolff–Schroeter rearrangement has been intensively investigated for diazoketones with cyclic substituents[253–257]. The photolysis of *endo*-6-diazomethyl-oxobicyclo[3,2,0]hex-2-ene in tetrahydrofuran yielded bicyclo[3,2,1]octa-3,6-diene-2-one—the product of the intramolecular cyclisation of the keten formed as a result of the normal Wolff rearrangement[254]:

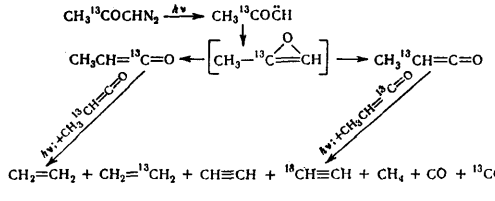


In contrast to the mechanism proposed previously for the Wolff–Schroeter rearrangement, where the formation of the intermediate keten was assumed to take place via a ketocarbene, it has been shown[258] that the ketocarbene is converted into the keten via acetylene oxide [oxiren].

Franzen achieved the photochemical decomposition of azibenzil containing a labelled carbon atom in the carbonyl group. The position of the labelled atom was established by the oxidative decarboxylation of the resulting diphenylacetic acid. Subsequently the radioactivity of the carbon dioxide formed was measured. The author concluded that the ketocarbene is stabilised as a result of the migration of the phenyl group with formation of diphenylketen[259]:

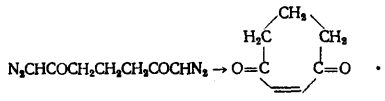


The results of this study agree with earlier data[260]. The gas-phase photolysis of diazoacetone and 2-diazo-3-butanone with a labelled carbon atom in the carbonyl group leads to the formation of a large number of products[258]: non-radioactive and radioactive unsaturated hydrocarbons, carbon monoxide, and methane. The appearance of these compounds can be accounted for by the intermediate formation of an oxiren according to the mechanism

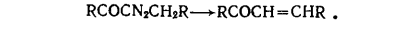


Evidently additional studies are necessary to prove unambiguously the validity of the above mechanism.

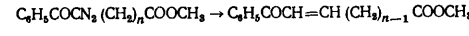
The rearrangement of a ketocarbene into ketens is not the only possible stabilisation pathway. For example, the decomposition of benzoyldiazomethane in the presence of copper(I) chloride in an inert solvent gives a 60% yield of 1,2-dibenzoylethylene[261], which is a valuable product for the synthesis of heterocyclic compounds[262,263]. Thermolysis of 1,7-bisdiazo-2,6-heptanedione in benzene in the presence of copper(II) oxide leads to the formation of 3,7-dioxocycloheptene[264]:



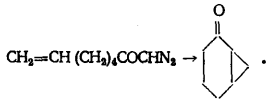
Under analogous conditions, cyclic diazoketones form polymeric products in addition to the dimers[265–267]. When diazoketones in which a CH group adjoins the diazo-group decompose under the influence of light or silver oxide, αβ-unsaturated ketones are formed as a rule[21]. The ketocarbene is stabilised as a result of the migration of the hydrogen atom:



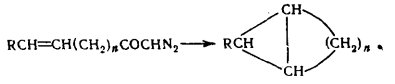
Recently a number of unsaturated ketoesters were synthesised in this way[268]:



If the decomposition of unsaturated diazoketones is carried out in inert solvents, the ketocarbene formed may be stabilised in yet another way, namely via intramolecular addition of the carbon atom with an incomplete octet to the double bond, resulting in the formation of a cyclic product. Thus, when 1-diazo-oct-7-en-2-one is refluxed in cyclohexane in the presence of copper bronze, bicyclo-[0,1,4]-2-heptanone is formed[299]:

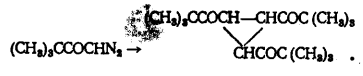


The intramolecular reaction of unsaturated diazoketones was investigated in greater detail by Fawzi and Gutsche[270], who note that substituents at the double bond do not have a significant influence on this reaction:



If the diazomethyl group is separated from the double bond by a benzene ring or the double bond is located in a ring, polycyclic systems are formed[271–274].

Low yields of cyclopropanes may be obtained by the thermal decomposition of diazoketones[275]. When the reaction is carried out in thioanisole in nitrogen and in the presence of copper bronze, the yield of the cyclic compound may be increased[276]:

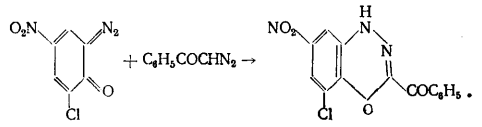


The decomposition of diazoketones in the presence of liazoalkanes leads to the formation of azines[259,277]:

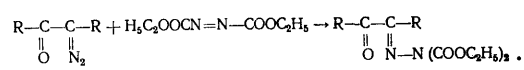


The decomposition of *o*-quinone diazides in the presence of α-diazoketones and diazoacetic ester does not terminate at the stage involving the formation of azimes but leads to

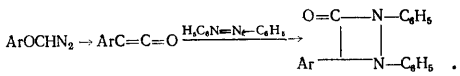
the formation of bicyclic products[278]. Thus, when 6-chloro-4-nitrobenzoquinone 2-diazide [6-chloro-2-diazo-4-nitro-1-oxobenzene?] was heated with diazoacetophenone, 2-benzoyl-8-chloro-6-nitro-4*H*-benzo-1,3,4-oxadiazine was isolated:



α-Diazoketones react with azodicarboxylic acid diesters on heating with formation of the monohydrazones of 1,2-dicarbonylcompounds[279,280]:



The reaction with azobenzene takes place under the influence of ultraviolet light. This involves the formation of ketens which are subsequently coupled to the azo-group with formation of heterocyclic compounds[281]:



2-Diazo-1,3-dicarbonyl compounds react similarly with azo-derivatives[282].

V. SOME ASPECTS OF PRACTICAL APPLICATIONS

In a discussion of the practical applications of diazoketones, one must emphasise in the first place their great preparative value for the synthesis of various classes of organic compounds: aliphatic, aromatic, heterocyclic, and heterochain compounds, and polymers. The possibilities of diazoketones in the synthesis of products which are difficult and sometimes impossible to obtain by other methods are unsurpassed. In this sense comparison of aliphatic diazocompounds with the "Genie of Aladdin's Lamp", made in one of Huisgen's studies, describes graphically and accurately their role in organic chemistry.

The biological activity of certain diazoketones has been investigated. 6-Diazo-5-oxonorleucine inhibits the metabolic process in photosynthesis in algae[283]. The same compound, diazotetronic acid, and *O*-diazoacetyl-L-serine inhibit the growth of malignant tumours[284-288]. The antileukaemic action of 1,2-bisdiazoacetylethane has been studied. The preparation exhibits a wide spectrum of antitumour activity, inhibits or completely suppresses the growth of many experimental tumours (sarcoma-45, Geren [spelling uncertain (Ed. of Translation)] carcinoma, Walker carcinosarcoma, carcinoma-755, sarcoma-180, and Ehrlich ascites tumour)[289]. It was noted recently that certain diazoketones exhibit antitumour activity against three ascites tumours in mice: ARE-G, S-180, Nkly, and haematocytoblastosis La in mice of strain C_{57}bl.[136]

1,8-Bisdiazo-octane-2,7-dione shows a powerful mutagenic activity over a wide spectrum of mutations[290-293].

It is interesting that 1,7-bisdiazo-4-nitro-4-azaheptane-2,6-dione exhibits a weak antibacterial activity, is relatively non-toxic, and does not show neurotropic, anticonvulsant, antitremor, analgesic, and soporific effects[294].

Unfortunately we were unable to find any publications dealing with systematic studies of the biological activity of diazoketones, although, as pointed out by Berlin and Yaguzhinskii[295], they are of undoubted interest in this respect.

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