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The Schmidt Reaction with Ketones

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The Schmidt reaction with ketones is reviewed. Particular attention has been devoted to the mechanism and kinetics of the interaction of ketones with hydrazoic acid. The side reactions accompanying the main process and the applications of the Schmidt reaction have been indicated.
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I. INTRODUCTION

The Schmidt reaction with ketones belongs to a large group of reactions known as sextet rearrangements. A characteristic feature of these reactions is the formation of an intermediate compound with a sextet of electrons at the nitrogen atom. The reaction is interesting because of its synthetic possibilities. The problems associated with its mechanism include the behaviour of weak bases in strongly acidic media, the characteristics of the reactivity of carbonyl compounds, the capacity of substituents to migrate, and some others. The Schmidt reaction is also a convenient model for the investigation of acid-catalysed processes.

The method is suitable for the preparation of substituted amides, tetrazoles, and ureas which are not otherwise available; some of these compounds exhibit high biological activity and have practical applications[1,2].

Numerous studies have been made on the Schmidt reaction and these have been reviewed by Wolff[3] and Smith[4] who describe the experimental data obtained up to the end of 1962. This review takes into account certain studies which were published later, particularly the recent kinetic investigations, and in this connection the mechanism of the reaction is considered in greater detail.

II. MECHANISM OF THE SCHMIDT REACTION WITH KETONES

1. Overall Characteristics of the Reaction and Its Mechanism according to Smith[4]

The rearrangement of carbonyl compounds under the influence of hydrazoic acid in the presence of acid catalysts was discovered by Schmidt in 1923.[5] It was found that carboxylic acids are converted into amines, ketones into amides, and aldehydes into nitriles and formamides:

$$RCOOH + HN_3 \xrightarrow{H^+} RNH_2 + CO_2 + N_2 , \quad (1)$$

$$RCOR' + HN_3 \xrightarrow{H^+} RNHOCR' + RCONHR' + N_2 , \quad (2)$$

$$RCHO + HN_3 \xrightarrow{H^+} RCN + RNHOCH + N_2 . \quad (3)$$

In the presence of an excess of hydrazoic acid, tetrazoles, aminotetrazoles, and ureas are formed from ketones:

$$RCOR + 2HN_3 \rightarrow R{-}N{=}\underset{\underset{N}{\|}}{C}{-}R , \quad (4)$$

$$RCOR + 3HN_3 \rightarrow R{-}NH{-}\underset{\underset{N}{\|}}{C}{-}N{-}R , \quad (5)$$

$$RCOR + 2HN_3 \rightarrow RNHOCNHR . \quad (6)$$

Schmidt postulated that the reaction involves the cleavage of hydrazoic acid into an imino-radical [NH] and nitrogen. The imino-radical forms with the carbonyl compound an adduct, which isomerises directly to the reaction products or is converted into an oxime with subsequent Beckmann rearrangement[6]:

$$RCOR + [NH] \rightarrow \begin{cases} [R{-}\overset{OH}{\overset{|}{C}}{-}R] \\ [R{-}\overset{NOH}{\overset{\|}{C}}{-}R] \end{cases} \rightarrow RCONHR . \quad (7)$$

However, in later studies by other investigators it was shown that this hypothesis is erroneous. Modern hypotheses concerning the mechanism of the Schmidt reaction have been put forward by Oliveri–Mandala[7], Hurd[8], Sanford et al.[9], and Newman and Gildenhorn[10]. The results of these studies and his own investigations have been reviewed by Smith[11]. Taking into account certain modifications introduced in subsequent years by Smith[4], the mechanism of the Schmidt reaction in ketones can be represented as follows:

$$R{-}\underset{\underset{HO\ \ N_3}{|}}{C}{-}R' \rightleftarrows R{-}CO{-}R' \ (a) \xrightleftharpoons{H^+} R\overset{+}{C}(OH)R'$$

$$R{-}\underset{\underset{H_2O_+\ \ N_3}{|}}{C}{-}R' \ (b) \qquad R{-}\underset{\underset{HO\ \ HN_2}{|}}{C}{-}R' \ (b')$$

$$R{-}\underset{\underset{NN_2}{\|}}{C}{-}R' \ (c) \qquad R{-}\underset{\underset{N_2N}{\|}}{C}{-}R' \ (c')$$

$$R{-}N{=}\overset{+}{C}{-}R' \ (d) \qquad R{-}\overset{+}{C}{=}N{-}R' \ (d')$$

$$R{-}NH{-}\underset{\underset{OH}{|}}{\overset{+}{C}}{-}R' \ (e) \qquad R{-}\underset{\underset{OH}{|}}{\overset{+}{C}}{-}NH{-}R' \ (e')$$

$$R{-}NH{-}\underset{\underset{O}{\|}}{C}{-}R' \qquad R{-}\underset{\underset{O}{\|}}{C}{-}NH{-}R' \quad (8)$$

Regardless of the pathway (*A* or *A'*) followed by the rearrangement, the first reaction stage is always the interaction of the carbonyl compound (in a free or protonated form) with hydrazoic acid, which leads to the azidohydrin (*b*). Subsequent dehydration leads to the iminodiazonium ion (*c*).

As a result of the sp^2 hybridisation of the central carbon atom, the iminodiazonium ion can assume two conformations—*syn*- and *anti*-(*c* and *c'*). The assumption of the existence of two conformers of the iminodiazonium ion accounts for the formation of two isomeric amides from asymmetric ketones. The loss of nitrogen by the iminodiazonium ion is accompanied by the migration of the substituent (R or R') in the *anti*-position in relation to the diazo-group. The iminocarbonium ion (*d*) arising under these conditions interacts with water or with any other nucleophilic agent, forming the reaction products.

The mechanism [Eqns. (8)] proposed above explains satisfactorily the principal features of the reactions of ketones with hydrazoic acid although cases are known which do not fit these concepts. A detailed examination of the reaction mechanism is best made by examining the individual stages of the process, beginning with the state of the reactants in the reaction medium.

2. Behaviour of Ketones and Hydrazoic Acid in Strong Acid Solutions

The commonest catalyst of the Schmidt reaction with ketones is sulphuric acid. In most cases sulphuric acid is employed in a 10–20-fold excess in relation to the carbonyl compound and serves also as the reaction medium. In this connection it is desirable to examine the behaviour of ketones and hydrazoic acid in aqueous sulphuric acid solutions.

Ketones are typical weak organic bases which are protonated in strong acid solutions at the oxygen of the carbonyl group[9]:

$$RCOR' + H^+ \rightleftarrows [RCOHR']^+ . \qquad (9)$$

The first quantitative studies on the protonation of ketones were performed by Hammett[12]. Stewart and Yates[13] determined spectrophotometrically the pK_a for a large series of substituted acetophenones and showed that the compounds investigated belong to the series of Hammett bases. However, in a later study[14] it was found that the protonation of acetophenone and certain other conjugated ketones can be satisfactorily described by the amide acidity function H_A. Benzophenones have an individual H_B acidity scale[15]. Reinvestigation of the basicity of the series of aromatic compounds recently showed that the protonation of acetophenone and benzophenone is more satisfactorily described by the H_0 Hammett function than by H_A.[16] It is believed[17] that these discrepancies are associated with the inadequate interpretation of the experimental data by different investigators. The reason for this is the insufficient rigour of the postulates adopted in the development of methods for the calculation of the ionisation ratio of the bases.

The protonation of aliphatic ketones has been less well studied. It has been found that the ionisation constants of their conjugate acids are mainly in the range $pK_a = -6 - 8$.[18,19] The introduction of electronegative substituents into the ketone molecule greatly reduces the basicity of such compounds[20,21]. It has been shown[20,22] that the protonation of acetone, 2-butanone, 2-hexanone, and many nitroketones is satisfactorily described by the Hammett equation.

The interpretation of the protonation of ketones in terms of mechanism (9) is undoubtedly a simplification and does not reflect all the essential features of the process. Hauldna and coworkers[23–25] believe that the following equilibria are characteristic of certain ketones in solutions of strong inorganic acids:

$$S \cdot sH_2O + H^+ xH_2O \rightleftarrows S\cdots H^+ \cdot nH_2O + (s + x - n)\,H_2O ,$$
$$S\cdots H^+ nH_2O \rightleftarrows SH^+ + nH_2O , \qquad (10)$$

where S is the base (ketone). Consequently the results obtained in the study of the protonation of aliphatic ketones refer to equilibrium (10) and not (9).

In many cases there are data confirming these hypotheses. At the same time the results of the study of the activity coefficients of 2-butanone in sulphuric acid obtained by the same investigators[26] are inconsistent with this approach.

Eqn. (9) altogether fails to take into account the effect of the solvent. There is reason to believe[27] that both forms of ketones (S and SH^+) are hydrated and the protonation process may be represented as follows:

$$S \cdot bH_2O + H^+ xH_2O \rightleftarrows SH^+ \cdot mH_2O + (b + x - m)\,H_2O . \qquad (11)$$

Evidently, the final solution of this problem requires combined studies on the protonation of ketones and the kinetics of their acid-catalysed reactions.

Hydrazoic acid is a weak inorganic acid which is protonated in strongly protogenic systems:

$$HN_3 + H^+ \rightleftarrows [H_2N_3]^+ , \qquad (12)$$

$$[H_2N_3]^+ + H^+ \rightleftarrows [H_3N_3]^{2+} . \qquad (13)$$

The basicity of hydrazoic acid has been investigated by partition in sulphuric acid[28] and it has been found that the partition coefficient and hence the activity coefficient of the non-protonated form of hydrazoic acid remain constant as the concentration of sulphuric acid is varied from 25 to 40%. A sharp change in the partition coefficient was observed only in approximately 80% sulphuric acid, which is believed[28] to be due to the protonation of hydrazoic acid. The ionisation constant of $[H_2N_3]^+$ was calculated with the aid of the Hammett equation and proved to be $pK_A = -6.9$†. The anomalous variation of the partition coefficient in sulphuric acid at higher concentrations (>95%) made it impossible to characterise the second protonation process of hydrazoic acid in terms of Eqn. (13). An approximate value $pK_A = -10.9$† was adopted[30] for $[H_3N_3]^{2+}$.

It should be noted that evidence for the applicability of the function H_0 in this case is at present unavailable. Therefore the equilibrium constants obtained may not be the thermodynamic values. Here it would be useful to investigate the kinetics of the acid-catalysed reactions involving hydrazoic acid, for example the Schmidt reaction.

Sometimes hydrochloric, polyphosphoric, trichloroacetic, and trifluoroacetic acids are employed as catalysts of the Schmidt reaction. The reactions of ketones and hydrazoic acid in such media are analogous to those in sulphuric acid. However, here solvation effects play a greater role: in media of low acidity there is a possibility of the formation of a hydrogen-bonded complex of the carbonyl compound with the medium.

When the Schmidt reaction is catalysed by Lewis acids, the reaction species is probably the complex formed by the interaction of the ketone with the aprotic acid[24].

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† The values of H_0 are based on Vinnik's data[29].

The Schmidt reaction is sometimes carried out in the presence of inert solvents (chloroform, benzene) immiscible with sulphuric acid. Under these conditions, the interaction evidently takes place in an acid layer or at the interface between two phases. These features may have a definite influence on the mode of reaction.

Thus one may suppose that the reactive species in the Schmidt rearrangement is the protonated form of the ketone or its complex with the acid. However, it would be incorrect to rule out completely the involvement in the reaction of the non-protonated form of the carbonyl compound, particularly for ketones with a high reactivity.

3. Addition of Hydrazoic Acid to the Carbonyl Group

The principal characteristics of the addition of nucleophilic reagents to the carbonyl group in the case of acid catalysis have been examined in reviews[31,32]. The available literature data on the Schmidt reaction suggest that these characteristics refer also to the addition of hydrazoic acid to ketones.

As shown above, when ketones are dissolved in aqueous sulphuric acid solutions with a sufficiently high acidity, they are protonated. This leads to an appreciable increase of the polarity of the carbonyl group and promotes the addition of a nucleophilic agent such as hydrazoic acid. In solutions where the carbonyl compound is not protonated, the Schmidt reaction takes place with difficulty.

However, in media with a high acidity ($H_0 > -9$) the rearrangement is retarded owing to a decrease of the concentration of the non-protonated form of hydrazoic acid. The interaction of hydrazoic acid with a ketone leads to the iminodiazonium ion (c'). The azidohydrin (b') is then formed as an intermediate:

$$\underset{(a)}{RCOR'} \overset{H^+}{\rightleftarrows} \overset{+}{RC}(OH)R' + HN_3 \rightleftarrows \underset{(b')}{R-\overset{OH}{\overset{|}{C}}-R'\ \overset{+}{HNN_2}} \overset{-H_2O}{\rightleftarrows} \underset{(c')}{R-\overset{+}{C}-R\ \ddot{N}N_2} \quad (14)$$

An azidohydrin of type (b') was obtained and identified in the reaction of perfluorocyclobutanone with hydrazoic acid[33].

An azidohydrin with a higher energy content than the initial compound tends to regenerate the double bond. There is then a possibility both of the formation of the initial compounds and of stabilisation as a result of dehydration. Dehydration is promoted by the protolytic equilibrium

$$\underset{\overset{|}{HNN_2}}{R-\overset{OH}{\overset{|}{C}}-R'} \overset{-H^+}{\rightleftarrows} \underset{\overset{|}{NN_2}}{R-\overset{OH}{\overset{|}{C}}-R'} \overset{+H^+}{\rightleftarrows} \underset{\overset{|}{\ddot{N}N_2}}{R-\overset{+OH_2}{\overset{|}{C}}-R'} \quad (b) \quad (15)$$

and the consequent formation of the stable iminodiazonium ion (c):

$$\underset{\overset{|}{NN_2}}{R-\overset{+OH_2}{\overset{|}{C}}-R'} \overset{-H_2O}{\rightleftarrows} \underset{\overset{+}{\ddot{N}N_2}}{R-\overset{+}{C}-R'} \quad (c) \quad (16)$$

Compared with the hydroxycarbonium ion, the ion c has a lower energy content, which promotes a shift of equilibrium (14) to the right. However, dehydration can also take place by a bimolecular mechanism. In this case water or the hydrogen sulphate ion can play the role of the base.

The ease of addition of hydrazoic acid to ketones should depend on the electronic and steric properties of the substituents. Usually substituents with a $+I$- or $+M$-effect lead to an increase of the basicity of the ketone, but lowers its reactivity in relation to the nucleophilic agent. Conversely, substituents with a $-I$- or $-M$-effect reduce the basicity of the ketone, enhancing at the same time its reactivity.

The effect of substituents on the addition of hydrazoic acid to ketones and subsequent dehydration is more complex. Substituents with a $+I$- or $+M$-effect hinder the addition of the acid but facilitate the dehydration of the azidohydrin; substituents with a $-I$- or $-M$-effect have the opposite influence.

The experimental data for the reaction of ketones with hydrazoic acid are in general consistent with the above relations. It is known that aliphatic ketones are more reactive in the Schmidt reaction than alkyl aryl ketones, which are in turn more reactive than diaryl ketones. Since the basicity of the corresponding ketones increases in approximately the same sequence, it has been suggested that the rate of reaction of ketones with hydrazoic acid is determined by their basicity[11]. However, the attempt to account for the observed behaviour only on the basis of differences in the basicity of the ketones must be regarded as insufficiently justified. For example, certain substituted benzophenones are known to be weaker bases than aliphatic ketones[34].

Steric factors play a major role in the reaction of ketones with hydrazoic acid. In this sense, the accessibility of the positively charged carbon atom of the protonated carbonyl group is important. Although there are no systematic quantitative data on the effect of the structure of the carbonyl compound on the rate of the Schmidt reaction, it is known that sterically hindred ketones, such as t-alkyl ketones and *ortho*-substituted benzophenones react more slowly than straight-chain dialkyl ketones and unsubstituted diphenyl ketones[4].

4. Stereochemistry of the Reaction

The iminodiazonium ion formed as a result of the dehydration of the azidohydrin is capable of isomerisation of the same type as that observed in oximes [see mechanism (8)]. The contents of the *syn*- and *anti*-isomers in the equilibrium mixture are determined by the reaction conditions and also by steric and electronic factors. The assumption of the existence of geometrically isomeric forms of the iminodiazonium ion is exceptionally important, since it explains the formation of isomeric amides from asymmetric ketones. The problem has been analysed by Smith and coworkers[35-37]. In 1950 Smith and Horwitz[35] observed that the same ketones give a mixture of amides with the same content of isomers both in the Schmidt reaction and in the Beckmann rearrangement[38]. This enabled them to postulate a similarity of the equilibrium proportions of the isomeric oximes and the stereoisomeric forms of the iminodiazonium ion.

It has been shown for alkyl phenyl ketones and benzophenones[35] that the proportions of the amides formed are greatly influenced not by the electronic but by the steric properties of substituents. Thus in the reaction of alkyl phenyl ketones with hydrazoic acid

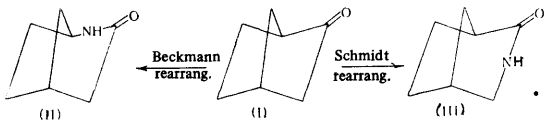
$$\underset{(A)}{C_6H_5NHCOR} + HN_3 \rightarrow C_6H_5NHCOR + \underset{(B)}{C_6H_5CONHR}, \quad (17)$$

where R = CH_3, C_2H_5, or $CH(CH_3)_2$, the ratio of the

isomeric forms A/B is 95/5, 85/15, and 50/50 respectively. At the same time isomeric amides in proportions close to 1 : 1 are always formed from the benzophenones p-$RC_6H_4COC_6H_5$, where R = CH_3, C_2H_5, Cl, NO_2, or OCH_3, regardless of the nature of the substituent.

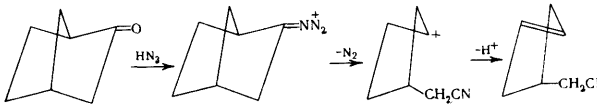
Thus the type of migration of the substituents in asymmetric ketones is in most cases satisfactorily described by an empirical rule according to which the most bulky substituent, occupying the *anti*-position in relation to the diazo-group in the iminodiazonium ion, migrates.

Similar relations hold also for many aliphatic and acyclic ketones. Thus Schechter and Kirk[39] showed for α-substituted cyclohexanones and cycloheptanones that in such ketones the reaction takes place preferentially on the substituted side of the ring. Similar observations have been made for bicyclic ketones[40] and for open-chain ketones[41]. However, in norcamphor and cyclopentanocamphor, migration from the unsubstituted side of the ring is observed[42]. At the same time the Beckmann rearrangement of the oximes of these ketones is accompanied by the formation of lactams with the "normal" structure:



(18)

It should also be noted that the yields of the corresponding amides in the Schmidt reaction are about 30%. Possibly the absence from the reaction products of the lactam (II) is associated with the formation of an unsaturated derivative of acetonitrile according to the mechanism

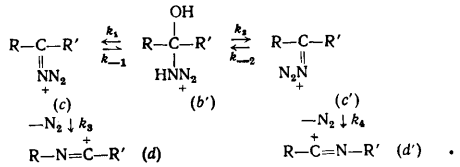


(19)

Remarkable relations have been observed for phenylalkyl ketones $C_6H_5(CH_2)_nCOCH_3$.[10,11] Acetophenone (n = 0) gives a C_6H_5/CH_3 migration ratio of 95/5, phenylacetone (n = 1) gives $C_6H_5CH_2/CH_3$ = 50/50, benzylacetone (n = 2) gives $C_6H_5(CH_2)_2/CH_3$ = 95/5, and 5-phenyl-2-pentanone gives $C_6H_5(CH_2)_3/CH_3$ = 80/20; this type of variation is probably continued with ketones having n = 4 and 5.

In most cases N-substituted acetamides are formed from alkyl methyl and aryl methyl ketones. Two cases are known where preferential migration of the methyl group was observed: N-methylcinnamide and N-methylcyclopropanecarboxamide are formed from benzylideneacetone[43] and cyclopropyl methyl ketone[44]. Extremely interesting results were obtained in a study of the isomeric ratio of the amides formed from *ortho*-substituted benzophenones[37,45] (Table 1). Contrary to expectation, it was found that these compounds do not obey the empirical rule of the preferential migration of the more bulky substituents. Similar deviations have been observed also for 2-substituted fluorononones[46].

According to the mechanism of reaction (8), two isomers of an iminodiazonium ion are formed from a protonated azidohydrin:



(20)

If the energy barrier to the $c \rightarrow d$ rearrangement is lower or comparable to that in the interconversion of the iminodiazonium ions c and c', the ratio of the resulting amides is mainly influenced by the $c \rightleftharpoons c'$ equilibrium. When the energy barrier to the rearrangement is higher, one must expect (according to the Curtin–Hammett principle[47]) that the ratio of the amides will be determined by the difference between the energy barriers to the $c \rightarrow d$ and $c' \rightarrow d'$ rearrangements.

This conclusion follows also from kinetic considerations[47,48]. If the rearrangement (k_3 and k_4) is faster than the interconversion of the isomers c and c', one can write

$$\begin{aligned} d(c)/dt &= k_1(b) - k_3(c)\,, \\ d(c')/dt &= k_2(b) - k_4(c')\,, \\ d(d)/dt &= k_3(c) = k_1(b) - d(c)/dt\,, \\ d(d')/dt &= k_4(c') = k_2(b) - d(c')/dt\,. \end{aligned} \qquad (21)$$

After integration of the last two equations and division of one by the other, we have

$$\frac{(d)}{(d')} = \frac{k_1\int(b)/dt - (c)}{k_2\int(b)/dt - (c')}\,. \qquad (22)$$

This ratio will be equal to k_1/k_2 and k_1k_3/k_2k_4 at $t = \infty$ and $t = 0$ respectively.

Table 1. Ratios of the isomeric amides from *ortho*-substituted benzophenones[45].

Substituent	$C_6H_5NHCOAr/ArNHCOC_6H_5$, %	Substituent	$C_6H_5NHCOAr/ArNHCOC_6H_5$, %
CH_3	78:22	Br	82:18
C_2H_5	78:22	CH_3	50:50
$(CH_3)_2CH$	82:18	NO_2	30:70
Cl	75:25	COOH	3:97

If the slow stage is the rearrangement, the ratio of the amides should be determined by the energy barriers to the $c \rightarrow d$ and $c' \rightarrow d'$ rearrangements and not the thermodynamic stabilities of compounds c and c'. Indeed, according to Eqn. (20) the equilibrium $c \rightleftharpoons c'$ is described by the product k_1k_2/k_2k_1 and the concentration ratio of d/d' is determined as $(k_1k_2/k_2k_1)k_3k_4$. Having denoted the first multiplier by K, we find that the concentration ratio $d/d' = Kk_3/k_4$.

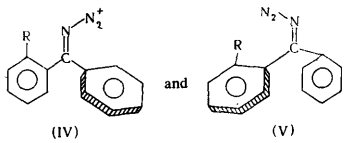
Thus the slower are the rearrangement stages with the constants k_3 and k_4 compared with the rates of interconversion of the iminodiazonium ions (k_1, k_2, k_{-1}, and k_{-2}), the most important will be the electronic factors influencing the tendency of the substituent to migrate. Under these conditions, the thermodynamic equilibrium between c and c' will be correspondingly less important.

However, the extreme cases described will hardly occur in a "pure" form. The ratio of the amides formed is more likely to be affected by all the factors enumerated. Only some of them will of course be decisive. Smith and Antoniades analysed these factors[37].

The difficulty of interpreting the available data consists in the fact that the relations applicable to one series of ketones need not necessarily obtain in another series. This last factor is evidently associated with a possible change in the rates of individual stages as a function of the nature of the ketone and with the competing effect of electronic and steric factors on the structure of the iminodiazonium ion.

As an example, one may refer to the "anomalous" behaviour of *ortho*-substituted benzophenones, in which preferential migration of the unsubstituted phenyl ring has

been observed. At the same time *ortho*-substituted acetophenones give rise to aryl migration products. Smith and Antoniades gave a convincing explanation of this phenomenon.[37] In benzophenones only one phenyl ring is conjugated with the carbonyl group, which leads to the breakdown of the coplanarity of the system. The iminodiazonium ion derived from such compounds can exist as two steric isomers (IV) and (V):



(IV) (V) (23)

If the *ortho*-substituent promotes the conjugation of the substituted phenyl group to the carbonyl group, conformation (IV) predominates and preferential migration of the *ortho*-substituted phenyl ring is observed. When the substituent does not have an appreciable effect on the capacity of the phenyl group for conjugation, conformation (V) predominates and the migration of the unsubstituted phenyl ring is significant.

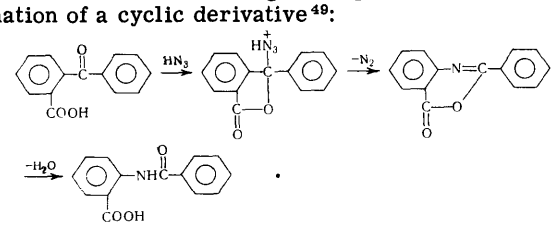
Table 2. Ratios of the isomeric amides (phenyl/substituted phenyl) from benzophenones as a function of the concentration of sulphuric acid[50].

Compound	H_2SO_4	
	88 wt.%	90 wt.%
para-Substituted benzophenones	1:1	1:1
m-Nitrobenzophenone	1:2.16	1:5.02
m-Chlorobenzophenone	1:1.12	1:3.06
m-Methylbenzophenone	0.98:1	7.00:1
p-Methyl-3,5-dinitrobenzophenone*	1.32:1*	0.27:1*

*p-Tolyl/3,5-dinitrophenyl.

The effect of electronic and steric factors on the conjugation of the substituted phenyl group is clearly shown in ketones such as *o*-ethyl- and *o*-methoxy-benzophenones. The ethyl and methoxy-groups are sterically almost equivalent, but the methoxy-group is more effectively conjugated with the phenyl ring. This difference has a marked effect on the migration ratio. The corresponding anilide is mainly formed from *o*-ethylbenzophenone, while *o*-methoxyphenone gives a 1:1 mixture of amides[45].

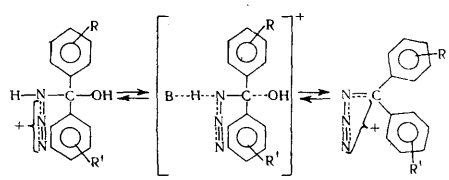
The behaviour of *o*-carboxy-, *o*-nitro-, and *o*-phenylbenzophenones, which exhibit a preferential migration of the substituted aryl group, becomes understandable if it is assumed that the rearrangement proceeds via the formation of a cyclic derivative[49]:



(24)

In many cases the isomeric composition of the mixture of amides formed from asymmetric ketones is influenced significantly by the reaction conditions (temperature and nature of the medium). It has been established that an increase of reaction temperature leads to a change of the ratio of isomeric amides towards an increase of the fraction of the isomer obtained in a smaller amount at a lower temperature[37,39].

Interesting results were obtained by Brackenridge[50] in a study of the effect of the concentration of sulphuric acid on the ratio of isomeric amides in the case of substituted benzophenones and aryl pyridyl ketones (Table 2). The results in Table 2 show that, on increase of the concentration of sulphuric acid from 88 to 99%, there is a sharp change in the migration ratio. Such considerable changes are evidently associated with an increase of the polarity of the medium on passing to more concentrated acid. This assumption may be made on the basis of the following considerations. The dehydration of the azidohydrin *b* proceeds via the transition state in scheme (25):



(25)

where B = H_2O or HSO_4^-. The degree of polarity of the transition state depends on the nature of the substituent and the position of the substituted phenyl ring in relation to the diazo-group. The transition state will be more polar when the *meta*-substituted phenyl ring (with an electronegative substituent) is in the *anti*-position with respect to the diazo-group. The transition state will be less polar when the *meta*-substituted phenyl ring (with an electron-donating substituent) is in the *syn*-position. The rate of dehydration of the azidohydrin depends more on the polarity of the solvent the greater the polarity of the transition state. Consequently, with increase of the polarity of the medium (increase of the concentration of sulphuric acid), the reaction will proceed via a polar transition state. As a result, there is a considerable change in the ratio of the isomeric amides.

Para-substituted benzophenones are almost insensitive to the effect of the medium, since substituents in the *para*-position do not have such a significant influence on the polarity of the transition state. An analogous change in the ratio of isomeric amides was observed by Tomita et al.[51] for 1-indanones and 1-tetralones when sulphuric acid was replaced by trichloroacetic acid.

In general, the problems of the stereochemistry of the Schmidt reaction are fairly complex. The earlier hypothesis of the similarity of the ratio of isomeric amides in the Schmidt reaction and in the Beckmann rearrangement proved to be very approximate when more extensive studies were made. In many cases, particularly for ketones with a complex structure[52,53], it is impossible to predict the mode of reaction. Each year an increasing amount of data accumulates, indicating the breakdown of the rules elaborated previously and further studies are therefore necessary for the solution of this problem.

5. Reaction Kinetics

The kinetics of the Schmidt reaction of ketones have been inadequately investigated. The reason for this is evidently the considerable difficulties of a quantitative study of such complex processes. A systematic investigation of the kinetics of the Schmidt reaction was only undertaken in recent years.

When the rate of reaction of certain ketones with hydrazoic acid was measured in hydrochloric and sulphuric acids, it was shown that the reaction has an overall second order and is of first order with respect to each component[54]. The expression for the rate of the process includes the acidity of the medium: $d(N_2)/dt = kh_0[HN_3]$ [ketone]. Thus the early observations of the dependence of the rate of reaction on the concentration of the acid (catalyst) were confirmed.

It has also been established that the more basic ketones react at a higher rate. On this basis, attempts were made to relate the activity of ketones to their basicity. Fichel et al.[55] studied the kinetics of the reactions of various acetophenones with hydrazoic acid in aqueous sulphuric acid. The data for *meta*- and *para*-substituted acetophenones are inconsistent with the expectations based on the migration capacities of the substituents. Certain *ortho*-substituents (OH, CH_3, OCH_3) retard the reaction, while others (NO_2, Cl) accelerate it.

The changes in the entropies and enthalpies of activation indicate the existence of an isokinetic relation. To some extent these results are consistent with Howell's data[54], but they do not reveal the principal characteristics of the reaction.

The kinetics of the Schmidt reaction involving certain aromatic ketones were studied by Mirek[56,57]. The observed rate of reaction decreases for ketones with electron-donating substituents, which is in general consistent with the effect of these substituents on the position of the carbonyl group band in the infrared spectra. On this basis, the author suggested that the slow reaction stage is the addition of hydrazoic acid to the hydroxycarbonium ion. However, since the reactions investigated are heterogeneous, the results obtained should be treated with caution because the process may be influenced by additional factors.

Quite different data have been reported by Bak[58]. The rate constant for the reaction of phenanthrenequinone with hydrazoic acid decreases appreciably when the concentration of sulphuric acid increases, which is inconsistent with earlier observations. In order to resolve these contradictions, the author suggested that the reaction may involve not only free hydrazoic acid but also its protonated form ($H_2N_3^+$). He made similar assumptions also in a study of the Schmidt reaction with benzoic acid[59].

All the investigations quoted are fragmentary and unsystematic. These and other causes have hitherto precluded an appreciable advance in the understanding in the mechanism of the Schmidt reaction. Certain problems of the formal kinetics of the reaction with ketones can be conveniently examined in the simplest case where only one of the isomeric amides is formed. Here the kinetics of the process based on the suggested reaction mechanism (8) can be represented as follows:

$$A + B^+ \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \underset{(a)}{C^+} \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} \underset{(b)}{D^+} \xrightarrow[-N_2]{k_3} \underset{(c)}{E^+}, \qquad (26)$$

where A is non-protonated hydrazoic acid, B^+ the protonated ketone, C^+ the protonated azidohydrin (I), D^+ the iminodiazonium ion (II), and E^+ the iminocarbonium ion (III).

One of the stages—the rearrangement of the iminodiazonium ion (stage *c*) accompanied by the liberation of N_2—is undoubtedly irreversible. Under these conditions, the occurrence of the rearrangement via a many-centre mechanism or via an intermediate nitrene is kinetically equivalent. In principle, stages (*a*) and (*b*) may be reversible.

It has been shown[60] that the rates of consumption of HN_3 and of liberation of nitrogen in the reaction of 2-hexanone with hydrazoic acid in aqueous sulphuric acid solutions are equal. This implies that the concentrations of the intermediates (I) and (II) are fairly low and may be neglected. The changes in the concentrations of (I) and (II) during the reaction can also be disregarded and therefore in the treatment below the principle of the steady-state has been employed.

If the rate of the process is limited by stage (*c*), the overall rate is

$$\frac{dN_2}{dt} = -\frac{d[A]_{st}}{dt} = k_3 K_2 K_1 [A][B^+]. \qquad (27)$$

On the other hand, if stages (*b*) and (*a*) are rate-limiting, the rate is expressed by Eqn. (28) and (29) respectively:

$$\frac{dN_2}{dt} = -\frac{d[A]_{st}}{dt} = k_2 K_1 [A][B^+], \qquad (28)$$

$$\frac{dN_2}{dt} = -\frac{d[A]_{st}}{dt} = k_1 [A][B^+], \qquad (29)$$

where $[A]_{st}$ is the stoichiometric concentration of HN_3. The variation of the concentration of the protonated ketone and non-protonated hydrazoic acid with their basicity constants and with the acidity of the medium has been omitted. The experimentally observed overall second order of the reaction and the first order with respect to each component are formally consistent with the hypothesis that the slower stage may be any one of the following three: (*a*), (*b*), and (*c*).

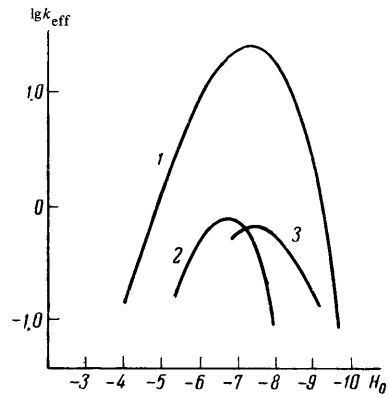


Figure 1. Variation of the logarithm of the observed (effective) rate constant for the Schmidt reaction ($\lg k_{eff}$) in sulphuric acid solutions with acidity: 1) for 2-hexanone; 2) for acetophenone; 3) for *m*-nitroacetophenone[61,62].

Certain characteristics of the mechanism of the reaction of ketones with hydrazoic acid were discovered in a study of the process over a wide range of acidities of the medium. Fig. 1 shows the observed variation of the effective rate constant for the reaction with the acidity function H_0 for 2-hexanone and for acetophenones with substituents in the phenyl ring[61,62]. With increase of the concentration of sulphuric acid, the rate of reaction rises to a maximum

and then falls. It should also be noted that the rate of the Schmidt reaction with carboxylic acids increases continuously with sulphuric acid concentration up to 96.6%,[63] which is evidence of differences in these processes.

Relations of this kind (Fig. 1) in nucleophilic addition to the carbonyl group can be accounted for either by an acid–base equilibrium of the initial reactants or by a change in the rate-limiting stage[31].

If the acid–base equilibrium of the ketone and hydrazoic acid (in the present case in sulphuric acid) is the decisive factor, the effective rate constant for the rate-limiting stage (addition) is[61,63]

$$k_{\text{eff}} = \frac{k' h_0}{K_1\left[1+\frac{h_0}{K_1}\right]\left[1+\frac{h_0}{K_2}+\frac{h_0 h_+}{K_2 K_3}\right]}, \qquad (30)$$

where k' is the true reaction rate constant, h_0 and h^+ are the acidity functions for the neutral bases and singly-charged cations respectively, and K_1, K_2, and K_3 are the basicity constants of the ketone, hydrazoic acid, and monoprotonated hydrazoic acid ($H_2N_3^+$) respectively.

Eqn. (30) is valid only when the ketone and hydrazoic acid behave as Hammett bases. Despite certain difficulties in the solution of this problem, to a first approximation one may postulate that 2-hexanone and acetophenones substituted in the phenyl ring[61,62] satisfy this requirement. The behaviour of hydrazoic acid as a Hammett indicator is assumed.

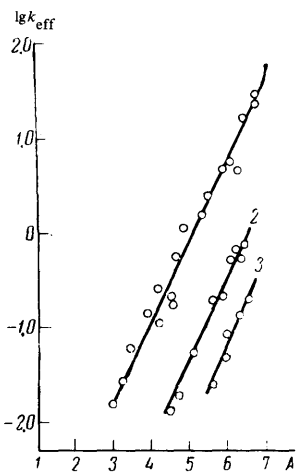


Figure 2. Correlation between $\lg k_{\text{eff}}$ and A in the Schmidt reaction: 1) for 2-hexanone; 2) for acetophenone; 3) for *m*-nitroacetophenone. $A = -H_0 - \lg(1 + h_0/K_1) - \lg(1 + h_0/K_2 + h_0 h_+/K_2 K_3)$, where H_0 is the Hammett acidity function, K_1, K_2, and K_3 are the basicity constants of the ketone, NH_3, and $H_2N_3^+$ respectively, and h_+ is the acidity for singly-charged bases.

Fig. 2 presents the observed correlations between A and k_{eff} determined by Eqn. (30).[61,62] A is the acidity function of the medium corrected for the acid–base equilibrium of the initial reactants.

The linearity of the correlations (Fig. 2) shows that, regardless of which reaction stage is rate-limiting, the reactants are first protonated in sulphuric acid and then the protonated ketone reacts with non-protonated hydrazoic acid.

The satisfactory correlation suggests that the reaction mechanism remains unchanged over a wide range of acidities of the medium. Moreover, one may postulate that the rate constant for the elementary stage does not vary, i.e. is independent of the acidity function.

The experimentally determined ranges of H_0 (Fig. 1) where the effective rate constant is a maximum agree satisfactorily with calculations by the equation

$$h_0^{\max} = \sqrt{K_1 K_2}, \qquad (31)$$

where K_1 and K_2 are the basicity constants of the ketone and hydrazoic acid respectively.

The higher absolute effective reaction rate constants for $h_0^{\max}$ correspond to the more basic ketones. This can be readily explained by the fact that for a more basic ketone, $h_0^{\max}$ is displaced towards lower acidities where the relative concentration of non-protonated hydrazoic acid is higher. The validity of the suggested mechanism (8) has been confirmed by the determination of the basicity of hydrazoic acid using a kinetic method[61]. The value obtained is relatively close to the basicity of hydrazoic acid found by a partition method[28].

The determination of the rate-limiting reaction stage is the most difficult step in the study of the mechanism of multistage processes. This problem has been examined by Smith[4] in relation to the Schmidt reaction with ketones but he did not arrive at a final solution. At the same time, determination of the rate-limiting stage of the process yields exceptionally valuable information about the reaction mechanism as a whole.

Studies on the kinetics of sextet rearrangements, which include the Schmidt reaction, showed that the rate of the process increases on introduction into the molecule of the initial compound (amide, hydroxamic acid, or carboxylic acid) of electron-donating substituents (the value of ρ in the correlation equation is negative). The absolute values of the reaction constants are fairly considerable: 2.58 for the Hoffman reaction[63], 2.51 for the Lossen reaction[64], and 1.76 for the Schmidt reaction[65] (in the last case the reaction series comprises aromatic acids).

A negative value of ρ was obtained also for the reaction of aliphatic acids with hydrazoic acid and it was shown convincingly that the rearrangement stage is rate-limiting[66]. In the absence of stages complicating the process the observed negative sign of the reaction constant ρ may be attributed to the rearrangement itself[67].

A positive reaction constant is observed only when the rate-limiting stage is nucleophilic addition to the carbonyl group[31].

The constant $\rho = +1.79$ has been determined[62] for many substituted acetophenones by correlating the logarithms of the true rate constants with Brown's σ^+ constants (Fig. 3).

The observed positive reaction constant for substituted acetophenones is in general an overall quantity comprising the reaction constants for the rate-determining and preceding stages. However, analysis shows[62] that the slowest stage probably consists in the nucleophilic addition of hydrazoic acid to the carbonyl group. The activation parameters for the Schmidt reaction with ketones are consistent with this hypothesis (Table 3). According to the theory of absolute rates, the enthalpy of a complex reaction, with the exception of cases where intermediates accumulate, may be attributed to the rate-limiting stage.

The observed values of $\Delta H^{\neq}$ are characteristic of the stage involving nucleophilic addition to the carbonyl group. Moreover, it has been shown[60] that the activation energies for the reactions of 2-hexanone with hydrazoic acid in sulphuric acid are similar in different acidity ranges. This yet again confirms that the reaction mechanism does not alter over a wide range of sulphuric acid concentrations.

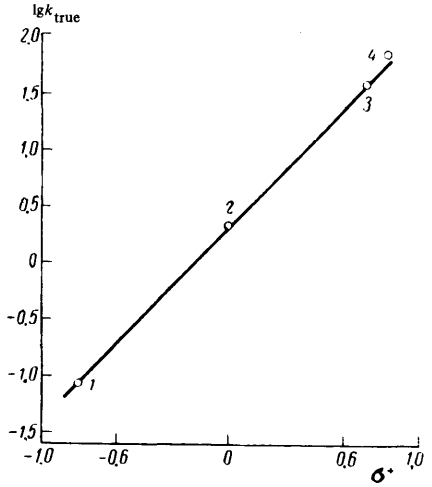


Figure 3. Correlation between the logarithm of the true rate constants for the Schmidt reaction and the electrophilic constants of the substituents:
1) *p*-methoxyacetophenone; 2) acetophenone;
3) *m*-nitroacetophenone; 4) *p*-nitroacetophenone.

The activation entropies for multistage processes are overall quantities, which gives rise to additional difficulties in their interpretation. Therefore it is useful to compare the values of $\Delta S^{\neq}$ for the Schmidt reaction involving ketones and acids. In the latter case the slowest stage is the rearrangement. A small negative value of $\Delta S^{\neq}$ can be explained by a considerable contribution due to the stage involving the liberation of nitrogen and an increase of entropy[66]. For ketones, the activation entropies are more negative, which is satisfactorily consistent with the finding that the experimental $\Delta S^{\neq}$ consist of the entropies of the protonation stage and the stage involving nucleophilic addition to the carbonyl group.

The kinetic isotope effect in the Schmidt reaction involving 2-hexanone and acetophenone has been measured[68]. In both cases the rate increases appreciably when H_2SO_4 is replaced by D_2SO_4 (Table 4). Such acceleration of the reaction is characteristic of processes with a protonation pre-equilibrium[69]. The results obtained by Koldobskii and coworkers[60-62] make it possible to resolve the apparent contradictions between the previous kinetic studies.

In their investigation of the effect of substituents on the rate of the Schmidt reaction with ketones, Fichel et al.[55] and Mirek[57] arrived at opposite results. This is evidently because the authors employed sulphuric acids of different concentrations. Fichel et al.[55] did not indicate which rate constants were employed in the calculations—the effective or true values. Evidently their conclusion is based on the effective rate constants in 67.8% sulphuric acid, which is confirmed by the plot in Fig. 1. Indeed at this concentration of sulphuric acid ($H_0 = -5.6$) the effective rate constants increase when electron-donating substituents are introduced into the ketone molecule. On the other hand, Mirek et al.[57] employed concentrated sulphuric acid (about 93%) and the sign of the effect of substituents was reversed. Correct conclusions can be arrived at only by using the true rate constants, which are independent of the acidity of the medium.

Table 3. Activation parameters and relative rates of the Schmidt reaction for substituted acetophenones[55].

Substituent	Relative rate	$\Delta H^{\neq}$	$\Delta S^{\neq}$
p-CH_3	9.50	8.26	−41.60
m-OH	1.13	—	—
H	1.00	—	—
p-Br	0.69	9.98	−36.22
m-Br	0.58	—	—
p-OCH_3	0.38	—	—
p-NO_2	0.15	14.83	−22.59
m-NO_2	0.10	—	—

The retardation of the reaction of phenanthrenequinone with hydrazoic acid as the acidity of the medium increases can be explained similarly. According to Eqn. (31), the optimum acidity (h_0^{max}) for this ketone ($pK_a = -7.8$) corresponds to $H_0 \simeq -7.4$ and since the process occurs at H_0 between −8 and −9, the rate of reaction falls as the acidity rises.

Table 4. Kinetic isotope effect (k.i.e.) in the Schmidt reaction[68].

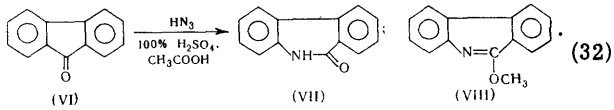
Ketone	k.i.e., litre mole^{-1} s^{-1}, 15°C		$\frac{k_D}{k_H}$
	H_2SO_4 60.5 wt.%	D_2SO_4 60.5 wt.%	
2-Hexanone	0.81	2.50	3.24
Acetophenone	0.02	0.12	6.00

Thus the available kinetic data for the Schmidt reaction involving ketones agree satisfactorily with the reaction mechanism proposed by Smith[4]. However, kinetic methods alone do not yield exhaustive information about the reaction mechanism as a whole. Here it is necessary to employ other physicochemical research techniques.

6. Other Views on the Mechanism of the Reaction of Ketones with Hydrazoic Acid

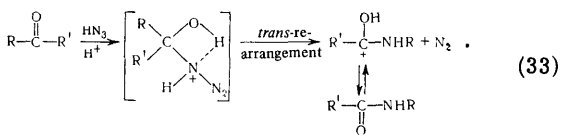
The failure in some cases of the empirical rule that the more bulky substitutent migrates preferentially in the Schmidt reaction with asymmetric ketones[44,45] led some investigators to revise the reaction mechanism proposed by Smith[4,11]. Arcus et al.[46] questioned the possibility of the existence of the iminodiazonium (*c*) and iminocarbonium (*d*) ions [mechanism (8)]. As evidence they quote data

for the Schmidt reaction with fluorenone (VI) in 100% sulphuric acid. They believe that, when an iminocarbonium ion is formed, its hydration is difficult under these conditions and dilution of the reaction mixture with an excess of methanol should lead to 9-methoxyphenanthridine (VIII):



(32)

However, the only reaction product proved to be the phenanthridone (VII). These results were interpreted as unambiguous proof of the absence of an intermediate iminocarbonium ion. As a possible alternative, they proposed a mechanism involving the formation of an intermediate four-membered ring:



(33)

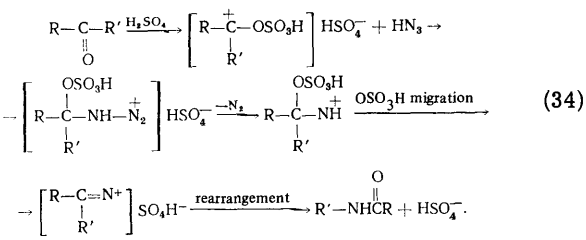
However, in subsequent studies[37,56] it was shown that the arguments put forward by Arcus et al. in favour of the mechanism with a four-membered intermediate are inadequate.

In Schmidt's early studies[70] it was already known that iminoethers are formed when ketones are treated with hydrazoic acid, provided that the reaction is carried out in alcohol. Arcus and coworkers diluted the reaction mass with alcohol only after the process had been completed, when the iminocarbonium ion had already been converted into the protonated amide as a result of hydration.

The fact that the iminocarbonium ion is nevertheless capable of being hydrated under these conditions is confirmed by the well known hydrolysis of nitriles in concentrated sulphuric acid[71,72]. Moreover, if the hydration process were thermodynamically impossible, the formation of iminocarbonium ions from amides should be expected when the latter are dissolved in sulphuric acid. However, the attempts by Newman and Deno to achieve such transformation of amides proved unsuccessful[73]. In addition it is known that, in the presence of an excess of hydrazoic acid, ketones form tetrazoles (see section III). It is not clear how such products could be formed if they were really preceded by the four-membered intermediate shown in mechanism (33).

Finally, it is noteworthy that the hydrogen bond energy is clearly insufficient for the formation of a strained four-membered ring and therefore the existence of such a structure is altogether unlikely.

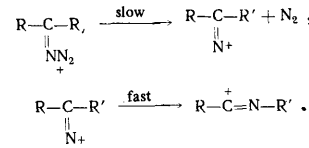
Recently Mirek[56,57] proposed the following mechanism for the Schmidt reaction with ketones:



(34)

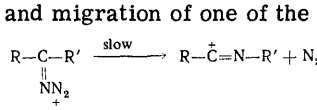
However, this mechanism has no significant advantages over the generally accepted Smith mechanism[4]. Experimental data confirming the validity of this pathway are so far lacking.

In a study of the Schmidt reaction with ketones the problem of the mechanism of the rearrangement proper is exceptionally important. According to mechanism (8), the rearrangement takes place in two stages:



(35)

On the other hand, the process can proceed via a many-centre (push-pull) mechanism with simultaneous elimination of nitrogen and migration of one of the substituents:



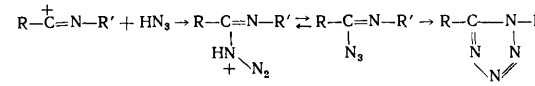
(36)

Since there is no direct proof for a particular mechanism, it is difficult to give preference to any one of them. One can only suppose, by analogy with the related Curtius, Lossen, and Hofmann reactions[74,75], that the synchronous mechanism can also operate in the Schmidt reaction.

III. CONCOMITANT REACTIONS

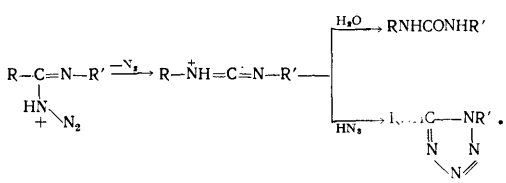
Usually the interaction of ketones with hydrazoic acid leads to the formation of amides. In certain cases, depending on the reaction conditions and the properties of the substrate, tetrazoles, aminotetrazoles, ureas, iminoethers, and certain other compounds may be obtained. Tetrazoles, which exhibit a high biological activity[76] and are used in medical practice as stimulators of cardiac activity[2], are the most important.

Tetrazoles are formed as a result of the reaction of the iminocarbonium ions *d* with an excess of hydrazoic acid:



(37)

The protonated imidoazide is capable of eliminating nitrogen with formation of a carbodi-imide which is converted into an aminotetrazole or urea as a result of secondary reactions with hydrazoic acid or water:



(38)

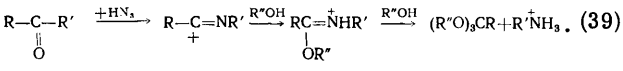
If the reaction is carried out in the presence of water, then, even if there is a large excess of hydrazoic acid, tetrazoles are always obtained in a mixture with amides. Thus benzosuberone was converted into a lactone in 82% yield when sodium azide was added slowly to a solution of the ketone in trichloroacetic acid[77]. When a mixture of the ketone and hydrazoic acid is treated with concentrated sulphuric acid, a tetrazole is formed[78]. Similarly mixtures of the corresponding amides and tetrazoles are formed from di-isobutyl-ketone[79] and cyclohexanone[80].

The formation of aminotetrazoles and urea in the Schmidt reaction takes place extremely rarely and is characteristic only of ketones such as benzophenone[81]. Tetrazoles are formed in a small amount from benzil[82].

Despite the fact that the synthesis of tetrazoles by the Schmidt reaction has found wide application, systematic

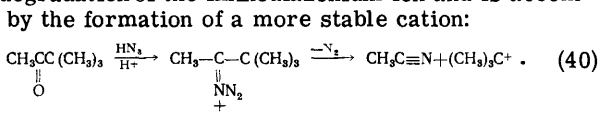
studies have not been made in this field. It is not clear how the structure of the ketone affects its capacity for conversion into a tetrazole, although such a relation undoubtedly exists. One can also suppose that the amide : tetrazole ratio (when a mixture of these products is formed) is determined by the ratio of the activities of hydrazoic acid and water and also by the acidity of the medium. Extensive kinetic studies are required for the solution of this problem.

Alcohols can enter into the reaction with the iminocarbonium ion together with water and hydrazoic acid. In this case there is a possibility of the formation of iminoethers [70]. Since in the presence of acids these substances readily undergo alcoholysis, the rearrangement products are orthoesters and amines [4]:



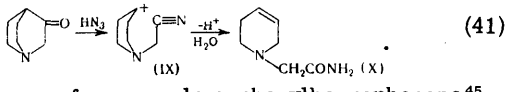
(39)

The composition of the Schmidt reaction products depends to a considerable degree on the structure of the ketone. Ketones such as pinacolone [83], pivalophenone [35], 2-n-butyl-2-phenylbutan-3-one, [84] and certain others [85] react with hydrazoic acid to form the corresponding nitriles. The formation of nitriles takes place as a result of the degradation of the iminodiazonium ion and is accompanied by the formation of a more stable cation:



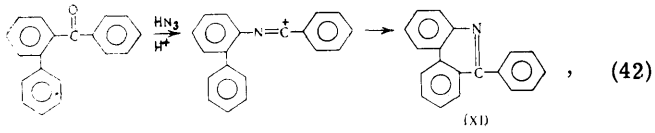
(40)

Even more far-reaching transformations are undergone by 3-quinuclidone [86,87]. In this case the carbonium ion (IX) is stabilised by the removal of a proton, which leads to the formation of an unsaturated amide (X):

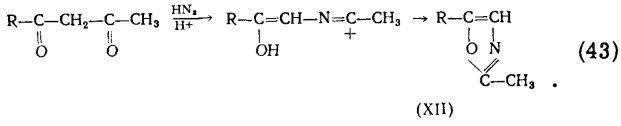


(41)

Certain ketones, for example *o*-phenylbenzophenone [45], acetylacetone, and benzoylacetone [88], give rise to cyclic products (XI–XII) as a result of the Schmidt reaction:



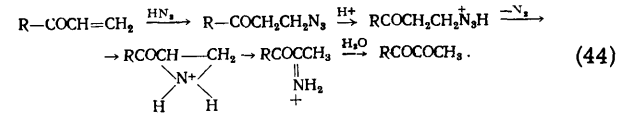
(42)



(43)

Phenylphenanthridine (XI) and oxazole (XII) are formed via an electrophilic attack by the iminocarbonium fragment on the adjacent nucleophilic centres.

The complex reaction involving unsaturated ketones such as methyl vinyl ketone gives rise to diketones [89]:



(44)

IV. APPLICATIONS OF THE SCHMIDT REACTION

The Schmidt reaction with ketones has come to be widely used as a convenient method for the synthesis of *N*-substituted amides with different structures, tetrazoles, and certain other compounds. Compared with other methods, it has the advantage of simplicity, ready availability of the reactants, and mild reaction conditions. The Schmidt reaction may be catalysed by protic and aprotic acids; sulphuric acid is normally employed for this purpose [11,36,90]. In many cases satisfactory results have been obtained using trichloroacetic acid [51,90] and particularly polyphosphoric acid [91,92].

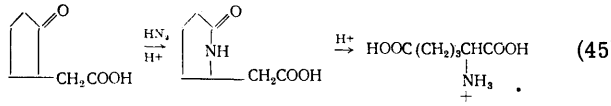
Solutions of hydrazoic acid required for the reaction are prepared beforehand or sodium azide is added directly to the reaction mixture. The use of hydrazoic acid *in situ* makes it possible to avoid direct contact with this explosive and poisonous compound.

Ketones of different structures, ranging from the simplest compounds to alkaloids [93], readily enter into the Schmidt reaction. The few failures reported in the literature can be accounted for by an unsuitable choice of reaction conditions.

The reaction of the carbonyl group of ketones with hydrazoic acid takes place selectively and does not involve functional groups such as the carboxy-, [94] ester [95], nitrile [40], and certain other groups.

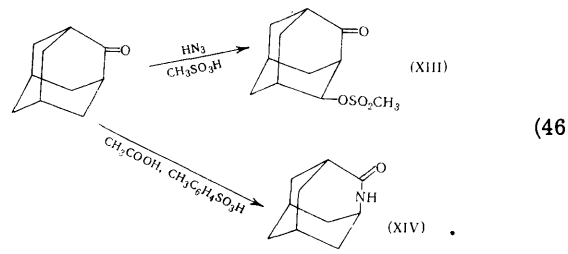
Aliphatic ketones react most readily. The reaction is frequently employed to determine the structure of the ketone or to synthesise the corresponding amide. In some cases amines containing other functional groups are obtained by this procedure. Thus α- and β-aminoacids are formed from acetoacetic or laevulinic acid esters.

The reaction with acyclic ketones takes place with ring expansion and leads to the formation of lactams [39]. Cyclic ketones containing carboxy- or ester groups are converted into lactams, which are hydrolysed under the reaction conditions to dicarboxylic acids [94,95]:



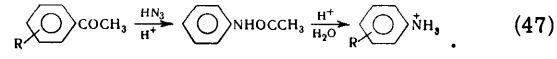
(45)

Depending on the reaction conditions, 4-methylsulphoxyadamantone (XIII) or the corresponding lactam (XIV) are formed from adamantone [96,97]



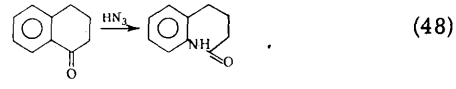
(46)

Alkyl aryl ketones have been investigated in the Schmidt reaction more than other carbonyl compounds. It has been shown that the reaction of substituted acetophenones with hydrazoic acid gives acetanilides in high yields [11,95,98]. This reaction is a convenient method for the preparation of various aromatic amines:



(47)

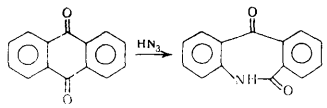
Cyclic alkyl aryl ketones such as tetralone [78] and benzosuberone [77] are converted into lactams under analogous conditions:



(48)

Compared with alkyl aryl ketones and aliphatic ketones, benzophenones are less reactive. However, when sulphuric acid is employed as a catalyst, satisfactory results are obtained[35,45]. Substituted benzophenones are of considerable interest, since the study of these ketones yields valuable information about the migration ratios in the Schmidt reaction.

Aromatic diketones behave somewhat differently in the Schmidt reaction. A complex mixture of products is obtained from benzil[82] and phenanthrenequinone[99] is converted into phenanthridone. Only one carbonyl group in anthraquinone and its amino-derivatives reacts[100]:



(49)

Ketones containing heteroatoms (nitrogen and sulphur) enter into the Schmidt reaction with formation of normal rearrangement products. Thus it has been shown that various carbonyl derivatives of thiophen are converted under the influence of hydrazoic acid in the presence of polyphosphoric acid into the corresponding amides in high yields[92,101]. A similar behaviour has been observed also for other heterocyclic ketones[102-104]. Ketones with a more complex structure, for example certain triterpenoids, give a mixture of amides and tetrazoles under the conditions of the Schmidt reaction[105].

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