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KINETIC STUDIES ON THE MECHANISM OF THE SCHMIDT REARRANGEMENT

by
David M. Howell

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KINETIC STUDIES OF THE MECHANISM OF THE SCHMIDT REACTION

by David M. Howell

The Schmidt reaction on ketones, $R_2CO + HN_3 \xrightarrow{H^+}$ $R\text{-}NH\text{-}CO\text{-}R + N_2$ has been investigated kinetically by measuring the rate of nitrogen evolution. The measurements were made on reactions with cyclohexanone, diisopropyl ketone, and acetophenone, catalysed by hydrochloric acid, sulphuric acid, and ethanesulphonic acid, in aqueous solution and in mixed organic solvents (carbon tetrachloride, chloroform, tetrachloroethane, methylene dichloride, nitrobenzene).

The measurements in all runs conformed to the rate law $\frac{d(N_2)}{dt} = k\, h_o\, (\text{ketone})(HN_3)$, where h_o stands for the effective proton-donating intensity of the solution and k is the specific reaction rate constant. Where appreciable differences existed between the h_o values for the solution and either the "activity" of the acid or its molarity, concordant results could only be obtained by use of h_o. The reaction was found to be non-autocatalytic, but was found to be retarded by accumulation of the product (amide), especially when the ratio of catalysing acid to amide was small. This effect is in concordance with the ability of amides to reduce the h_o of the solutions.

The average rate constant for cyclohexanone in aqueous solution at 25° C. was found to be 5×10^{-5} sec.$^{-1}$ moles^{-2} l.^{2}; in a range of non-aqueous solutions it maintained a value of about 40×10^{-5}. For diisopropyl ketone the rate constant was

about 40×10^{-5}, and for acetophenone it was 2×10^{-5}, both in a range of non-aqueous solvents.

These results have been compared in detail with the several proposed mechanisms for the Schmidt reaction, and they confirm those based on initial formation of a hydroxy-carbonium ion (Sherk et al., Newman and Gildenhorn, Smith). In addition, an alternative explanation is now proposed which consists of modification of the Smith mechanism by the concerted displacement, or "push-pull", concept of Bartlett et al. By means of a critical comparison of the kinetically acceptable mechanisms with non-kinetic information on the Schmidt reaction now available, the superior ability of the mechanisms involving dehydration to an iminodiazonium ion to explain the facts of the reaction has been demonstrated.

A derivation is given of a method whereby from experimental kinetic data derived from measurements of gas volumes the order of a reaction may be determined without the need of vapor pressure corrections.

To G. E. K. Branch, who inspired interest in the less usual aspects of organic chemistry.

ACKNOWLEDGEMENT

I wish to express my appreciation to Doctor Peter A. S. Smith for his patience and interest which served as an inspiring stimulus toward the completion of this problem, and for his guidance in my development of an independent attack in consideration of chemical problems.

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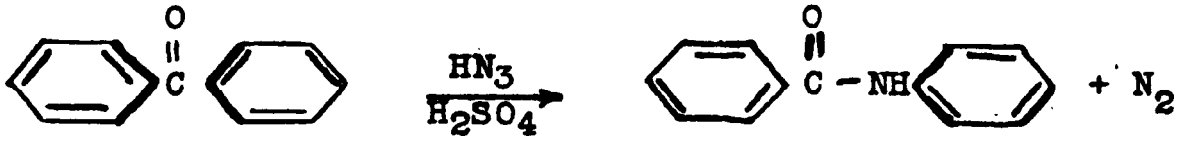
INTRODUCTION

Discovery, Application, and Conditions for the Schmidt Reaction

In the studies of Karl Friedrich Schmidt undertaken in 1923 on the decomposition of hydrogen azide, HN_3, in sulphuric acid solution, it was found that hydrazine and aniline were among the products formed in the decomposition in the presence of benzene.[1,2,3] The amount and ratios of the products varied with the temperature of the reaction. Schmidt postulated the NH radical as an intermediate in the reactions he had observed.[1,2,3,4] A test for that hypothetical substance was made, consisting of the introduction into the reaction mixture of various substances which might react with NH.[1,2,3] The introduction of some of these test compounds resulted in no change in the reaction from the ordinary acid-catalysed decomposition. The introduction of benzophenone, however, brought about a very rapid reaction with the quantitative formation of benzanilide and nitrogen.



This discovery became the first example of what is now commonly called the Schmidt reaction or Schmidt rearrangement. The reaction of a carbonyl group with hydrazoic acid in the presence of an acid catalyst is general, not only for the unmodified carbonyl group present in most ketones and aldehydes,[1,2,3]

$$RCOR' \xrightarrow[H_2SO_4]{HN_3} \begin{matrix} RCONHR' \\ \text{and/or} \\ RNHCOR' \end{matrix} + N_2$$

but also for the modified carbonyl group present in the carboxylic acids,[5,6] provided that strong enough acid catalysts be used.

$$RCOOH \xrightarrow[H_2SO_4]{HN_3} RNH_3^+ + HSO_4^- + N_2 + CO_2$$

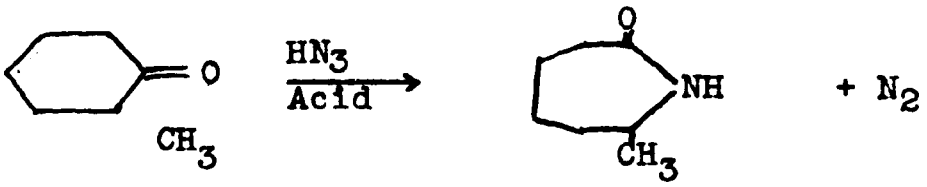
Because of the large number of compounds which will react in this fashion, with the introduction of an NH group into the molecule, sometimes with, sometimes without the accompanying loss of carbon dioxide, the Schmidt reaction has come to be recognised as a reaction whose products are useful as synthetic intermediates or as keys to the structure of the compound degraded. Although the literature on this reaction was reviewed in 1945, a discussion in somewhat more detail than is customary is presented in the succeeding pages, because of the many significant contributions which have appeared since that time, or which have for other reasons escaped inclusion in the existing review.

Following Schmidt's original discovery of the reaction involving hydrazoic acid and benzophenone, this reaction was slowly extended to other carbonyl compounds. Schmidt himself tested the reactions of aldehydes such as benzaldehyde as early as one year after the discovery of the original reaction,[1,2,3] and extended it to ß-keto esters that same year.[2,3] The preparation of aminoacids in this manner represented the first reaction on unsymmetrical ketones.

Schattner found that alcoholic solutions of mineral acids could be used as the medium for the Schmidt reaction on some aldehydes and ketones instead of the usual aqueous solutions.[7] Imidoesters are produced by this modification, and are obtained in the reaction medium as salts of the acid used for catalysis.

$$CH_3COCH_3 \xrightarrow[HCl]{HN_3 + C_2H_5OH} CH_3C(OC_2H_5)=\overset{+}{N}HCH_3 + Cl^-$$

The next extension of Schmidt's reaction was made by von Braun, who treated 2-methylcyclohexanone with hydrazoic acid in the presence of sulphuric acid, and obtained the lactam of ϵ-aminoenanthic acid in 45% yield.[8] The preparation of this cyclic amide was the first example of the application of the Schmidt reaction to an unsymmetrical ketone, other than a ß-ketoester, in which a pair of isomeric amides might be formed. In this case the two possibilities were α-methyl-ϵ-caprolactam and the ϵ-enantholactam actually isolated by von Braun.



Just one year later, von Braun found that carboxylic acids,[5,6] such as dodecamethylenedicarboxylic acid,[6] as well as the more simple carbonyl compounds, would also undergo the Schmidt reaction, if the conditions were made vigorous enough.

Rapidly following von Braun's application of the Schmidt reaction to the degradation of naphthenic acids to amines,[5] the Schmidt reaction was tried on an ester, ethyl benzoate;[9,10,11] an anhydride, acetic anhydride;[10,11] and a acid chloride, benzoyl chloride; [10,11] and patents obtained for these uses.

In 1932, Oesterlin found that keto acids, such as levulinic acid, reacted in the same way as did the keto esters,[12]

$$CH_3COCH_2CH_2COOH \longrightarrow \underset{\text{(major product)}}{CH_3CONHCH_2CH_2COOH} + CH_3NHCOCH_2CH_2COOH \ .$$

More recently, a ß-keto acid, benzoyl-acetic acid has been subjected to the Schmidt reaction.[13]

Carbonyl groups which are ß to sulphone,[13] nitro,[13] amide,[13] and nitrile[13,14] groups also satisfactorily undergo the Schmidt reaction.

The Schmidt reaction was first applied to substituted malonic acids in 1939 by Adamson, who found that only one of the carboxyl groups reacts, giving ∠-amino acids.[15] This discovery was also made independently at about the same time by L. H. Briggs in New Zealand.[9]

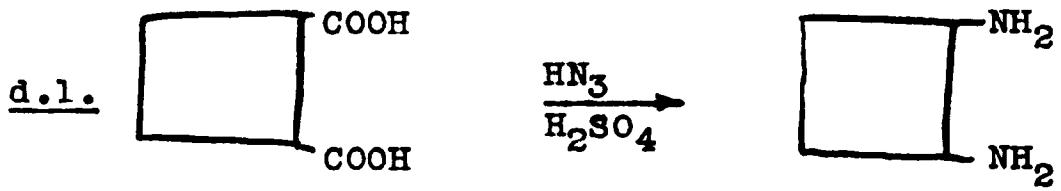
The formation of 1,5-disubstituted tetrazoles from ketones in the presence of an excess of hydrazoic acid was noted by Schmidt[16,17] shortly after his original discovery. It was later found that large rings, even with equivalent amounts of hydrazoic acid, tended to give small amounts of tetrazoles as by-products.[18] Likewise, Spielman and Austin noticed the formation of tetrazoles from benzil.[19] Benzoyl-acetic acid gives carboxy-tetrazoles as the major product of the Schmidt reaction.[13] Tetrazoles can be made the major product if a large excess of hydrazoic acid is used.[2,3]

Although Schmidt's applications of the reaction that he had discovered were to the unmodified carbonyl group of aldehydes and ketones,[1,2,3,10,11,16,17,20,21,22,23,24,25,26,27,28,29] most of the useful applications of the Schmidt reaction to organic syntheses in the laboratory during the first twenty years after its discovery used the carboxylic extension, discovered by von Braun and introduced by him in the preparation of amine degradation products of naphthenic acids eight years after Schmidt's original discovery.[5,6] Since that time, the Schmidt reaction has been used in many fields, both as a tool in organic synthesis and as an aid in the proof of structure of complex organic molecules.

Jansen and Pope have applied the Schmidt reaction to the preparation of optically-active amines containing no asymmetric carbon atoms.[30,31] These amines, optically active because they are attached to a spiro-ring system, were prepared from similar spiro acids.

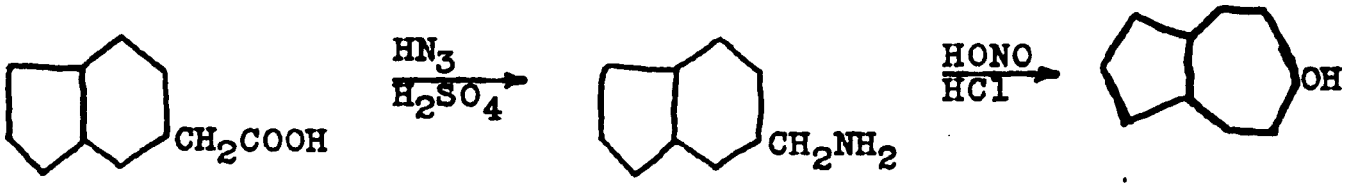


Buchman, Reims, Skei, and Schlatter have used the Schmidt reaction to prepare cyclobutyl amines from cyclobutane carboxylic acids.[32]

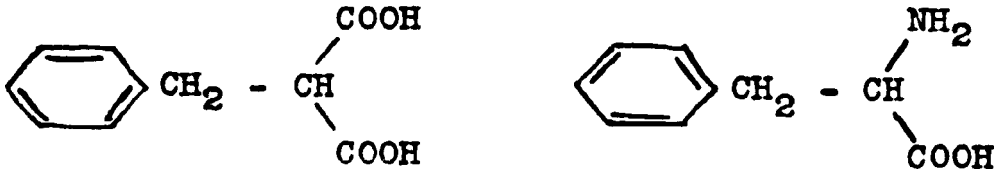


Arnold used the Schmidt reaction to prepare aminomethylhexahydroindane derivatives, which when subjected to the

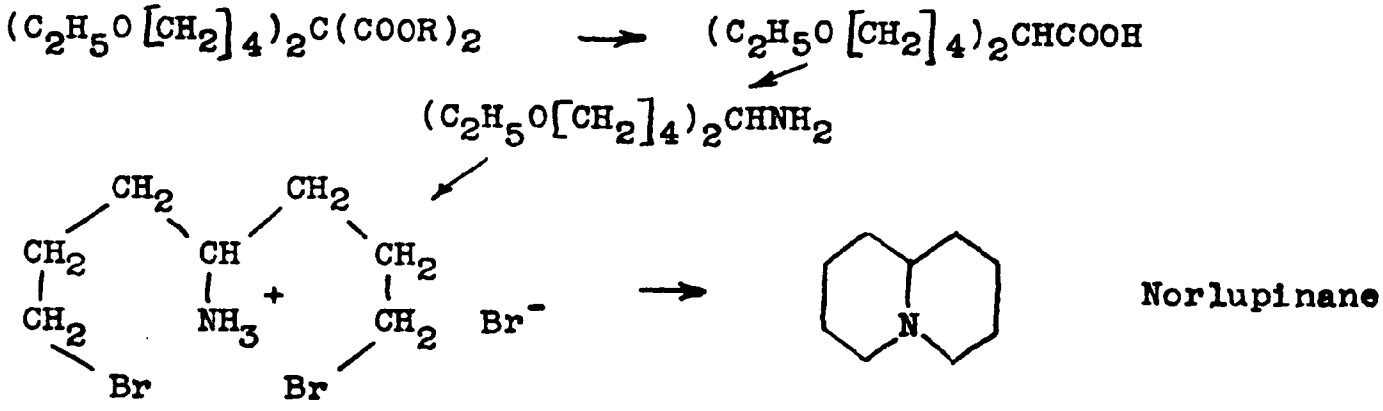
Demianov rearrangement, gave azulene derivatives.[33]



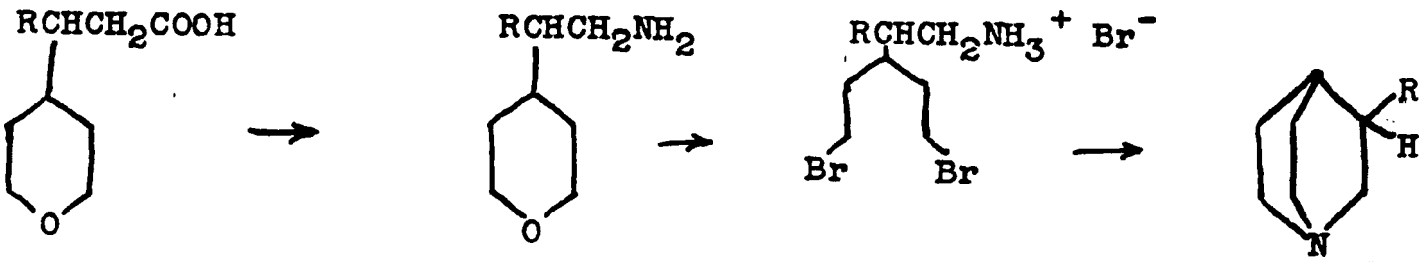
Tetrahydroquinolines have been prepared by Briggs and his coworkers from dihydrocarbostyril, the product formed by the Schmidt reaction on hydrindone.[34] Later Briggs extended the use of the Schmidt synthesis to the preparation of other physiologically active compounds, such as phenylalanine.[29]



Prelog used the Schmidt reaction to prepare intermediates in the synthesis of heterocycles, such as nor-lupinane,[35]

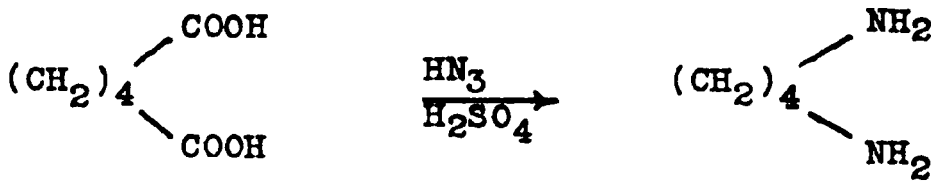


Some of these compounds were related to quinuclidine, one of the component moieties of the cinchona alkaloids.[36,37]

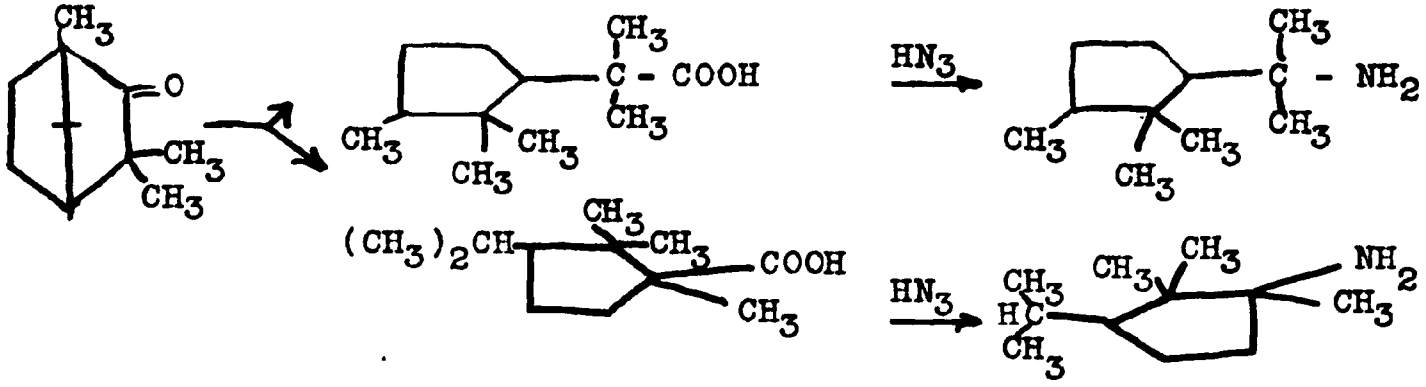


Prelog applied the Schmidt reaction to the preparation of other alkaloids containing nitrogen at the bridgehead as well,[38,39,40,41] and in addition used this reaction in preparing spasmolytic compounds.[42]

In addition to his work on naphthenic acid, von Braun extended the Schmidt reaction into the studies of spermidine and related compounds,[43]

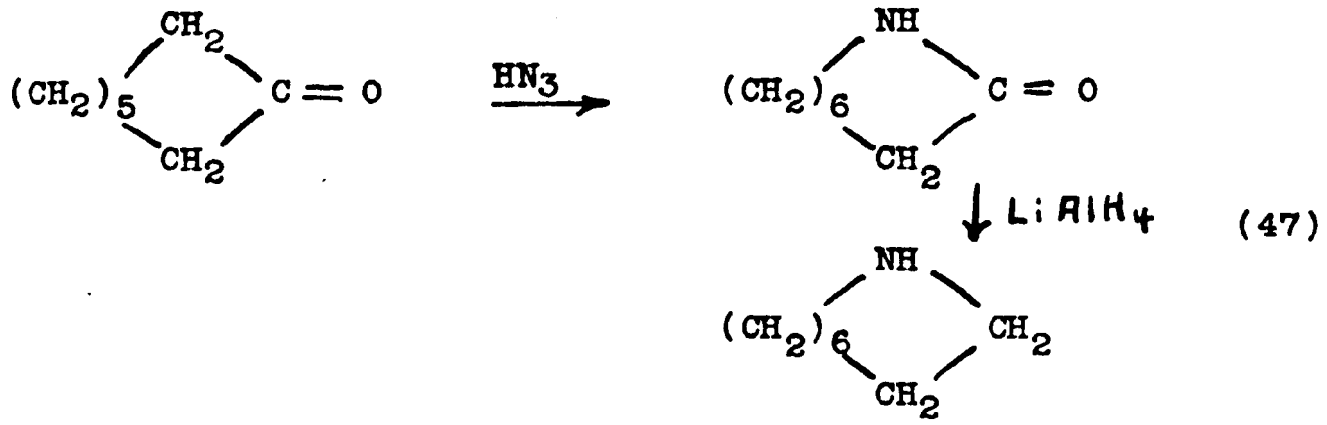


the preparation of amines for exhaustive methylation studies,[6] and degradation of optically active acids to optically active amines in studies of camphor and the terpenes.[44]



Cosciug also has reported application of the Schmidt reaction to the naphthenic acids.[45]

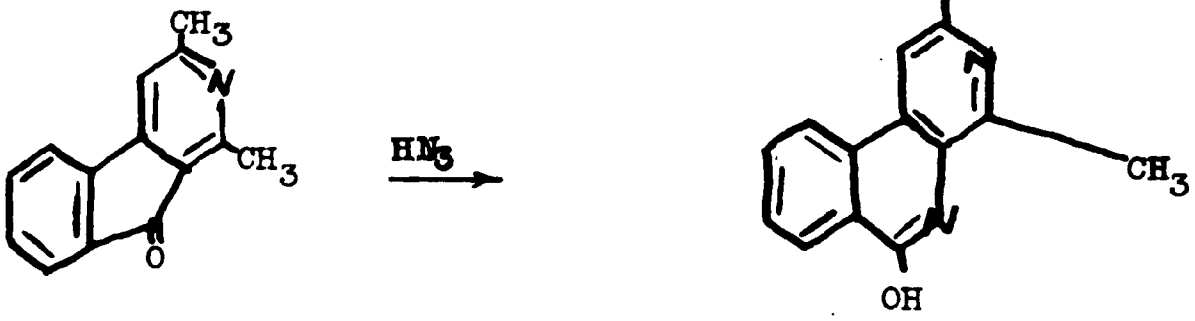
The Schmidt reaction has been used by Ruzicka in the synthesis of large ring cyclic lactams as intermediates for the synthesis of polymethylene imines.[46]



(47)

Since the review published by Wolff (1945),[48] the Schmidt reaction has been used in several other fields of application.

Petrow has used the Schmidt rearrangement of azafluorenones, the pyridine analogs of fluorenones, to prepare azaphenanthridones, which may be considered as substituted 2-pyridones.[49] These compounds may be reduced to give diazaphenanthrenes.



Ruzicka has extended the uses of the Schmidt reaction by applying the rearrangement to cyclohexanone derivatives such as 2,2,3,5-tetramethyl cyclohexanone.[50] This application was introduced in Ruzicka's studies on irone. More recent applications of the Schmidt reaction have been its use in the preparation of aminophenanthrenes,[51] and aminofluoranthenes.[52]

The Schmidt reaction has also been used to elucidate

the structure of the ketones resulting from acetylation or benzoylation of 5-haloacenaphthenes.[53]

Specific Schmidt Reactions

The Schmidt reaction of carbonyl compounds and hydrogen azide in the presence of acid catalysts may be conveniently divided into two classes. The first of these classes includes those compounds in which the "carboxylic" carbonyl group of organic acids, esters, anhydrides and halides undergoes the Schmidt reaction. The second of these classes includes those compounds in which the unmodified carbonyl group of ketones and aldehydes undergoes the Schmidt reaction.

The carboxylic carbonyl compounds such as the organic acids generally give amines as their products.[5,6]

$$RCOOH \xrightarrow[HN_3]{H_2SO_4} RNH_3^+ HSO_4^- + N_2 + CO_2$$

However, carboxylic acids with branching in the α-position give carbon monoxide, ketones, primary amines, alcohols, and ammonia as by-products by side-reactions.[54,55]

Ketones nearly always give amides in which the NH group is adjacent to the original carbonyl group.[1,2,3]

$$RCOR' \xrightarrow{HN_3} RCONHR' + N_2$$

Aldehydes give mixtures of nitriles and amides, in which the nitrile predominates. The proportions depend upon the conditions of the reaction.[2,3,17,18]

$$R\text{-}CHO \longrightarrow R\text{-}C{\equiv}N \text{ (Major product)} + RCONH_2 + RNHCHO$$

The Schmidt reaction has been tried on very few aliphatic aldehydes; acetaldehyde, gives a high yield of acetonitrile.[17,18]

$$CH_3CHO \xrightarrow[H_2SO_4]{HN_3} CH_3CN + H_2O + N_2$$

All other aldehydes give the corresponding nitriles,[2,3,17,18,56,57,58] but formamides, and the corresponding hydrolysis products have been isolated as well.

The ratios of nitrile to formanilide produced from benzaldehydes have been found to vary with the acid strength of the solution.[2,3,17,58] In general, the proportion of formanilide was found to increase with the acid concentration. In some cases this increase was large enough to make formanilide the major product.

Ketones

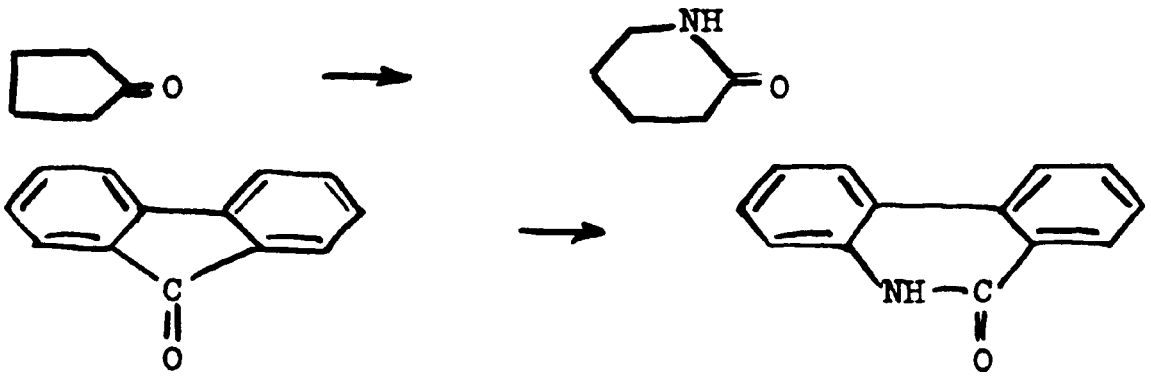
I. Symmetrical Ketones

Only a few examples exist of the performance of the Schmidt reaction on symmetrical ketones. Since Schmidt's initial work with benzophenone, the reaction has been applied to strictly aliphatic ketones such as acetone,[2,3] cyclic ketones such as the aliphatic cyclopentanone,[8] and the aromatic fluorenone.[59]

$$CH_3COCH_3 \longrightarrow CH_3CONHCH_3$$

In all these cases N-substituted amides are the sole products of the reaction unless tetrazoles are formed due to the

presence of excess hydrogen azide. With cyclic ketones the amides are, of course, lactams.

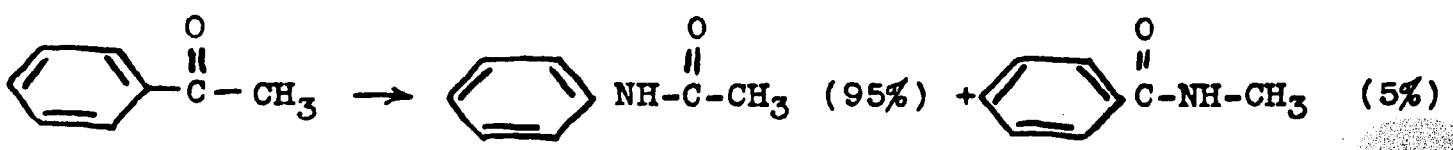


II. Unsymmetrical Ketones

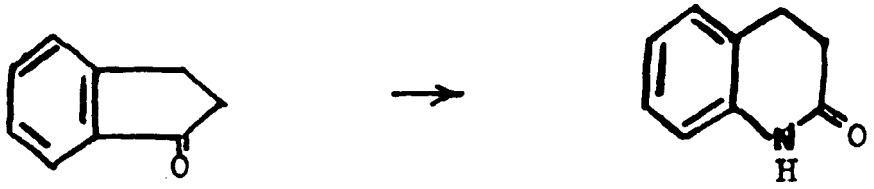
The first unsymmetrical ketones subjected to the Schmidt reaction were methyl ketones possessing carboxylic acid or ester groups (ß-ketoesters, levulinic acid).[2,3,12] These compounds yielded as the main product ß- or ∝-acetylamino acids, recovered upon hydrolysis as ∝- or ß-amino acids, and as a by-product, an ∝- or ß-N-methylcarbamido acid, recovered upon hydrolysis as an amine.

The Schmidt reaction has also been applied to unsymmetrical cyclic ketones, such as ∝-methylcyclohexanone, as has been mentioned (p.4). In Schechter's recent reinvestigation of this ketone, again only the one compound, N-methyl-∝-piperidone, was isolated.[14,15]

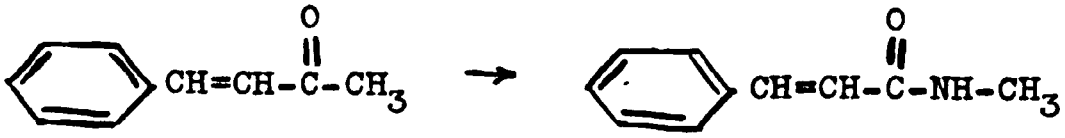
Acetophenone, a mixed alkyl aryl ketone, has been found to give acetanilide as the major reaction product.[35] Recent work shows that 95% of the amide product is acetanilide, 5% of the amide product is N-methyl benzamide.[60]



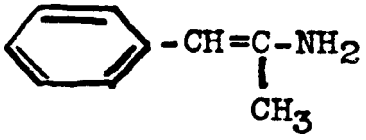
Similarly, the cyclic ketone, hydrindone, in which the carbonyl group is attached to a benzene ring, has been found to yield dihydrocarbostyril as the only reaction product which could be isolated.[31]



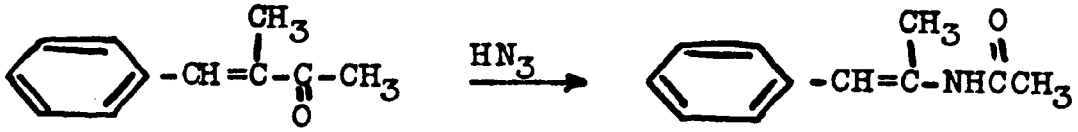
From the unsaturated ketone, benzalacetone, only N-methyl-cinnamamide is obtained.[9,60]

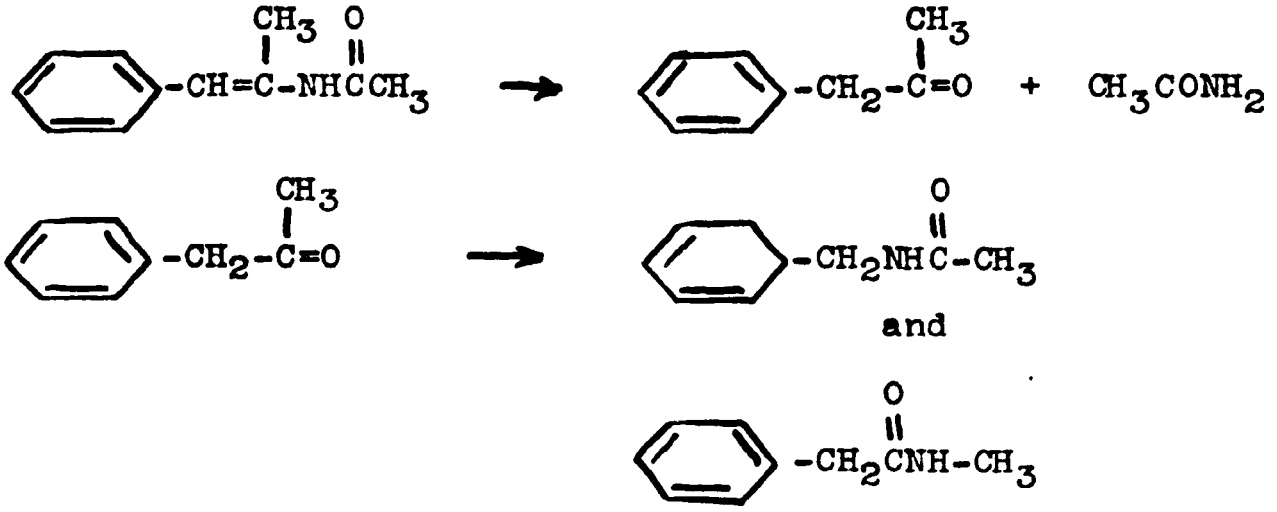


However, when the related compound, 3-benzalbutanone-2,[60] was subjected to the Schmidt reaction, the products isolated were N-benzylacetamide, and N-methylphenylacetamide, the usual products of the Schmidt reaction on phenylacetone. It can be concluded from these results that the methyl-styryl group becomes attached to the NH group. The resulting vinyl-amine,

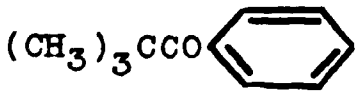


would easily be hydrolysed by the concentrated hydrochloric acid present to phenylacetone, which then undergoes the Schmidt reaction itself.





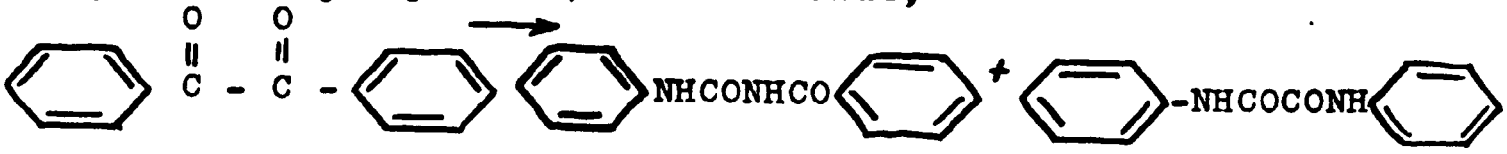
When pivalophenone,



was subjected to the Schmidt reaction, the larger t-butyl group did all the migrating.[60] However it ultimately became separated from the rest of the molecule. In this case, large amounts of benzonitrile with some benzamide, benzoic acid, N-t-butyl benzamide, ammonia and methylamine were formed.

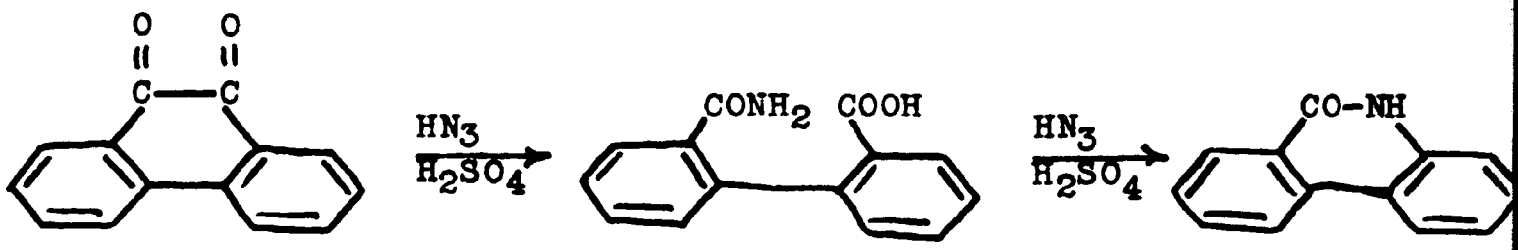
III. Diketones

Spielman and Austin ran the first Schmidt reaction on a diketone (benzil).[20] The main products were N-benzoyl-N'-phenylurea (major product) and oxanilide,



Since that time, other substituted cyclic benzils (orthoquinones) have been subjected to the Schmidt reaction.[13,61,62,63,64,65,65a] Imides, amido acids, phenanthridones, diamines, and even anhydrides have been isolated. For instance, one mole of hydrogen azide on phenanthraquinone gave diphenanic acid as

the major product, while two moles of hydrogen azide gave phenanthridone as the major product. Diphenamic acid itself gives phenanthridone when subjected to the Schmidt reaction.[61,63,64]

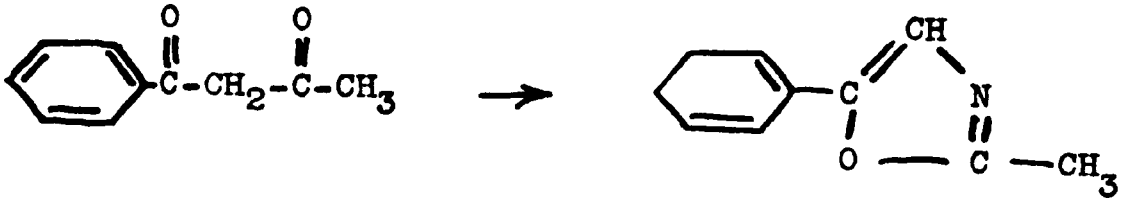


No further studies have been made on acyclic α-dicarbonyl compounds.

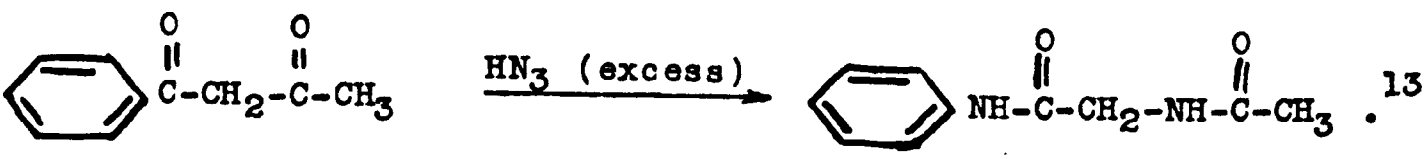
In studies on ß-ketoaldehydes and ß-diketones,[13,64] it was found that an aldehyde group reacts before a ketone group in the Schmidt reaction, and that in a diketone the most basic of two keto groups reacts first. As in most Schmidt reactions, the bulkier group migrates to the nitrogen.

1,3-Indandione was found to react with only one molecule of hydrogen azide, to give 2,4-dihydroxyquinoline (the second carbonyl group is transformed by tautomerisation).[13]

In the presence of one mole of hydrogen azide, benzoylacetone gives 2-methyl-5-phenyloxazole,[13,64]



but with excess hydrogen azide, α-acetamido acetanilide was formed,



.[13]

Studies on γ-diketones show that these compounds behave much like monoketones, although furans are formed as by-products by cyclisation of the γ-diketones in acid solution.[66]

Usual Conditions for the Schmidt Reaction

A partial review of the different compounds which have been subjected to the Schmidt reaction, the modifications of the reactions used, and the yields obtained by various workers up to 1945 is available in Organic Reactions.[48] It is the intention here to summarise briefly those conditions covered in Wolff's review, and to review the recent investigations of the Schmidt reaction, covering those facts pertinent to the present investigation.

Hydrazoic acid for the Schmidt reaction may be furnished in three different ways. The hydrogen azide may be added as a solution, either in the diluent for the reaction, which may be water,[2,3,9] or an alcohol,[7] or in an inert organic solvent. An alternative procedure used by Sanford, Blair, Arroya, and Sherk consists in the introduction of gaseous hydrogen azide into the mixture of reactant, catalyst, and an indifferent organic solvent.[67] The third method makes unnecessary the handling of the hydrogen azide except in the actual reaction mixture; the hydrogen azide is produced *in situ* by addition to the reaction mixture of either solid sodium azide or a solution of it, whichever is desired.[12]

In general, the temperatures used in the Schmidt reaction are near room temperature. The Schmidt reactions of carboxylic acids are usually run at a higher temperature than the

corresponding reactions on aldehydes and ketones, which have sometimes been run at temperatures as low as 0°. In general, raising the temperature increases the rate of reaction greatly;[1,2,3] reactions of aldehydes and ketones are controllable at room temperature only if relatively basic[59] solvents are used or if the carbonyl compounds are not very reactive.

The yield, and rate, of the Schmidt reaction falls off at temperatures above 60° because of the greater rate of disappearance of hydrazoic acid, by its own decomposition,[1,2,3,64] reaction with solvents such as benzene,[1,2,3] and by evaporation from the solution.*

Solvents

The Schmidt reaction has been run homogenously in one phase, either organic or aqueous,[12,59] and has also been run heterogeneously, usually with the carbonyl compound distributed between an organic solvent and the acid catalyst.[1,2,3]

Benzene and chloroform are typical examples of the solvent-diluents used in the two-phase procedure, while water, dioxane,[9] ether,[9] and alcohol have been used as solvents for mineral acids to obtain a single phase. One-phase systems have also been obtained by use of a strong organic acid, such as trichloracetic,[59] trifluoroacetic and heptafluorobutyric acids,[69] as the catalyst-solvent or as a solvent-diluent in the presence of a stronger mineral acid.

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* The boiling point of hydrogen azide is 37°.[68]

An optimum solvent for a particular Schmidt reaction would be one which would dissolve both reagents and catalysts, and whose basic strength was low enough to permit the reaction to go at a convenient rate.

Catalysts

A very large number of catalysts, all acids in the Lewis sense,[70] have been applied to the Schmidt reaction. Briefly, they can be divided as follows: ordinary mineral acids, such as sulphuric acid, hydrochloric acid,[13] phosphoric acid;[16,17] their anhydrides, such as mixed acid anhydrides, as phosphorus oxytrichloride; strong organic acids such as trichloroacetic acid and the sulphonic acids;[16,17] and the weak-salt-types of Lewis acids, such as aluminum chloride, ferric chloride, and stannic chloride. Ultraviolet light has also been used as a catalyst for certain related reactions.

It has been found that, in general, the least acidic catalyst that may be used for a specific Schmidt reaction is generally the best one as far as rate of reaction and yields are concerned.[59]

Products of the Schmidt Reaction and Their Separation

The different types of compounds produced in the Schmidt reaction on acids, ketones, and aldehydes are recovered in various ways depending upon the physical and chemical properties of the product. Amines produced from the Schmidt reaction on acids may be isolated by filtration of the amine sulphate, by steam distillation of the alkalised water extract, or by ether

extraction of the alkaline solution. Amides and lactams produced from the Schmidt reaction on ketones may be isolated as such from the reaction medium if they are relatively insoluble in water. The more soluble amides may be isolated by extraction from the alkalised solution by an organic solvent, in the same manner as amines.

Amino acids must be isolated by the special means appropriate to such amphoteric substances. Imidoesters resulting from the Schmidt reaction ketones in alcoholic solution may be isolated as the salt of the acid used as catalyst (usually hydrochloric) by evaporation of the solvents.[7,25,26]

Nitriles are sometimes resistant to the Schmidt reaction, and may be isolated from the reaction mixture as such.[2,3,16,17,56,57,58,60] Cyano groups originally present may come through the Schmidt reaction unchanged as has been observed with meta-cyanobenzoic acid[71] and 2-cyanocyclohexanone.[13,14] However some nitriles have been found to give 1-alkyl-5-amino-tetrazoles slowly upon addition of hydrogen azide in concentrated acid.[72,73] On treatment of nitriles with hydrogen azide for three to five days at 150° without a catalyst, unrearranged 5-alkyl-tetrazoles have been obtained.[74]

Formanilides may be isolated from the Schmidt reaction mixture just as any other amide-products. Due to the greater instability of these compounds toward acidic and basic hydrolysis, the corresponding anilines of these compounds are usually obtained from the alkalised solution.[2,3,56,58]

Tetrazoles formed during a Schmidt reaction have occasionally

been isolated by preparation of the mercuric chloride complex followed by decomposition of the complex with hydrogen sulphide, but many tetrazoles do not form such complexes. Many of them are sufficiently insoluble to precipitate completely when the reaction-mixture is diluted with water without neutralization; others may be isolated by extraction in the same manner as amines and amides.[18,20,21,72]

Safety Precautions

Safety precautions are sometimes necessary in carrying out the Schmidt reaction because of the explosiveness and toxicity[23,24] of hydrogen azide. The danger may be minimized by running the reaction in solution, avoiding handling the free hydrogen azide, and by performing operations with this compound in closed systems or in a good forced-draft.

Although Sanford, Blair, Arroya, and Sherk have reported running the Schmidt reaction by bubbling gaseous hydrogen azide into the mixture of ketone and catalyst,[67] this procedure is not preferred for routine preparation because of the extra danger involved. The reactions using hydrogen azide dissolved in chloroform or other organic solvents, or still better, the production of the hydrogen azide *in situ* by the addition of sodium azide to a mixture of the carbonyl compound, acid catalyst, and diluent, if desired, are much safer.[12] As soon as the hydrogen azide is produced, it is used in the Schmidt reaction.

Where solutions of hydrogen azide are used, the possibility of distillation of pure hydrazoic acid onto the side of flasks

containing stock solutions of hydrogen azide, with the accompanying chance of explosion upon slight shocks, may be avoided by addition of a small amount of ether,[61] or a low boiling petroleum solvent such as pentane. The ether or other volatile compound vaporises with the hydrazoic acid and condenses with it; thus dilution of the acid takes place, lessening the chance of explosion.

Determination of Gas Evolution

Although Wolff's review on the Schmidt reaction[48] mentions the use of the rate of nitrogen evolution in the reaction, as measured by bubbles in a wash bottle, as a method of following the speed of the reaction in order to control it, only one quantitative measurement of this gas evolution had been made at the start of this study.

In 1943, Briggs and Lyttleton quantitatively determined the nitrogen evolved from Schmidt reactions[71] on various substituted benzoic acids. Their apparatus was arranged as follows:

A weighed amount of the benzoic acid was dissolved in trichloroethylene. The solution of acid was added to a solution of hydrogen azide in trichloroethylene contained in a three-necked flask equipped with mercury-sealed stirrer, a dropping funnel sealed into the reaction and measurement system, containing the sulphuric acid catalyst previously warmed to 40°, and a reflux condenser. The flask was immersed in a constant temperature bath kept at 40° C.

Upon addition of the sulphuric acid catalyst, stirring

of the solution was commenced. The nitrogen evolved passed through the condenser, out a connecting tube at the condenser's upper end, through a soda-lime absorption tube into a burette filled with fifty per cent potassium hydroxide. This gas measuring tube was kept at a known constant temperature by means of a water jacket. The stirring was continued until the rate of gas evolution dropped below four cc. per hour, at which point the observations ceased.

Mechanisms

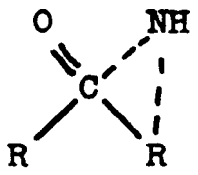
The first tentative mechanism for the Schmidt reaction was proposed by Schmidt.[2] He was led to discovery of the reaction now named for him by his search for reactions of the particle NH, formed upon decomposition of hydrogen azide in acid solutions.

$$HN_3 \xrightarrow{H_2SO_4} NH \text{ or } NH_2^+ + N_2$$

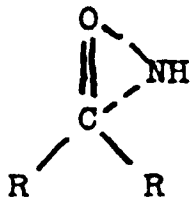
Within one or two years after his initial discovery, Schmidt advanced two possible reaction paths, both involving NH.[3,76] The first of these routes involved direct incorporation of the NH radical into the ketone.

$$RCOR + NH \longrightarrow RCONHR$$

This was presumably made possible by decrease of the forces between the carbonyl group and one of the alkyl or aryl groups by the disturbing effect of the NH radical, and at the same time, the formation of new bonds with the carbonyl group and the alkyl or aryl group. On the basis of the theory of absolute reaction rates,[77] such a reaction might have in the transition state a three center complex;



The second route suggested by Schmidt involved the initial addition of NH with formation of an oxime, followed by a Beckmann rearrangement of the oxime in the acid solution. In this case the NH radical would presumably attack the carbon-oxygen bond of the carbonyl group, weakening it, while at the same time establishing new nitrogen-carbon and nitrogen-oxygen bonds. An intermediate transition state for the first step of this series might be formulated as



No preference was given by Schmidt for either of these mechanisms. These two paths for the reactions of NH with ketones could equally well, or better, be interpreted in terms of the kindred radical NH_2^+.[78]

$$HN_3 \xrightarrow{H_2SO_4} \left[H_2N\text{-}N_2\right]^+ \longrightarrow NH_2^+ + N_2$$

In 1925, a comparison was made by Oliveri-Mandalá[79] between the Schmidt reactions supposedly involving NH, and aldehydes and ketones, and the reaction of nitroxyl, NOH, with aldehydes which Angeli found to give hydroxamic acids.[80]

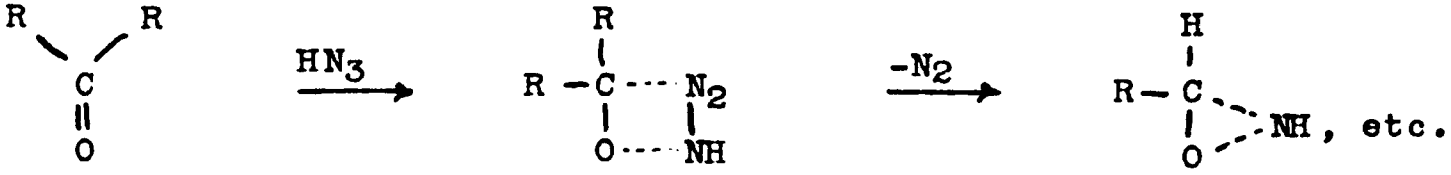
$$RCHO \xrightarrow{NOH} RCONHOH$$

Oliveri-Mandalá concluded that while some of the high temperature

reactions of hydrazoic acid in sulphuric acid solution might go by way of NH or NH_2^+, the reactions proceeding at low temperatures, where hydrogen azide was relatively stable, must go via attack by the HN_3 molecule, not the NH radical.

In reality, Schmidt himself contributed to the evidence for the belief that NH is not the intermediate in the Schmidt reaction. He found that in the benzene-catalysed decomposition of hydrogen azide at a temperature of 60-70°, aniline sulphate was formed in high yield, while at room temperature hydrazine sulphate was formed very slowly.[1,2] The Schmidt reaction on ketones, however, was known to go at much lower temperatures, where HN_3 did not decompose. This fact was responsible for Oliveri-Mandalà's views. It is now known that the Schmidt reaction may sometimes be run at temperatures as low as 0°,[59] at which temperature hydrogen azide is not detectably decomposed by any of the catalysts for the Schmidt reaction.

Two possible mechanisms for this attack by the hydrogen azide molecule were suggested by Oliveri-Mandalà. One of these involved the formation of a transient heterocyclic intermediate (A),

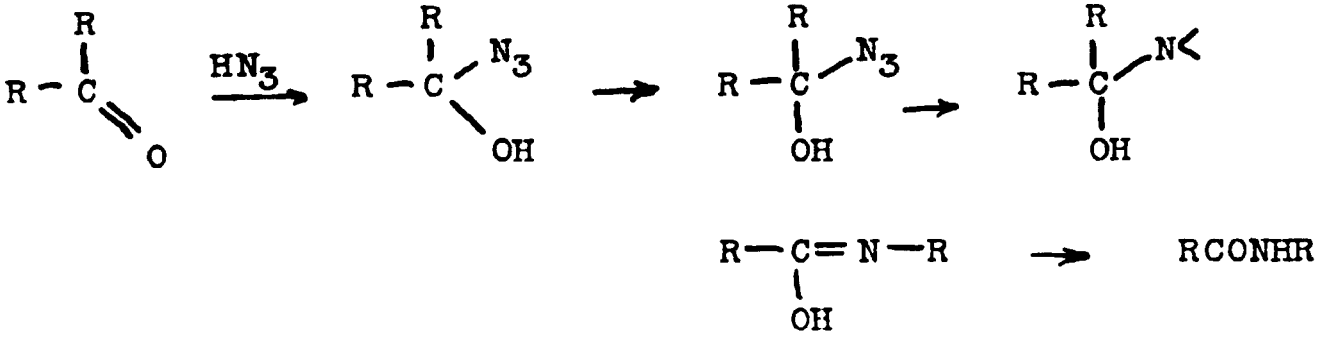


A

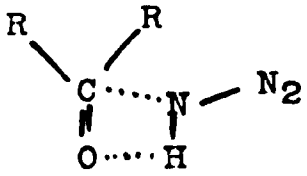
Later, this same type of intermediate was suggested by Morton,[81] in analogy to the heterocyclic intermediate used by L. I. Smith

to explain some reactions of diazomethane[82] and originally proposed by Schlotterbeck.[83] The "dihydrooxatriazole" was used by Morton to correlate some reactions of hydrogen azide and diazomethane.

The second mechanism proposed by Oliveri-Mandala[79] involved the addition of the proton from the hydrogen azide to the oxygen of the carbonyl group and the addition of the azide group to the carbon of the carbonyl group, followed by formation of univalent nitrogen fragment and rearrangement in the manner proposed by Stieglitz[84] for the Curtius rearrangement of acid azides.[85]



The first step of this path may be interpreted as having a four-center transition state;



The other route, via a heterocyclic intermediate, may be terminated in two ways, involving either direct collapse to an amide, or, as suggested by Schmidt, involving intermediary formation of an oxime, which subsequently undergoes the Beckmann rearrangement. The second route proposed by Oliveri-Mandala

does not so readily lend itself to the interpretation of an oxime intermediate.

No further suggestions as to the mechanism of the Schmidt reaction were made until a few years after von Braun's application of the reaction to carboxylic acids.[5] In 1937, Whitmore suggested another path for the Schmidt reaction on the basis of the analogy with the Curtius rearrangement.[86] The Schmidt reaction on carboxylic acids

$$RCOOH + HN_3 \longrightarrow RNH_2 \text{ (as salt)} + CO_2 + N_2 ,$$

is formally very similar to the Curtius rearrangement,

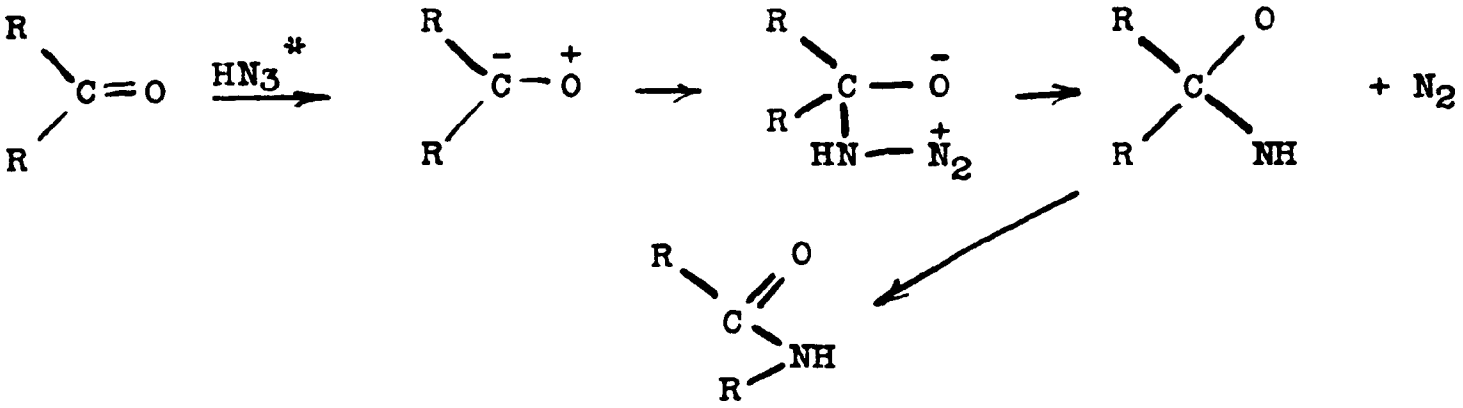
$$RCON_3 \longrightarrow \underset{+N_2}{RNCO} \xrightarrow{\text{Acid}} RNH_2 \text{ (as salt)} + CO_2$$

in that both syntheses are based on the reaction of a derivative of a carboxylic acid to give an amine containing one less carbon atom. Whitmore postulated that the Schmidt reaction proceeded through conversion of the carboxylic acid to an azide, followed by rearrangement as in the Curtius reaction. Whitmore's mechanism was not supported by experimental evidence.

In 1938, Hurd advanced a different route for the reaction of ketones with hydrogen azide.[87] Hurd's hypothesis contained several novel features. The action of the hydrogen azide in concentrated sulphuric acid solution was explained by a preliminary activation of the hydrazoic acid by the sulphuric acid catalyst.

$$HN_3 \xrightarrow{H_2SO_4} \overset{*}{HN_3} \quad (H\text{-}\overset{+}{N}\text{-}N\equiv N)$$

This "activated" or polarised form of hydrogen azide was then presumed to attack the carbonyl group. The intermediate formed in this manner would then lose nitrogen and rearrange.



The "activation" of hydrazoic acid by the sulphuric acid was not further explained, and was assumed to be sufficient to make it react with the ketone. Hurd did not cite experimental results to substantiate his mechanism.

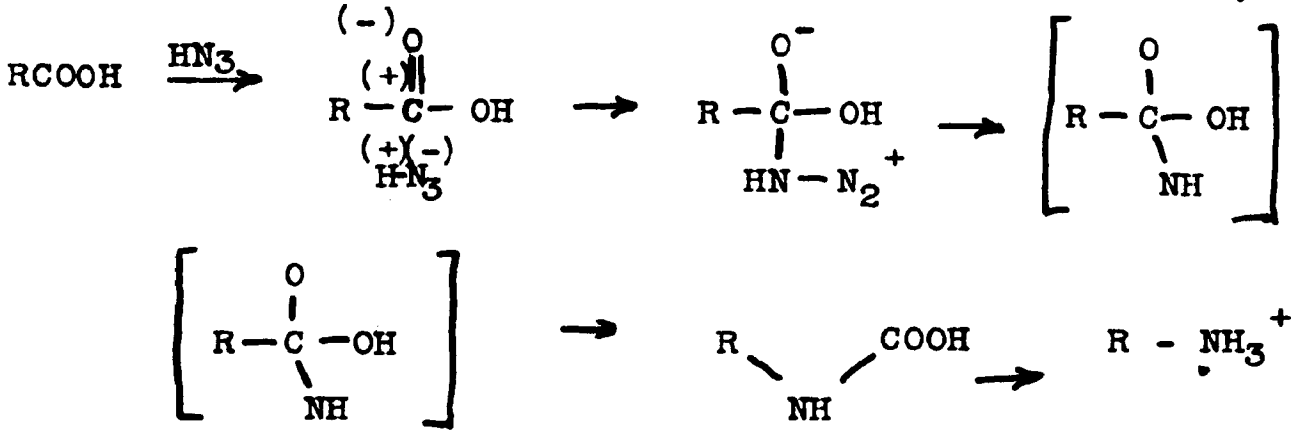
In 1937, Spielman and Austin undertook some studies on the Schmidt reaction on the di-ketone, benzil, and its derivatives.[19] They found that the Schmidt reaction on this compound would take place readily in mixtures of hydrogen azide and sulphuric acid, under conditions where the corresponding oximes, γ-(amphi-) benzildioxime, would neither rearrange nor react in any other way.[19]

Independently, Briggs and De Ath[34] found that another, simpler ketone, hydrindone, would undergo the Schmidt reaction to produce dihydrocarbostyril under conditions much milder than those found necessary by Kepping[88] to produce the Beckmann rearrangement on the corresponding oxime. The evidence presented by these two studies clearly indicated that the Schmidt reaction does not go by way of an oxime

intermediate, as Schmidt originally proposed, but instead proceeds through a more labile intermediate.

In rate studies of the Schmidt reaction on various substituted benzoic acids, Briggs and Lyttleton[89] found that nucleophilic groups, such as methoxy and methyl groups, which generally increase the base strength of basic compounds, and decrease the acid strength of acidic compounds, promoted the velocity of the Schmidt reaction on benzoic acids, while electrophilic groups, such as cyano and nitro groups, which act in the reverse manner, decrease the velocity of the Schmidt reaction.

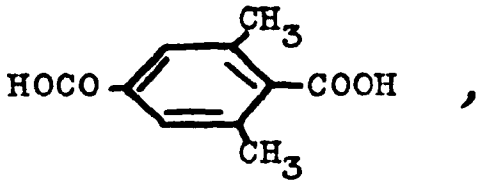
On the basis of their rate studies and the elimination of an oxime as a possible intermediate, Briggs and Lyttleton postulated a new mechanism for the Schmidt reaction on carboxylic acids. This mechanism entailed attack upon the carboxylic acid by the HN_3 molecule, loss of nitrogen to form a radical, and rearrangement of the radical to a carbamic acid which decarboxylated to an amine (as the salt). It may be seen that the mechanism presented by Briggs and Lyttleton is essentially the same as that proposed by Hurd for ketones.



The possibility that a hydroxy-carbonium ion is the intermediate in the Schmidt reaction was first suggested as

the initial step in a reaction mechanism proposed by Smith in 1944,[90] and later independently by Sanford, Blair, Arroya and Sherk[67] on the basis of some apparent similarities between the Schmidt reaction and certain reactions involving hydroxylamine-O-sulphonic acid.[18,91] Sherk and his coworkers proposed this carbonium ion intermediate for the Schmidt reaction on the basis of a comparison with other reactions of carbonyl compounds, such as semicarbazone[92,93] and oxime formation,[94] in acid solution, which proceed by formation of a hydroxy-carbonium ion followed by attack by the basic reagent.[92]

The formation of a hydroxy-carbonium or an oxocarbonium ion as a primary intermediate in the Schmidt reaction was later proposed by Newman and Gildenhorn as a result of their observation that only the hindered carboxyl group in 2,6-dimethylterephthalic acid,



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reacted to given an amine by the Schmidt reaction, and this same specificity was observed in esterification by pouring the sulphuric acid solution of the compound into alcohol.[95] The esterification of compounds which contained hindered carboxyl groups by solution in concentrated sulphuric acid and dilution with alcohol had already been shown to go via an oxo-carbonium ion.[96] Newman and Gildenhorn found compounds which gave oxo-carbonium ions[95] in sulphuric acid solution underwent the Schmidt reaction at 0°, while compounds which they had found

to give the hydrated, dihydroxy-carbonium ions did not undergo the Schmidt reaction in these conditions, but did react with hydrogen azide at higher temperatures. Considering these facts, they postulated a mechanism for the reaction of oxo-carbonium ions with hydrogen azide,

$$RCOOH + 2H_2SO_4 \rightarrow RCO^+ + H_3O^+ + 2HSO_4^-$$

$$R\text{-}CO^+ + HN_3 \rightarrow \left[R\text{-}C(=O)\text{-}HN\text{-}N_2^+ \right] \rightarrow \left[C^+(=O)\text{-}NHR \right] + N_2$$

$$RNHCO^+ + H_2O \rightarrow RNH_3^+ + CO_2$$

and a comparable mechanism for dihydroxy-carbonium ions.

$$RCOOH + H_2SO_4 \rightarrow RC^+(OH)(OH) + HSO_4^-$$

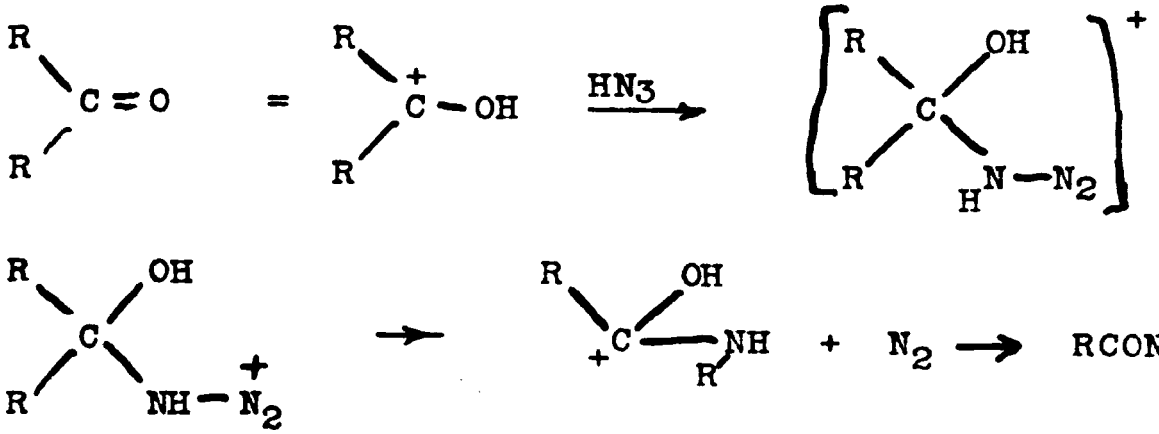
$$RC^+(OH)(OH) + HN_3 \rightarrow R\text{-}C(OH)(HN_3^+)(OH) \rightarrow {}^+C(OH)(OH)\text{-}NHR$$

$$RNHC^+(OH)_2 \rightarrow RNH_3^+ + CO_2$$

Higher temperatures may favor the dehyration of dihydroxy-carbonium ions to oxocarbonium ions.

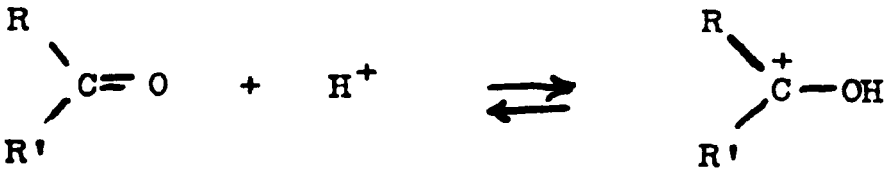
$$RC^+(OH)(OH) \rightleftharpoons RCO^+ + H_2O$$

Newman and Gildenhorn also advanced a mechanism for the Schmidt reaction on aldehydes and ketones, based mainly on the carbonium-ion suggestion of Sherk, et al.,



At the same time, an alternative mechanism was published by Smith.[59] This mechanism and the observations on which it was based will be discussed here in detail as it forms the basis for the present studies. This mechanism and that suggested by Newman and Gildenhorn differ significantly at step 3.

(1)



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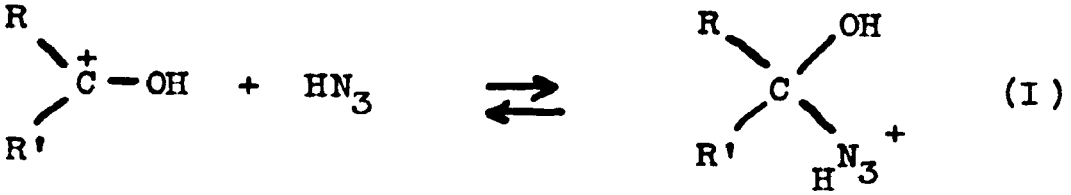

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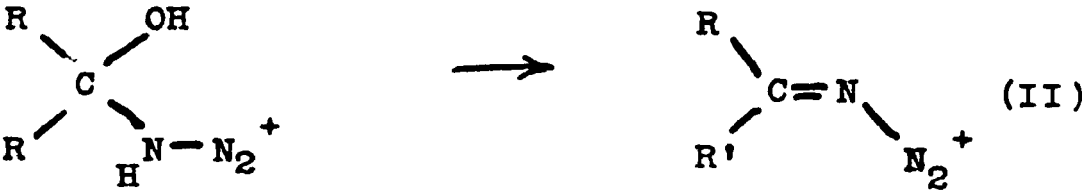
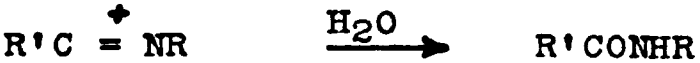


(4)



(5)



The most significant feature of this mechanism is the postulation of an intermediate containing a carbon-nitrogen double bond, which would therefore be capable in principle of geometric isomerism when derived from unsymmetrical ketones (and aldehydes).

Two conclusions may be drawn from this mechanism. The first implication is that the occurrence of the Schmidt reaction is dependent upon both the extent to which the carbonyl compound undergoes steps (1) and (2), and the polarising power of the particular carbonium ion in step (3). The possibility of geometrical isomers in the intermediate (II) produced in step (3) implies the second conclusion, that if that intermediate should have a finite existence, there should be a geometrical factor determining the group that migrates in unsymmetrical ketones. The occurrence and rate of the Schmidt reaction should depend upon the equilibrium concentration of carbonium ion produced by step (1) if step (4) is rate determining.

The qualitative comparison of the Schmidt reactions of nineteen carbonyl compounds of different types in seven solvents of different basicity and with five catalysts of different acid strength supported the first conclusion. The occurrence of the Schmidt reaction was governed only by the acidity of the medium as determined by the acid strength of the catalyst, the basic strength of the solvent, and the basic strength of the carbonyl compound undergoing the reaction.

Investigation of the consequences of possible geometrical

isomerism was undertaken by Smith and Horwitz. They have obtained results confirming the presence of a geometrical effect in the Schmidt reaction.[66] The same conclusion has since been reached by others on the basis of their work with unsymmetrical ketones.[13,14] These results will be discussed more fully in connection with the interpretation of the results of the present investigation.

Although the qualitative studies of Smith and the additional evidence of Newman and Gildenhorn[95] support the carbonium ion mechanism, it was nevertheless felt that a quantitative study of the rate of the Schmidt reaction would be desirable as further support for this hypothesis and to correlate the course of the Schmidt reaction with other reactions of the carbonyl group.

Statement of Problem

A thorough understanding of a reaction provides answers to certain practical questions, and conversely, the answering of these questions can contribute materially to a thorough understanding of the reaction.

How does a change in the solvent affect the rate, path and products of the reaction? An answer to this question would indicate the best solvents for a particular application, and would provide information on the ionic characteristics of the reaction.

How does temperature influence the rate, choice of path, and products of the reaction? Solution of this question might

provide means of selecting at will any of the possible competing reaction paths, and would provide information about the energy barriers involved.

How do various types of compounds, potential catalysts or inhibitors, affect the rate, path, and products of the reactions? This is not entirely separable from solvent effects, and would provide information of similar significance.

How does a change in type of substrate influence the rate, path, and products of the reaction? An answer to this question would indicate the special conditions which might be possible for a particular application of the reaction, and would provide information about the relative roles of steric and polar factors.

How do changes in concentration affect the rate, path, and products of the reaction? This question is important as its answer may determine experimental choice of diverging paths, and may enable a choice to be made among the several plausible mechanisms.

It is intended in this investigation to attempt to provide at least partial answers to the questions outline above as they may be applied to the Schmidt reactions of ketones with hydrogen azide in acid solutions, supplementing published information with new experimental results. The scope of the present studies is largely confined to factors influencing the kinetics of the Schmidt reaction at constant temperature.

EXPERIMENTAL

General Experimental Approach

After consideration of the background of data on the various phases of the Schmidt reaction, it was decided to undertake a kinetic study of the reaction in both aqueous and non-aqueous solutions in the general manner which will now be described.

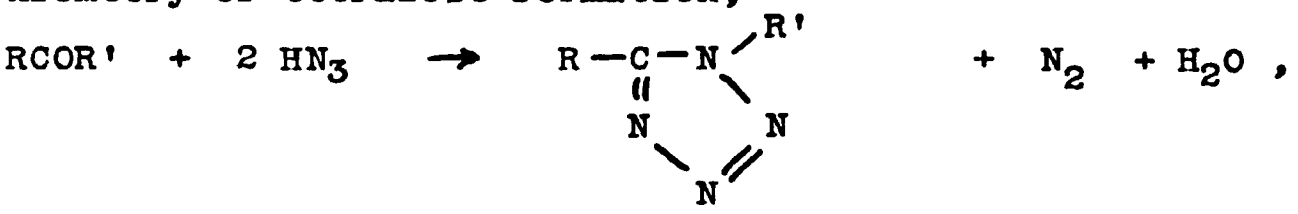
Since water itself is a base,[98] in the study of the Schmidt reaction on ketones, substrates would have to be chosen which possess sufficient affinity for protons to react to an appreciable extent despite the competition of the water for the acid. Use of such ketones would also make possible the use of more dilute acids, with satisfactorily measurable rates of reaction.

It seemed possible that the Schmidt reaction on different ketones might proceed by entirely different paths. These different paths might conceivably lead two ketones to react at the same rate under one set of conditions, but not in others. For this reason, rate studies on several different ketones of different structure and solubility in water were desired. In addition, the use of several different acids of different types and strengths was felt desirable to determine whether the reactions were subject to general or specific protonic-acid catalysis.[99,100]

Data on Schmidt reactions starting with the same initial concentration of ketone and acid catalyst, but with different initial concentrations of hydrogen azide were also sought in order to ascertain the influence of the concentration of

azide. This would be information beyond the simple fact that large excesses of hydrogen azide bring about tetrazole formation (p.4).

It was determined by investigation of the products of the experiments in aqueous solutions described here that tetrazole formation occurred in not more than negligible quantities. Since tetrazole formation presumably results from a step which occurs after the release of nitrogen, it would not be expected to affect the measured rate of nitrogen evolution except by depleting the supply of hydrogen azide at an enhanced rate. Such an effect can be calculated from the stoichiometry of tetrazole formation,



and its possible existence was taken into account in the interpretation of the results.

Since scattered data recorded in the literature indicate that temperature changes exert an influence on the path of the Schmidt reaction, it was necessary to conduct all experiments at the same temperature insofar as this would result in measurable rates. In addition to the use of constant temperature baths during the course of the runs, special adjustments were made to eliminate the effect of the sometimes considerable heats of mixing.

There was (at the start of this investigation) no recorded data to indicate that the Schmidt reaction is not

autocatalytic; that is, that the products of the reaction do not catalyse it. Therefore amides as well as other potential catalysts for the Schmidt reaction were given appropriate study so that any influence upon the course of the reaction that they possess might be found.

The above considerations were felt to be necessary and are believed to be sufficient to guide the studies conducted to the objectives expressed in the statement of the problem.

Choice of Ketones

In view of the fact that unsymmetrical ketones and aldehydes in many cases have been shown to give two products in the Schmidt reaction, (p. 11) rate studies on these compounds may, in reality, be studies of two different reactions proceeding at rates which may not necessarily be the same. These two reactions may be considered as proceeding by the same or different paths. Such conditions can be represented mathematically as follows,

$$\left(\frac{d\,(\text{ketone})}{dt}\right)_{\text{Total}} = \left(\frac{d\,(\text{ketone})}{dt}\right)_{R_1} + \left(\frac{d\,(\text{ketone})}{dt}\right)_{R_2}$$

If rates are the same,

$$\left(\frac{d\,(\text{ketone})}{dt}\right)_{R_1} = \left(\frac{d\,(\text{ketone})}{dt}\right)_{R_2} = \frac{1}{2}\left(\frac{d\,(\text{ketone})}{dt}\right)_{\text{Total}}$$

If different,

$$\left(\frac{d\,(\text{ketone})}{dt}\right)_{R_1} > \frac{1}{2}\left(\frac{d\,(\text{ketone})}{dt}\right)_{\text{Total}} > \left(\frac{d\,(\text{ketone})}{dt}\right)_{R_2}$$

In the latter case, assignment of the portions of the total rate of disappearance of carbonyl compound to the different reactions becomes difficult, if not impossible, without simultaneous determinations of the ratios of the two possible products formed.

The preliminary studies on the rate of the Schmidt reaction were, therefore, studies of symmetrical ketones. From such ketones, the two possible products that could be formed would not only be identical, but would also be produced by identical reaction paths having identical rates of reaction. This eliminates an unnecessary and undesirable complication in the interpretation of the data obtained.

Very few examples of the many possible Schmidt reactions on symmetrical ketones have been reported. Six such reactions; those on the aliphatic ketone, acetone; the cyclo-aliphatic ketones, cyclopentanone, cyclohexanone, cyclooctanone, and cyclohexadecanone; and the aromatic ketone, benzophenone, are listed in Wolff's summary of Schmidt reactions.[48] A cycloaromatic symmetrical ketone, fluorenone, and more recently, p,p'-dichlorobenzophenone, have been used by Smith and Horwitz.[59,60] These eight ketones were given first consideration as possible substrates in rate studies of the Schmidt reaction.

Recently, the basic strengths of carbonyl compounds and their derivatives have been correlated with the reactivities of these compounds towards reactions involving electrophilic reagents and catalysts.[101] For strongly basic compounds,

these base strengths may be determined in the usual way, by titration, either potentiometrically or with an indicator. Weaker bases may not be titrated with the usual acids to a significant end-point in the solutions obtainable with the ordinary solvents. The base strength of such compounds has been determined by the shift in the ultra-violet spectra of the carbonyl groups[102,103,104] and by study of the effect of these compounds on the O-D or C-D infra-red adsorption frequencies in deutero-methyl alcohol[101,105] and deuterochloroform.[106] These results permit as a rough generalisation the assumption of the following order in the base strengths of different carbonyl compounds: cycloalkyl ketones > dialkyl ketones > alkyl aryl ketones > diaryl ketones > carboxylic acids.

Other than the three aromatic ketones mentioned above, all the symmetrical ketones which had been subjected to the Schmidt reaction were of the cycloalkyl and dialkyl types. These compounds have been found to react with hydrogen azide even in relatively weakly acidic solutions. Thus the range of acidity could be more carefully varied and controlled by use of such compounds as substrates.

It was decided that one dialkyl ketone, and one cycloalkyl ketone would be chosen as the compounds to be studied. Cyclohexanone was chosen as the cyclic ketone since it was readily available in a pure state. Acetone, the simplest ketone, and the only symmetrical dialkyl ketone used previously in the Schmidt reaction, did not seem a good prospect

for the rate measurements, although it is strongly basic, because of the aldolisation that occurs in the acidic solutions necessary to catalyse the Schmidt reaction. It was decided to use instead, diisopropylketone which has only one hydrogen atom on each of the two carbon atoms adjoining the carbonyl group. It was felt that this compound would still exhibit the basic properties of acetone, but would be less subject to the aldolisation reaction.

After making the rate studies of the Schmidt reaction on the two aliphatic ketones, it was decided that additional information might be obtained by studies on less basic ketones such as the aromatic ketones and by studies on unsymmetrical ketones. These two studies were combined as one, by using acetophenone as the substrate in further rate measurements. Acetophenone offered an excellent comparison to the symmetrical ketones, in which migration of either carbonyl-attached group leads to the same product (p. //).

Acid Catalysts

Many different acids have been recorded as effective catalysts for Schmidt reactions. In his review on the Schmidt reaction, Wolff[48] lists sulphuric acid as the main acid catalyst, but at least twelve others that have been used are also mentioned. Moreover, new information since Wolff's review shows that sulphuric acid need no longer be considered the best catalyst for the Schmidt reaction.[59]

For good rate measurements, the reaction must go quantitatively, without side-reactions, during the period in which

the measurements are taken. Aliphatic ketones will react with hydrazoic acid even in the presence of an acid as weak as phosphoric acid.[48] Therefore a strong acid, suitably diluted, could be used to produce the reaction at convenient rates and good yield, or a weaker acid used at higher concentrations to produce the same effects. This adaptability of the reaction makes possible the choice of the catalyst upon the basis of some physical and chemical properties other than its acid strength.

Three acids, hydrochloric, ethanesulphonic, and sulphuric acid, were chosen. Hydrochloric acid is a good example of a strong aqueous acid. Ethanesulphonic acid is soluble in slightly polar organic solvents.[27] Sulphuric acid, the acid most used in the past as a catalyst for the Schmidt reaction, not only is a strong acid in water, but also offers the advantage of an exceptionally great acidity (see p.93) in its more concentrated solutions which contain little water. Hence, it has an ability to catalyse reactions not possible with other catalysts.

Production of Hyrazoic Acid

Solubility Factors

Quite often hydrazoic acid is furnished for the Schmidt reaction *in situ* by the addition of solid sodium azide to a solution of acid and substrate (p.15). Sodium azide does not dissolve rapidly in all acids; in fact, the rate of addition of sodium azide in Schmidt reactions in hydrochloric acid does not usually have to be controlled: the addition is

internally controlled, as the sodium azide dissolves only slowly and the hydrogen azide reacts as fast as it is formed in the reaction mixture at the usual laboratory temperatures. The deposition of sodium chloride, which is insoluble in strong hydrochloric acid solutions, is presumably responsible for this. With methanesulphonic and ethanesulphonic acid, alone or in chloroform, the sodium azide added tends to froth and float until the reaction is completed. While this sluggishness of reaction is welcome in synthetic work, it is not at all desirable in the measurement of rates of reaction; therefore, hydrazoic acid for reaction in such solvents must be generated or added in some other manner such that the hydrazoic acid reaches its maximal concentration nearly instantaneously. For this purpose standard solutions of hydrogen azide in appropriate solvents were used.

Preparation and Storage of Hydrogen Azide Sources

A standard solution of sodium azide in water for furnishing the hyrazoic acid for aqueous reaction mixtures may be quite easily prepared by the solution of a weighed amount of solid sodium azide in a known volume of water. Aliquot portions may then be added to the chilled solution of ketone and water to furnish a known amount of hydrogen azide upon treatment with excess mineral acid. Examination of sodium azide showed that the material currently available commercially does not contain enough basic impurities (as sodium carbonate or sodium hydroxide) to alter the pH of its aqueous solution (ca.9).

For reactions in organic solvents, solution of hydrazoic acid in organic solvents such as chloroform may be prepared by the method given in Organic Reactions.[8] However, this procedure was thought unnecessarily complicated for the preparation of the hydrogen azide solutions for the rate studies. Moreover, more of the hydrogen azide may be extracted from the aqueous solution by modifying this preparation. It was decided to prepare the solutions of hydrogen azide in non-aqueous media by the following general procedure: a weighed amount of 50% sulphuric acid and the organic solvent or solvents are placed in an Erlenmeyer flask immersed in a salt-ice mixture. One mole of solid sodium azide for each mole of the sulphuric acid is then added slowly to the chilled mixture of acid and solvent. The cold mixture is shaken, the organic layer separated, and the sulphuric layer extracted with chilled fresh portions of the organic solvent. The combined extracts are dried with magnesium sulphate, and the concentration of the resulting solution determined by pipetting a measured amount of the solution into a glass-stoppered Erlenmeyer flask, shaking it with some distilled water to reduce the vapor pressure of the hydrogen azide, and titrating with a standard alkali solution.

Production of Hydrogen Azide in the Reaction Mixture

Since sodium azide is readily soluble in aqueous solutions, a standard solution of sodium azide can furnish a known amount of hydrazoic acid in aqueous solutions by reaction with a strong acid. For instance,

$$HCl + NaN_3 \longrightarrow HN_3 + NaCl$$

Sodium azide is not soluble in most organic solvents; therefore, in those solvents hydrogen azide may not be furnished by internal reaction but must be combined with the acid-catalyst and the ketone-substrate in as short a period of time as possible. For this purpose solutions of a known amount of hydrazoic acid in an organic solvent as diluent are the most satisfactory. Use of such solutions still largely avoids the toxic and explosive properties of the hydrazoic acid.

Diluents for the Schmidt Reaction

For reactions in aqueous solutions, water was the only diluent used. Its use was satisfactory in both dilute and concentrated solutions of the acids. However, it must be pointed out that in concentrated aqueous solutions of acids, the acidity is no longer strictly proportional to the molarity of the acid. Measurements on the acidities of various concentrated aqueous solutions have been reviewd by Hammett.[99,107]

The prospective diluents for non-aqueous solutions were chosen on the basis of the dipole moments of the compounds and their inertness to attack by acid or hydrogen azide. Carbon tetrachloride, chloroform, hexane, chlorobenzene, ethylene dichloride, acetone, nitromethane, and acetonitrile were used as solvents or diluents in Chapman's work on the related Beckmann rearrangement.[108,109,110] Of this list, acetone will react vigorously in the presence of hydrogen azide and an acid catalyst to give N-methylacetamide (p. 10),

and acetonitrile may react with hydrazoic acid to form tetrazoles in the presence of strong acid catalysts. All of the other compounds were thus possible diluents for the Schmidt reaction. At the beginning of these investigations, no Schmidt reactions had been run using hexane, chlorobenzene, and nitromethane. These compounds were therefore discarded and replaced by benzene and nitrobenzene, solvents previously used,[1,2,3,5,9] methylene chloride and ethylidene chloride. These chlorinated hydrocarbons of one and two carbon atoms are similar to carbon tetrachloride and chloroform in their chemical properties and most of their physical properties, but are different in their dipole moments. Recently, an article has appeared on rate studies on the Schmidt reaction on acids, in which nitromethane was a diluent.[54] The properties of those compounds finally used are summarised in the table below.

CCl_4	$\mu = 0$*	Diluent
C_6H_6	$\mu = 0$	Diluent
$CHCl_3$	$\mu = 1.15$	Diluent, Solvent
CH_2Cl_2	$\mu = 1.57$	Diluent, Solvent
CH_2ClCH_2Cl	$\mu = 1.8$	Diluent, Solvent
CH_3CHCl_2	$\mu = 2.05$	Diluent
$C_6H_5NO_2$	$\mu = 4.24$	Diluent, Solvent

* All values for dipole moments are in debyes.

Possible Catalysts

The products of a reaction occasionally serve as catalysts for the reaction which produced them. An outstanding

example of this sort of autocatalysis has been furnished by Chapman in his work on the Beckmann rearrangement.[108,109,110] Chapman found that benzanilide, a product of the Beckmann rearrangement of benzophenone oxime initiated by hydrogen chloride, would accelerate the rearrangement by markedly reducing the inhibition period. Since the Schmidt reaction is run on an analogous compound, a ketone, which in the presence of an acid catalyst and hydrazoic acid gives the same product as the Beckmann rearrangement, it seemed possible that autocatalysis might also occur in the Schmidt reaction.

Anions which might be present in the reaction mixture, and the cations which might be formed in small amounts by solution of the metal stirrers in the acid solutions were investigated for catalytic activity. Compounds which might have a catalytic effect on the Schmidt reaction could be tested for their catalytic activity by introduction into reaction mixtures and comparison of the rate with that observed in their absence. Since cyclohexanone and diisopropylketone were the two symmetrical ketones chosen for the Schmidt reaction studies, ϵ-caprolactam and N-isopropylisobutyramide were the corresponding amides which were tested for catalytic activity. As a check, each of these amides was tested in reaction studies of both ketones. The effect of cupric and chromic ions was also investigated, as these were felt to be the ions most likely to be introduced from the stirrer blade.

Ratios of Reagents

Since it has been reported that the preparation of tetrazoles (p. 4) instead of amides is quite easy sometimes, even when only one equivalent of hydrogen azide is used, it was desired to eliminate the formation of these compounds as much as possible. In order to accomplish this purpose, in the aqueous solutions the ketone substrates were used in large excess. Higher molecular weight ketones, especially, have been reported to give tetrazoles - another reason for limitation of rate studies to those ketones containing no more than eight carbon atoms.

In the non-aqueous solutions, the ratios of the concentration of ketone to that of hydrazoic acid were not always so large. The evolution of nitrogen in a reaction involving hydrogen azide in concentrated acid solutions might therefore not be quantitative. In order to determine whether the reaction, $RCOR' + HN_3 \rightarrow N_2 + RCONHR'$, was quantitative as far as nitrogen evolution was concerned, for the solutions studied, several experiments were planned. Some of the regular runs would be allowed to go to completion by letting them stand for a long period of time. The nitrogen evolved should prove to be the amount calculated for the amide-forming reaction. (Since this research was undertaken, an article by Schuerch and Huntress has appeared, in which it is shown that nitrogen evolution is not quantitative in the case of all carboxylic acids.[54,55]) Further runs at higher concentrations of the acid catalyst (about twice the usual concentration), which

might be more favorable for side reactions, were also planned.

Order of Addition of Reagents

Kuhn and Corwin found that the order of gradual addition of the reagents for the Schmidt reaction on an acid, benzoic acid,[111] resulted in a marked change in results from those obtained by Newman and Gildenhorn.[95] In the former study, the azide was added first to the acid catalyst, and then the substrate added slowly; in the latter, the substrate and the acid catalyst were first mixed, and then the azide added slowly.

In the studies reported here, the third possible method of addition was used. In every case the acid catalyst was added rapidly to mixtures of the substrate and the azide. This method of addition of reagents, the only method that has been applied to the reaction of aldehydes with hydrazoic acid,[49] avoids prolonged contact of the carbonyl compound with the acid catalyst; hence, this method was chosen for use in studies of the relatively reactive ketones. The completeness of the Schmidt reaction using this mode of rapid addition was tested as outlined above. No tests were made upon the quantitativeness of the Schmidt reaction under other conditions.

Qualitative Rates Studies

The rate of nitrogen evolution, which is stoichiometrically equal to the rate of amide formation, and hence the removal of the ketone from reaction, may be represented by

the equation,

$$\frac{d\,(N_2)}{dt} = \frac{d\,(\text{Amide})}{dt} = K\ (HN_3)^x(\text{Ketone})^y(\text{Acid})^z$$

where x, y, and z are exponents of positive, negative, or zero powers, to which extent the reactant or catalyst takes place in the reaction.

The sign for these exponents may easily be determined by qualitative experiments in which the concentration of each of the reactants and the catalyst is independently varied, while the concentrations of the other two compounds are kept constant. For those compounds for which an increase in rate of nitrogen evolution accompanies an increase in concentration, the signs of the exponents are positive; for those for which a decrease in rate accompanies an increase in concentration, the signs of the exponents are negative; while for those for which there is neither an increase nor a decrease, the exponent is necessarily zero.

Quantitative Rate Measurement

Design of Measuring Tube

The gas evolved from the Schmidt reaction consists mainly of nitrogen but may possibly contain hydrazoic acid volatilised from the acid solution, carbon monoxide, carbon dioxide, and water.[54,55] This gas, to be properly measured, must be purified from possible contaminants, led into a measuring device, and there the volume determined under conditions of known temperature and pressure. This process of

measurement must be capable of showing instantaneous changes in volume due to the further occurrence of the reaction. The connection between the measuring apparatus and the reaction apparatus must be flexible and not subject to attack by any gases that may be carried through it.

A gas-measuring apparatus of this type has been used by Eyring and Daniels in their studies on the decomposition of nitrogen pentoxide.[112,113] Their apparatus was connected to the reaction flask by a number of fine glass spirals, which were able to withstand the stresses imposed upon them by the shaking of the reaction vessel. The gas to be measured was led into a glass eudiometer connected at the bottom with a side-arm which was open to the atmosphere. The pressure of the collected gas could be made equal to atmospheric pressure by adjustment of the liquid level in the side-arm.

An apparatus more suited to the present studies was used in following the decomposition of diazoacetic ester in acidic solutions,[114] which has been used for many years for the determination of the solvated hydrogen ion concentration in aqueous solution. The progress of this decomposition has been followed by measurement of the rate of nitrogen evolution from solution.[114,115,116] The diazoacetic ester decomposition was important as a background to the experimental work, not only because its course could be followed by the evolution of nitrogen from aqueous solutions, but also because the rate studies of this reaction were applied to non-aqueous solutions in aprotic solvents by Brønsted and Bell.[118]

For reactions in aqueous solutions, Brønsted and Duus[116] used connections between reaction flask and measuring apparatus similar to those described by Eyring and Daniels (p.49). An expansion joint of flexible glass capillary tubing allowed for some freedom of motion for the reaction flask. Measurement of the nitrogen evolved was not begun at the exact zero time of the reaction. Instead, the reagents were added, the system pumped out for a short time to remove gaseous impurities in the reagents, and shaking of the reaction flask was commenced. The decomposition of the diazo ester was slow enough that very little error was introduced in the measurements. The nitrogen formed by the reaction generated a pressure in the evacuated system, which was measured in a mercury manometer, and through calibration of the volume of the system gave the amount of nitrogen evolved by the reaction.

In their study of the diazoacetic ester decomposition in non-aqueous solutions, Brønsted and Bell[118] used essentially the same apparatus as used above, but with a few modifications. Important features of their work on non-aqueous solutions included sealing of the entry through which the reagents were introduced with an unlubricated ground glass cap, sealed by mercury, and a special mercury-seal for the vacuum side of the manometer. In the use of non-aqueous solutions, more care had to be taken in pumping out the system, both as to forcefulness and time of evacuation, since the solutions had an appreciable vapor pressure and might be concentrated by prolonged pumping.

Similar experimental techniques have been used in the

Van Slyke determination of primary amino groups.[119,120]

The decomposition of diazonium salts is a classical example of a unimolecular or first order reaction.[121,122,123] The treatise by Reilly and Rae lists several modifications of method in the measurement of the decomposition of these compounds.[124] The usual methods embody the same type of apparatus for the measurement of nitrogen. The gas, evolved from a well stirred thermostated solution, was passed into a water-jacketed azotometer and there measured in the usual manner. Reilly and Madden used a stream of pure carbon dioxide to remove the nitrogen,[125] which was collected over potassium hydroxide solutions, in which carbon dioxide dissolves.

Quantitative or semi-quantitative measurement of the nitrogen evolved in the Schmidt reaction itself had been undertaken by some previous investigators at the time this work was begun. The method employed by Briggs and his coworkers has been described (p.20). Since that time, papers have been published by Kuhn and Corwin,[111] and Schuerch and Huntress,[54,55] on the quantitative measurement of the nitrogen evolved from various Schmidt reactions. Kuhn and Corwin collected the nitrogen in a graduated cylinder by the displacement of saturated saline solution. The graduate was inverted over a large evaporating dish containing more saline solution. No mention is made in their paper on the correction of gas volume for atmospheric pressure, temperature, or water vapor pressure.

Schuerch and Huntress published data on the Schmidt

reaction on carboxylic acids, the gaseous products of which consist principally of nitrogen and carbon dioxide. The gases were collected under a slight negative pressure over 5% sulphuric acid saturated with sodium sulphate. Upon completion of the reaction the gas remaining in the reaction vessel was displaced by water and the total gas volume was determined. The carbon dioxide content of a 100 ml. sample was determined by absorption in 30% potassium hydroxide. The gases evolved in the reaction of secondary and tertiary acids were also analysed for carbon monoxide, and the nitrogen, as usual determined, by difference.

The apparatus designed for the present investigation is like those which have been discussed. The azotometer consisted of an ordinary gas measuring tube, fitted with an insulating air jacket, whose temperature could be measured by an inserted thermometer. The bottom of the azotometer was placed in a rubber holder, and the measuring tube itself and its air-jacket bolted to an iron stand for rigidity and to minimise erros of parallax. An air jacket was used rather than a water jacket, as the temperature of the air jacket would conform more closely to that of the connecting tube. A leveling bulb containing the liquid over which the nitrogen gas was collected in the eudiometer was attached to the base of the azotometer. The gas inlet in the bottom of the measuring tube which was designed for determinations of nitrogen by the Dumas method,[126] was sealed off, since it was found that use of this entry, with the necessary mercury seal to prevent leakage of the collecting solution into the reaction system,

gave erratic increases in the measured volumes, unsuitable for rate measurements. Instead, the nitrogen gas was led directly into the top of the measuring tube. Five per cent potassium hydroxide solution was chosen as the collecting liquid; this solution served to collect any traces of acidic gases that might pass into the measuring tube. The leveling bulb was attached to the eudiometer by a piece of rubber tubing, also filled with the potassium hydroxide solution.

The connecting tube between the measuring apparatus and the reaction apparatus was also of rubber tubing. Preliminary tests proved that this tubing was sufficiently impervious to the gases to permit its use. The rubber tubing was stronger and much more flexible than glass spirals would be, and the equipment was assembled in less time.

Design of Reaction Apparatus

The apparatus in which kinetic studies of the Schmidt reaction are run must have the following qualifications: the reagents and catalysts taking part in the reaction must be mixed rapidly and completely in order that the time of the beginning may be known exactly. The heat that may be evolved upon the mixing of these reagents and catalysts must be dissipated quickly, so that the reaction shall take place at a constant temperature. Maintained by a thermostat control, the temperature should be able to be measured accurately. Stirring of the reaction should be sufficient to prevent appreciable supersaturation of nitrogen. The apparatus, including the connections for carrying the evolved gases to

the measuring apparatus, the equipment for adding any necessary reagents, the stirring mechanism, and the temperature indicator, should be leak-free. The reaction apparatus should be designed not only to meet the requirements outline above, but must also be constructed so as to be of convenient size and resistant to the substances it is to contain. General discussions of possible arrangements of equipment are given in the treatises by Reilly and Rae[124] and Drucker.[127]

Aqueous Reaction Mixtures

Since the Schmidt reaction in aqueous mixtures can be initiated by addition of an acid catalyst to a mixture of a solution containing sodium azide and the ketone, producing hydrazoic acid in situ (p. 15) the reaction can be run with moderately large amounts. This permits an increase in the accuracy of determining the total volume of gas evolved, the time of reaction, and the amounts of reagents used.

This method of addition makes stirring imperative, particularly at the initial stages of the reaction. For such solutions, a stirrer of the Hershberg type works very efficiently.[72] Nichrome, Chromel, or copper wire proved adequately resistant to sulphuric and ethanesulphonic acid solutions. These stirrers were also used in hydrochloric acid solutions, even though in these solutions the wire was attacked slightly, since it was found that the traces of metal ions thus introduced had no effect on the rate.

The stirrer may be sealed into the reaction system by means of a graphite seal, formed by a graphite-saturated

asbestos packing enclosed in and compressed by a steel case;≠ a mercury seal, built in the usual manner;[75] or a ground-glass seal.* Although the ground-glass seals were found to withstand positive pressures, preliminary tests showed that these seals would not withstand a partial vacuum; air was sucked into the system, resulting in high readings. Graphite seals proved satisfactory in resisting both external and internal pressures, and some of the early measurements were made using this seal. However, use of the graphite-sealed apparatus resulted in a strain both on the stirring rod passing through the seal, and on the stirring motor, with constant danger of mechanical failure. The graphite seal was therefore abandoned, and in the subsequent experiments a mercury-sealed stirrer was used. The mercury seal not only was satisfactory towards slight positive and negative pressures, but also gave unmistakable warning if the internal pressure ever became great enough to cause leaking through the stirrer assembly.

It was decided that control of the temperature within one-tenth of a degree would be sufficient in determining the order of the Schmidt reaction with respect to the several reactants. While a closer tolerance in temperature control would be desired in precise determination of the rate constants for the reaction, this was not necessary for the simpler studies undertaken here. For the purpose of controlling the temperature, the reaction flask was immersed in a constant

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* Such as sold by the Ace Glass Co. ≠ Such as sold by the Scientific Glass Apparatus Co.

temperature bath capable of control both by the thermostatic control on the electrical heater, and by the flow of the cold water coil in the thermostat, to at least onetenth of a degree. This temperature could be measured both by an external thermometer, capable of measurement to .2° in the thermostat and a thermometer capable of measurement to .1° sealed into the reaction flask itself.

Despite the thermostatic control and good stirring, the contents of the reaction flask tended to heat upon the introduction of certain acid catalysts, such as sulphuric acid. To combat the exothermic effects of such a reaction, the substrate and solution of azide were chilled, before addition of the acid catalyst, by a weighed amount of ice. The exact ratio of ice to aqueous solution could be determined experimentally for each acid catalyst. This ratio was so chosen, that upon mixing of the acid with the other components of the reaction mixture in a well-stirred solution, the temperature immediately rose to within a degree of the desired reaction temperature. For convenience, and to minimise the amount of ice needed, the catalyst could be partially diluted with water and chilled before addition of the reaction mixture.

The instantaneous addition of the acid catalyst, necessary to obtain good readings at the start of the reaction, was made possible by the addition of a diluted solution of the catalyst through a stop cock with a relatively large bore (7 mm.) into a well-stirred solution. The entire amount of

diluted catalyst, a volume of about 25 ml., could thus be rapidly delivered and mixed with the solvent, substrate, and sodium azide solution. Since the reaction of a proton with an anion is almost always instantaneous, the hydrazoic acid could be formed immediately upon the addition of the acid catalyst to the solution with the concurrent disappearance of an equivalent amount of the acid catalyst.

Before addition to the reaction mixture the acid catalyst was stored in a cylindrical dropping-funnel sealed into the reaction system and provided with a pressure-equalising tube. By means of this provision, the air displaced by the entrance of the catalyst into the reaction mixture would not change the total volume of the system, and thus not affect the readings in the azotometer.

Non-Aqueous Solutions

The major considerations in the design of the reaction apparatus for non-aqueous solutions are the same as for aqueous solutions. The main differences in the equipment result from the fact that in non-aqueous solutions, the hydrogen azide must be added as such, and can not, as in the case of the aqueous reaction mixtures, be produced *in situ* by the addition of the acid catalyst. Although the properties of hydrogen azide are modified somewhat by solution in an organic solvent, nevertheless, it is still toxic and potentially explosive, and suitable precautions should therefore be taken. For these reasons, the reaction apparatus was revised; smaller amounts of ketone, acid, diluent, and hydrogen

azide were used, and the reagents were combined in an entirely different way.

The preliminary tests on the Schmidt reaction in non-aqueous solutions were made by placing the ketone, diluent, and hydrazoic acid in a thermostated test-tube equipped with a Standard Taper glass stopper. A measured quantity of diluted acid was introduced into the mixture, the stopper quickly replaced by the Standard-Taper connection to the nitrogen measuring system, the solution shaken to begin the reaction, and the measurements begun. This process offered many obvious disadvantages in the application to quantitative rate measurements. Evaporation of some hydrogen azide was hard to prevent in adding the catalyst. The acid catalyst, even though carefully poured on the side of the reaction tube, would tend to mix with some of the ketone and hydrazoic acid before the shaking and willful mixing took place. This mixing with concentrated acid solutions was found to cause some aldolisation, as well as premature start of the Schmidt reaction. It was difficult to approximate the pressure introduced into the system in the rapid closing of the tube. This test-tube arrangement did use small amounts of the reagents, substrate, and hydrazoic acid, and a constant temperature was easily obtained, since the temperature of the small volume of liquid immersed in the test-tube was easily controlled by the thermostat. Only one thermometer, one graduated by tenths of degrees, was needed. That thermometer was placed in the thermostat near the reaction test-tube. Shaking was most

easily provided for such an apparatus manually. When the reaction neared completion, shaking was necessary only immediately before readings.

A reaction vessel in the form of a Y-tube such as that used by Landolt[130] was found to incorporate the advantages, but none of the disadvantages, of the test-tube set-up. Such a tube allows introduction of all the reagents into the reaction system without actual mixing. When it was desired to start the reaction, vigorous shaking of the reaction flask mixed all the reagents into a homogenous solution almost instantaneously. The temperature control in such an apparatus is as good, if not better, than a straight tube. The usual procedure consisted of, first, the introduction of the ketone into one side of the Y; then the acid catalyst and the diluent, if any, were put in the other side of the Y, and finally the hydrogen azide solution was introduced into the first (ketone) side of the Y-tube. After the mixtures had come to thermostat temperature, the reaction could be started by mixing the two solutions by rapid shaking.

Solubility and Work on the Schmidt Reaction

Since most ketones whose molecular weights are over eighty (five or more carbon atoms) are not very soluble in water, the solubilities of the larger ketones had to be determined in the different mixtures to be used for the Schmidt reaction. Studies on heterogeneous two-phase systems are difficult to interpret kinetically, and it was therefore desired to avoid them. Likewise, the approximate solubilities

of substances whose catalytic activities were to be tested first had to be determined in the mixture in which those substances were to be used.

The two ketones, cyclohexanone and diisopropylketone, chosen for initial kinetic studies on the Schmidt reaction are not very soluble in water, but in acid solution they are more soluble, probably due to the formation of a hydroxy-carbonium ion to some extent in the solution. With this in mind, the solubilities of the ketones were studied in solutions in different acid concentrations. Cyclohexanone, because of its greater solubility and basic strength was tested in aqueous solutions of hydrochloric acid, sulphuric acid, and ethanesulphonic acid. Isopropyl ketone, of lesser solubility in water, was studied in sulphuric acid solutions only.

The solubilities of ketones in various solutions seemed most conveniently determined by titration of a known volume of solution of given acid concentration by the pure ketone until two phases were formed, as indicated by the formation of turbidity in the solution. Addition of a slight excess of the ketone, and measurement of the volumes of the two phases might give an indication of how close the system was to miscibility.

Ethanesulphonic acid is completely miscible with water, and no solubility studies were necessary for aqueous solutions.

Non-Aqueous Solutions

Cyclohexanone, diisopropylketone, and acetophenone are

soluble in solutions of common organic solvents such as benzene, chloroform, carbon tetrachloride, nitrobenzene, ethylene chloride, ethylidene chloride and methylene chloride. The problem of solubility in organic solvents thus was narrowed to the study of ethanesulphonic acid. Although there are some references in the literature concerning the solubility of ethanesulphonic acid, it was decided to determine its approximate solubility in the solvents in which it might be used as a catalyst for the Schmidt reaction. For those solvents in which ethanesulphonic acid was found to be completely insoluble, solubility tests were run for mixtures on the non-solvent with a known good solvent.

The solubilities of ethanesulphonic acid were determined by the same procedure as used with the ketones, a rough titration of a standard amount of the solvent with pure ethanesulphonic acid until the presence of two phases was indicated by the appearance of an opalescence. When the solution remained homogenous in the presence of a large excess of ethanesulphonic acid (over five times the volume of organic solvent), it was assumed that ethanesulphonic acid was probably infinitely miscible.

Amides

Amides like ϵ-caprolactam and N-isopropylisobutyramide are generally known to be soluble in polar organic solvents and water; however, since their solubilities in ketones were not known, these were approximately determined. This could be done roughly by finding the minimum volume of solvent

necessary to dissolve the amide. The solubility determined in this manner is obviously inaccurate, and is generally low. Nevertheless, such rough measurements give some idea of whether these compounds could be introduced into the reaction mixtures without the concomitant introduction of a solid phase. It was decided that if .01 mole or more, was soluble in 3 ml. of the solvent, the amide was soluble enough to be introduced into the reaction mixture.

Samples of ε-caprolactam, prepared either by the Beckmann rearrangement of cyclohexanone oxime or the Schmidt reaction were kindly furnished by Dr. B. Weissmann and Dr. P. A. S. Smith. These samples were recrystallised once before use.

Preparation of a Chloroform Solution of Hydrazoic Acid

In a 1 liter glass-stoppered Erlenmeyer flask was placed 370 ml. of chloroform and a solution of 65 g. (1 mole) of sodium azide in 65 g. of water. To this mixture, immersed in a salt-ice mixture, a chilled solution of 98 g. (1 mole) of sulphuric acid diluted with an equal weight of water was added in portions slowly with violent shaking between additions.

The chloroform layer was separated from the aqueous layer, which was again chilled and extracted by two 50 ml. portions of chloroform. The combined hydrogen azide solutions were dried over anhydrous sodium sulphate, and stored in a refrigerator. About 25 ml. of ether was added in order to decrease the possibility of explosion of the hydrogen azide by fractionation onto the walls of the flask.

The hydrogen azide was assayed by titration with sodium hydroxide. A 2.28 ml. portion was found to contain 3.36 m-moles (30.35 cc. of .1107 N NaOH).

Preparation of an Aqueous Solution of Sodium Azide

2.035 Grams (.03162 moles) of sodium azide (Paragon) was dissolved in about 35 ml. of water and made up to volume in a 100 ml. glass-stoppered volumetric flask. The resulting solution was .3162 M with respect to sodium azide.

Ten ml. aliquot portions of this solution were withdrawn to furnish 3.162 m-moles of sodium azide for the aqueous reaction mixtures.

Apparatus Design and Use

The apparatus for use in aqueous and non-aqueous solution were designed as described in the previous discussion. It is illustrated in Plate I.

Stirring was continuous in the aqueous solutions. In the non-aqueous solutions shaking was constant while gas evolution was faster than 0.01 ml./sec.; with low rates of gas evolution, the solution was shaken only just before readings.

Testing for Leaks

Before all runs, whether actual Schmidt reactions or just blanks, the complete system was tested for leaks by raising the leveling bulb and observing whether the position of the level of the liquid in the eudiometer rose or fell. When no such departure from a constant level was observed, it was concluded that there was no leak in the system and the run started.

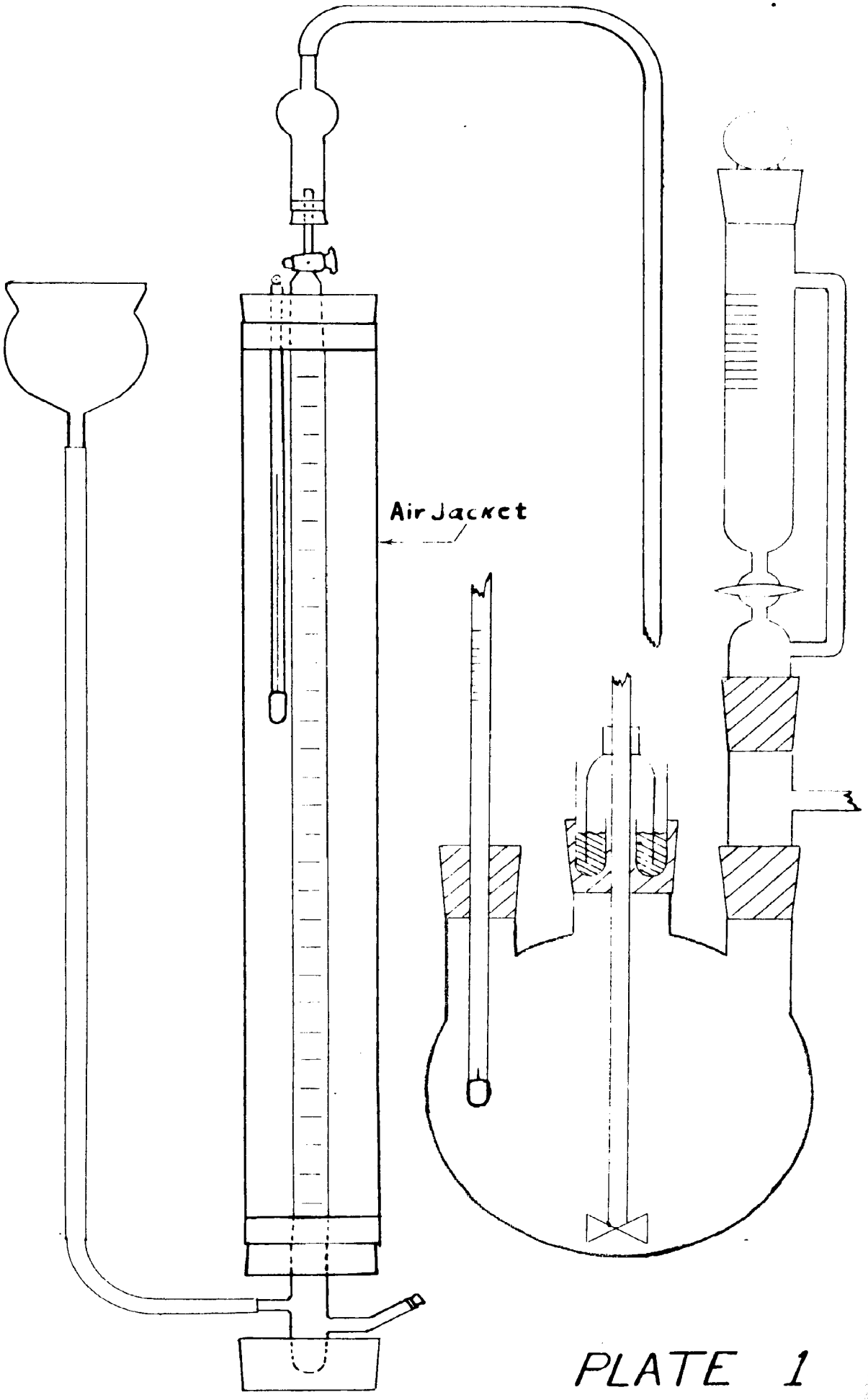


PLATE 1

A Sample Blank Run: Sodium Azide and Hydrochloric Acid

Ten ml. of an aqueous solution of 3.16 M sodium azide (containing 31.6 m-moles of the azide) was placed in the reaction flask used for aqueous solutions. Ten ml. of concentrated (12 M) hydrochloric acid was placed in the dropping funnel of the apparatus, and the system closed. After the system was tested for leaks by the leveling bulb, while the stirrer was going, all of the acid was added at once and the nitrogen evolution, and times, immediately observed. A very small amount of nitrogen (0.5 ml.) was formed in 24 hours.

A Sample Blank Run: A Mixture of Hydrazoic Acid and Cyclohexanone

2.28 Ml. (3.36 m-moles) of a solution of hydrogen azide in chloroform was added to 2.1 ml. (20.38 m-moles) of cyclohexanone placed in one lobe of the Y-tube used for non-aqueous reactions. Two ml. of chloroform was placed in the other side, and the system was sealed. The liquids in the two arms were mixed by rapidly shaking and rotating the tube, and the measuring tube was watched for possible nitrogen evolution. No measurable nitrogen was formed in 24 hours.

A Sample Blank Run: Ethanesulphonic Acid and Hydrazoic Acid

To 2 ml. (6.6 m-moles) of 3.30 M ethanesulphonic acid solution in chloroform in one lobe of the Y-tube used for non-aqueous reaction was added 2 ml. of chloroform diluent. 2.28 Milliliters (3.66 m-moles) of hydrogen azide dissolved in chloroform was placed in the other lobe of the Y-tube, and the reaction sealed into the system in the usual manner. After

testing for leaks the solutions were mixed by shaking the tube rapidly, and the nitrogen evolution was observed. No bubbles of nitrogen could be observed at room temperature. On standing for two days, less than 1 ml. of gas was collected.

Comparison Run of Cyclohexanone in Hydrochloric Acid

Ten ml. of a 3.16 M solution of sodium azide in water was mixed with 2.1 ml. of cyclohexanone (20 m-moles) in the apparatus for aqueous reaction. In this set of measurements, as in all others, an excess of cyclohexanone was used to prevent tetrazole formation. All of 10 ml. of a 3 M solution of hydrochloric acid was added at once to the stirred mixture of ketone, azide and water; the nitrogen, whose evolution began immediately, was led into the top of an azometer, and there measured, at measured time intervals, as the reaction took place.

Other Runs

Each run of the Schmidt reaction on cyclohexanone in hydrochloric acid was run in the same manner as the comparison run. For every new run, the initial concentration of one of the reactants or of the catalyst was changed.

A Sample Run: Cyclohexanone in Sulphuric Acid

Sodium azide (1.15 grams, .177 mole) was added to a mixture of 1 ml. (.0096 mole) of cyclohexanone and 15 g. of ice-water, in the apparatus for aqueous reactions, and the mixture stirred for about 15 seconds. A chilled solution of 47% sulphuric acid, prepared from 9 g. of concentrated sulphuric acid

and 10 g. of ice was added all at once from the container sealed into the system. The resulting solution of hydrogen azide, 27% sulphuric acid, and cyclohexanone, started immediate evolution of nitrogen.

An Alternative Method:

To 10 ml. of a solution containing 204.7 g. of sodium azide per liter (3.16 M) was added 1 ml. (.0096 mole) of cyclohexanone and 5 g. of crushed ice; cooled sulphuric acid was added as above, and the nitrogen collected as usual.

Preparation of Ethanesulphonic Acid Solution

Example: Ethanesulphonic Acid in Chloroform

26.67 Grams (20 ml.) of ethanesulphonic acid (furnished by the Standard Oil Company of Indiana) was dissolved in 53.3 ml. (80 g.) of chloroform and kept in a 125 ml. glass-stoppered Erlenmeyer flask. The resulting solution contained .242 moles of acid, and was 3.303 M, or 25% w/w or 27% v/v.

A Sample Run: A Ketone with Ethanesulphonic Acid in Chloroform

To 1.06 ml. (9.07 m-moles) of acetophenone was added 2.28 ml. (3.66 m-mole) of hydrogen azide (1.605 M) in chloroform. Two ml. of 25% w/w ethanesulphonic acid in chloroform was added in a closed system, the stop-watch started, barometer reading and air temperature noted, and readings of the nitrogen evolution immediately begun. The reaction apparatus was shaken by hand about 240 times (120 cycles) a minute while the reaction proceeded rapidly. Toward the end of the reaction, the vessel was shaken to prevent supersaturation before

each reading. On longer runs, the atmospheric pressure was measured every few hours, and the temperature of the air sheath around the eudiometer taken every 15 minutes.

A Heterogeneous Run: Isopropyl Ketone in Sulphuric Acid

Ten ml. of diisopropyl ketone, an amount in excess of the solubility in 40 ml. of 37.5% sulphuric acid, was mixed with 1.15 g. of sodium azide dissolved in 10 ml. of water. The sulphuric acid, a mixture of 15 g. of concentrated acid with 5 g. of water, was placed in an addition-tube sealed into the system. The acid was added immediately after adding 10 g. of ice to the reaction flask, the heat of dilution of the sulphuric acid thus being balanced by the melting of the ice. The mixture now contained a total of 25 ml. of water. The readings of nitrogen evolution were taken immediately upon the mixing of sulphuric acid and water.

Diisopropyl Ketone

352 Grams (4 moles) of isobutyric acid were added to 160 g. (2 moles) of U.S.P. magnesia in a 1 liter distilling flask. Two hundred milliliters of absolute alcohol and 100 ml. benzene were added. The salt formation proceeded quite exothermally with boiling of the ternary mixture. After the boiling ceased, the ternary mixture was distilled off. After all the liquid possible was removed, more benzene and alcohol (50 ml. and 25 ml.) were added, and the liquid again distilled off. No ketone could be detected in the distillate until the temperature was raised to 350°, although a small amount of

acid came over below this. The ketone itself was formed on heating the mixture to around 400°. Redistillation of the crude ketone gave about 150 ml. of diisopropyl ketone, boiling point at 122-126°, (95% at 124°) with a 5 ml. forerun with boiling point 80-115°, consisting mainly of methyl isopropyl ketone, methyl ethyl ketone, and ethyl isopropyl ketone.

After the ketone fraction distilled over, an unidentified solid of melting point greater than 240° distilled.

N-Isopropylisobutyramide

This compound was first prepared by Meyer and Warrington from isobutyl chloride and isopropylamine, and from the Beckmann rearrangement of diisopropylketoxime induced by acetyl chloride.[131] Meyer and Warrington report a melting point of 102° and the boiling point of 210°. A description of N-isopropylisobutyramide preparation by the Schmidt reaction is presented below.

Diisopropylketone (Eastman Kodak, Technical Grade)(19.4 grams)(1/6 mole) was mixed with 10 ml. of concentrated hydrochloric acid, and 28 g. (5/12 mole) of sodium azide was added. The reaction mixture was allowed to stand at room temperature. It proceeded at a moderate rate, controlled by the small solubility of the ketone in hydrochloric acid. After about 15 hours, the sodium chloride resulting in the reaction was filtered off, washed with 5 ml. of water, and part of the hydrochloric acid was blown off with an air jet. The remaining mixture was placed in a salt-ice bath and solid potassium carbonate was added to neutralise the acid. A solid consisting

of potassium chloride and the N-isopropylisobutyramide precipitated on the addition of the potash. The solid was washed once with water to remove the potassium chloride, and then several times with hot petroleum ether (90°-100°). On cooling in the refrigerator, the petroleum ether solutions rapidly deposited very fine, light-colored needles of the amide. These were filtered off and washed with fresh petroleum ether. A second crop was obtained by evaporation of the petroleum ether liquors to half their volume. A third crop may be also obtained. The product lost its color on standing in air. The yields on the various crops were 1st 5.7 grams, 2nd 5.0 grams, 3rd 1.3 grams, total 12 grams (55%). The melting point was 108-110°.

Determination of a Typical Solubility: Ketones in Acid

A series of 10 ml. samples of solutions containing ethanesulphonic acid in chloroform were prepared in increasing steps of 10% ethanesulphonic acid by weight. Ten ml. of isopropyl ketone was added to each of these solutions in turn, and the mixtures were examined for turbidity. All solutions were found to dissolve the ketone completely.

Solubility Tests: Ethanesulphonic Acid in Solvents

Examples:

1. Nitrobenzene

Ethanesulphonic acid was slowly dropped from a graduated pipette into 10 ml. of nitrobenzene, which was stirred during addition, and the mixture watched for the opalescence which

would indicate the presence of two phases. Over 5 ml. of pure ethanesulphonic acid dissolved completely in the nitrobenzene.

2.a) Benzene

Ethanesulphonic acid (.4 ml.) was slowly dropped from a graduated pipette into 10 ml. of benzene. Not even this amount of acid would completely dissolve in the benzene solution. Chloroform was slowly added from a graduated pipette to the heterogeneous benzene-ethanesulphonic acid mixture produced above. Addition of 10 ml. of chloroform did not reunite the two layers on shaking.

2.b) Benzene-nitrobenzene

Benzene was slowly dropped into a solution of 5 ml. of ethanesulphonic acid in 10 ml. of nitrobenzene. Over 20 ml. of benzene had to be added before two phases formed.

Preparation of Cyclohexylmethylamine Hydrochloride by the Schmidt Reaction

Methanesulphonic acid (100 ml.)(145 g.)(1.51 moles) was added to 1/10 mole (14.2 g.) of cyclohexaneacetic acid (Dow Chemical Co.) in a 250 ml. beaker. A transient red-orange color appeared, probably due to the formation of the hydroxycarbonium ion. The color faded as all of the solid cyclohexaneacetic acid dissolved. The beaker was immersed in a water bath kept at 40°, and 9.5 g. (about 1/7 mole) of solid sodium azide was added. The sodium azide dissolved slowly in the methanesulphonic acid; on stirring the rate of solution,

and of reaction, increased with consequent frothing. The reaction was allowed to stand for about six hours, and then cooled.

The acid solution was neutralised by a slight excess of sodium carbonate, and cyclohexylmethylamine steamed-distilled into a solution of concentrated hydrochloric acid. The water was blown off, and the yellow salt dissolved in hot alcohol and precipitated by the addition of ether. Evaporation of the alcoholic ether gave a dark green precipitate as a by-product. 5.91 Grams of the white hydrochloride was formed (39.5% yield). The unreacted cyclohexaneacetic acid was recovered from the alkaline mixture by reacidification with dilute hydrochloric acid, and extraction with several portions of chloroform (wt. 3.74 g., 34.2%).

Preparation of Cyclohexylmethylamine Hydrochloride by Lithium Aluminum Hydride Reduction

Into a dry 500 ml. 3-necked flask equipped with a stirrer, condenser with a calcium chloride tube, and an addition funnel, was placed 3.46 g. (10/109 mole) of lithium aluminum hydride and 100 ml. of anhydrous ether. The mixture was refluxed with stirring for two hours, and then 4 g. (4/109 mole) of cyclohexanecarbonitrile* dissolved in 50 ml. of anhydrous ether was slowly dropped into the stirred solution of the lithium aluminum hydride. After the addition, the solution was allowed to come to reflux, the stirring was continued for one-half hour longer, and then the excess lithium aluminum hydride was destroyed by the addition of 5 ml. of ethyl acetate over a

* The cyclohexanecarbonitrile was prepared by Dr. John Krapcho from cyclohexanecarboxylic acid.

period of 15 minutes. The mixture was made alkaline with 5% sodium hydroxide, the stirrer and condenser removed and replaced by plugs, and the ether removed through a Friedrichs take-off condenser.

The amine was then steam-distilled out of the reaction flask into 100 ml. of concentrated hydrochloric acid. The acid was evaporated to dryness, leaving 5.615 g. of the cyclohexylmethylamine hydrochloride (yield = 94.5%).

The results of the investigations on the Schmidt reaction are summarised in the following tables. The solvents used were the middle fractions of re-distilled Reagent Grade chemicals. The chloroform contained traces of ethanol in order to prevent phosgene formation. This small amount did not appear to affect the results significantly. The sulphuric acid and hydrochloric acid used were Reagent Grade materials diluted by weight. The ethanesulphonic acid solutions were made from weighed amounts of fresh commercial "Indoil" ethanesulphonic acid. It was found that ethanesulphonic acid decomposed on distillation. Ethanesulphonic acid which has been distilled at .05 mm. pressure has essentially the same acidity as the fresh commercial acid. It was decided that the errors inherent in the use of the commercial material were overshadowed by the assumptions made in calculating the non-aqueous rate results. The cyclohexanone and acetophenone, obtained from Eastman Kodak (white label) were redistilled twice, and the middle fractions taken. The diisopropylketone was distilled twice before use.

The entries in the tables are of necessity incomplete. They have been selected in such a manner as to be representative of each run, usually by taking every second or every third reading. The volume of the aqueous and non-aqueous solutions has been assumed constant, since no knowledge of the relative partial molal volumes of the ketones, amides, and hydrogen azide exists.

TABLE I

Determination of the Order of the Schmidt Reaction on Cyclohexanone in Hydrochloric Acid Solutions

Time (min.)	m.-moles N_2 evolved	M ketone	M HN_3	$k_3 \times 10^5$ (sec.$^{-1}$ moles^{-2} liter^2)
Run A		HCl = 3 M	$h_0 = 7.6$(M)	
0	0	.500	.158	-
4.50	.59	.470	.129	10.1
21.00	1.41	.430	.088	8.7
39.05	1.92	.404	.062	9.8
51.88	2.26	.387	.040	7.3
61.88	2.42	.374	.037	8.1
88.08	2.64	.368	.026	8.3
100.40	2.72	.364	.022	-
			Average	8.6
Run B		HCl = 3 M	$h_0 = 9.7$	
0	0	.250	.0792	-
7.28	.142	.243	.0730	-
27.53	.613	.220	.0485	6.0
27.75	.798	.210	.0392	6.2
47.67	.946	.202	.0319	6.4
71.22	1.186	.190	.0194	6.6
98.33	1.300	.185	.0142	6.0
121.00	1.345	.183	.0119	5.4
			Average	6.1
Run C	HCl = 3 M	$h_0 = 9.7$	ϵ-caprolactam = .50 M	
0	0	1.000	.158	-
5.63	.594	.970	.128	-
18.22	1.192	.940	.098	6.0
22.07	1.355	.932	.090	5.0
32.08	1.855	.907	.065	6.1
38.82	2.04	.898	.056	5.9
42.50	2.09	.896	.054	5.6
			Average	5.7

TABLE I (Cont'd)

Time (min.)	m.-moles N_2 evolved	M ketone	M HN_3	$k_3 \times 10^5$ (sec.$^{-1}$ moles^{-2} liter^2)
Run D		HCl = 1.5 M	h_o = 2.21 (M)	
0	0	.500	.158	-
7.58	.46	.477	.135	-
19.93	.59	.476	.128	5.4
46.63	.85	.458	.116	5.6
83.78	1.22	.439	.097	7.0
111.8	1.41	.430	.088	6.8
197.8	1.84	.408	.066	6.5
374.5	2.43	.378	.036	8.5
1034.	2.96	.352	.010	4.9
			Average	6.4
Run E		HCl = 1.5 M	h_o = 2.21	22° C.
0	0	.250	.158	-
120	.42	.229	.137	-
974	1.16	.192	.100	2.3
1407	1.40	.180	.088	1.9
2224	1.86	.157	.065	1.8
2894	2.20	.140	.048	1.9
3664	2.76	.112	.020	2.9
5466	2.98	.101	.009	3.1
			Average	2.3
Run F		HCl = 6.0 M	h_o - 50	
0	0	.500	.158	

This reaction went too rapidly for accurate readings to be made; the k_3 is of the order of magnitude of - 20×10^{-5} moles^{-2} sec.$^{-1}$ liter^2

All runs were made in the volume of 20 ml.
The temperature, unless otherwise indicated, is 25°.

TABLE II

Determination of the Order of the Schmidt Reaction on Cyclohexanone in Sulphuric Acid Solutions

Time (min.)	m.-moles N_2 evolved	M ketone	M HN_3	$k_3 \times 10^5$ ($sec.^{-1}$ $moles^{-2}$ $liter^2$)
Run A		27% H_2SO_4	h_o = 7.2 M	
0	0	.161	.610	-
.25	.341	.150	.598	-
3.85	1.047	.126	.575	7.2
5.60	1.308	.118	.566	7.2
7.52	1.570	.109	.557	7.3
10.35	1.962	.096	.544	7.6
17.00	2.434	.079	.527	7.0
			Average	7.3
Run B		27% H_2SO_4	h_o = 7.2 M	
0	0	.323	.539	-
3.08	1.304	.279	.496	-
7.57	2.220	.249	.465	5.6
12.95	3.136	.218	.435	5.6
19.00	4.05	.188	.404	5.8
27.92	4.97	.157	.374	5.6
40.02	5.88	.128	.343	5.5
52.60	6.40	.109	.326	5.0
76.42	6.93	.092	.308	4.1
			Average	5.4
Run C		27% H_2SO_4	h_o = 3.83	
0	0	.320	1.219	-
2.15	1.848	.262	1.157	-
6.55	2.878	.226	1.122	5.8
11.17	3.644	.201	1.097	5.7
15.23	4.61	.169	1.065	5.8
22.32	5.57	.137	1.016	5.7
31.45	6.53	.105	1.001	5.1
37.55	7.12	.085	.981	5.9
			Average	5.7

TABLE II (Cont'd)

Time (min.)	m.-moles N_2 evolved	M ketone	M HN_3	$k_3 \times 10^5$ ($sec.^{-1}$ $moles^2$ $liter^{-2}$)
Run D		27% H_2SO_4	h_o = 7.2 M	
0	0	.328	.596	-
1.55	1.78	.269	.587	-
3.57	2.77	.236	.504	12.7
7.00	3.76	.203	.471	10.6
10.28	4.76	.170	.438	10.2
14.75	5.75	.137	.405	10.8
20.53	6.74	.104	.372	11.3
27.63	7.54	.077	.345	11.8
			Average	11.0
Run E		27% H_2SO_4	h_o = 10.72	
0	0	.333	.316	-
1.68	.573	.314	.297	-
2.82	.956	.301	.284	8.9
4.73	1.531	.282	.265	8.4
9.90	2.636	.246	.228	7.5
15.92	3.63	.213	.195	7.8
27.65	4.97	.168	.150	7.6
51.62	6.12	.130	.112	6.8
139.78	7.25	.092	.074	6.2
			Average	7.6

TABLE IIa

Comparison of Rate Constants Based on h_o, Molarity, Activity

Run	h_o; $k_3 \times 10^5$	M; $k_3 \times 10^5$	a; $k_3 \times 10^5$
I - A	7.6 (M); 8.6	2.84 M; 23	3.65 (M); 18
I - B	9.7 6.1	2.94 20	3.81 12
I - C	9.7 5.7	2.84 19	3.65 15
I - D	2.21 6.4	1.34 21	1.23 12
I - F	ca. 50 20	5.84 171	ca. 15 65
II - A	7.2 7.3	2.68 20	.367 142
II - B	7.2 5.4	2.75 14	.379 103
II - C	3.83 5.7	2.07 11	.260 84
II - D	7.2 11	2.69 30	.360 220
II - E	10.72 7.6	2.97 28	.418 195

All runs were made in the volume of 30 ml.
The temperature, unless otherwise indicated, is 25° C.

TABLE III

Determination of the Order of the Schmidt Reaction on Cyclohexanone in Chloroform, with Ethanesulphonic Acid Catalyst

Time (min.)	app. m.-moles N_2 evolved	app. $\underline{M}$ ketone	app. $\underline{M}$ HN_3	$k_3 \times 10^{-5}$ (sec.$^{-1}$ moles^{-2} liter^2)
Run A	$C_2H_5SO_3H$ = 1.01 $\underline{M}$		v = 6.38 ml.	
0	0	3.16	.552	-
5.00	3.19	2.64	.497	41.0
7.00	3.24	2.63	.428	41.4
10.30	3.32	2.61	.301	38.5
24.25	3.43	2.60	.124	36.6
37.50	3.47	2.59	.065	37.2
45.50	3.49	2.59	.041	-
265.50	3.51	2.59	.0	-
			Average	39
Run B	$C_2H_5SO_3H$ = .50 $\underline{M}$		v = 6.38 ml.	
0	0	3.14	.552	-
6.38	2.49	2.74	.160	39.0
8.62	2.61	2.73	.140	36.2
13.27	2.75	2.71	.118	35.2
22.0	2.92	2.68	.092	35.0
46.90	3.19	2.64	.049	37.5
63.75	3.31	2.62	.030	-
103.47	3.58	2.58	0	-
			Average	36.6
Run C	$C_2H_5SO_3H$ = 3.30 $\underline{M}$		v = 6.38 ml.	
0	0	3.30	.542	-

This reaction went too rapidly to determine the rate constant accurately, but the k_3 is of the order of 40 x 10^{-5} sec.$^{-1}$ moles^{-2} liters^2.

TABLE III (Cont'd)

Time (min.)	app. m.moles N_2 evolved	app. $\underline{M}$ ketone	app. $\underline{M}$ HN_3	$k_3 \times 10^{-5}$ ($sec.^{-1}$ $moles^{-2}$ $liter^2$)
Run D	$C_2H_5SO_3H$ = .518 $\underline{M}$	Isopropylisobutyramide .172 $\underline{M}$		
0	0	3.14	.552	-
12.62	1.86	2.86	.260	4.55
21.82	2.02	2.83	.235	4.50
32.28	2.16	2.79	.212	4.34
51.03	2.31	2.76	.160	4.47
65.83	2.42	2.74	.134	4.35
98.05	2.49	2.70	.104	4.40
137.6	2.66	2.69	.097	4.93
204.7	2.84	2.62	.028	4.88
249	2.89	2.61	.013	4.94
796	3.33	2.60	.008	6.01
1442	3.50	2.59	.002	-
2252	3.51	2.59	0	-
			Average	4.74
Run E	$C_2H_5SO_3H$ = .525 $\underline{M}$	lactam = .209 $\underline{M}$	v = 6.38 ml.	
0	0	3.24	.559	-
11.38	1.34	2.99	.340	4.20
28.25	1.45	2.97	.323	4.23
43.0	1.54	2.96	.308	4.20
60.0	1.65	2.94	.291	4.26
105.7	1.80	2.92	.267	4.26
347.8	2.39	2.83	.175	4.70
1399	3.48	2.66	.004	-
1987	3.51	2.65	0	-
			Average	4.23

TABLE III (Cont'd)

Time (min.)	app. m.-moles N_2 evolved	app. $\underline{M}$ ketone	app. $\underline{M}$ HN_3	$k_3 \times 10^{-5}$ ($sec.^{-1}$ $moles^{-2}$ $liter^2$)
Run F	$C_2H_5SO_3H$ = .966 $\underline{M}$	lactam = .205 $\underline{M}$		v = 6.28 ml.
0	0	1.63	.558	-
4.53	2.86	1.18	.122	6.10
8.83	2.93	1.16	.092	5.61
23.13	3.16	1.12	.056	4.64
52.58	3.34	1.09	.028	3.42
807.0	3.48	1.07	.006	-
965.0	3.51	1.06	0	-
			Average	4.94

The temperature, unless otherwise indicated, is 25°.

TABLE IV

Determination of the Order of the Schmidt Reaction on Cyclohexanone in Mixed Organic Solvents; Ethanesulphonic Acid Catalyst

Time (min.)	app. m.-moles N_2 evolved	app. $\underline{M}$ ketone	app. $\underline{M}$ HN_3	$k_3 \times 10^5$ ($sec.^{-1}$ $moles^{-2}$ $liters^2$)
A: Runs in Methylene Chloride (μ=1.57) and Chloroform (μ=1.15)				
1-3: CH_2Cl_2 : $CHCl_3$ = 1 : 3.03 $C_2H_5SO_3H$ = .525 $\underline{M}$ v = 6.28 ml.				
0	0	3.19	.559	-
9.13	2.38	2.92	.187	31.8
13.83	2.48	2.91	.171	31.3
23.83	2.60	2.89	.151	30.6
34.32	2.70	2.88	.135	29.8
49.60	2.78	2.87	.121	29.4
69.13	2.85	2.86	.110	28.9
92.50	2.94	2.84	.095	28.0
175.08	3.01	2.84	.085	28.8
1655.08	3.49	2.81	.003	-
2020.08	3.51	2.80	0	-
			Average	30.0
2-0: CH_2Cl_2 : $CHCl_3$ = .75 : 3.28 $C_2H_5SO_3H$ = .517 $\underline{M}$ v = 6.38 ml.				
0	0	3.14	.549	-
10.67	2.10	2.91	.229	24.8
56.28	2.51	2.88	.164	23.7
97.25	2.66	2.87	.139	23.2
117.2	2.72	2.83	.129	23.1
287.3	3.02	2.81	.124	22.3
543.2	3.20	2.78	.051	22.1
1266	3.39	2.76	.020	24.4
1532	3.43	2.75	.013	24.4
1631	3.45	2.75	.010	24.4
2736	3.50	2.74	.001	-
2849	3.51	2.74	0	-
			Average	24.6

TABLE IV (Cont'd)

Time (min.)	app. m.-moles N_2 evolved	app. $\underline{M}$ ketone	app. $\underline{M}$ HN_3	$k_3 \times 10^5$ ($sec.^{-1}$ $moles^{-2}$ $liters^2$)

A: Runs in Methylene Chloride (μ=1.57) and Chloroform (μ=1.15)

2-3: CH_2Cl_2 : $CHCl_3$ = 1.75 : 2.28 $C_2H_5SO_3H$ = .517 $\underline{M}$ v = 6.38 ml.

0	0	3.13	.550	-
15.52	2.40	2.76	.175	39.3
25.03	2.49	2.73	.160	37.6
35.27	2.57	2.74	.148	37.2
64.00	2.72	2.71	.123	36.4
72.00	2.73	2.70	.122	36.4
86.10	2.77	2.70	.116	36.2
125.08	2.88	2.68	.098	35.7
170.50	2.98	2.67	.083	35.8
807	3.40	2.60	.017	36.9
931	3.44	2.59	.011	35.6
1130	3.45	2.59	.009	25.7
1462	3.49	2.59	.003	-
2135	3.51	2.58	0	-
			Average	**35.6**

B: Runs in Ethylene Chloride (μ=1.8) and Chloroform (μ=1.15)

3-0: CH_2ClCH_2Cl : $CHCl_3$ = .75 : 3.28 $C_2H_5SO_3H$ = .517 $\underline{M}$ v = 6.38 ml

0	0	3.13	.549	-
6.42	2.22	2.78	.201	**43.2**
10.78	2.37	2.76	.180	42.4
20.82	2.52	2.74	.155	41.5
43.07	2.68	2.72	.131	40.7
66.17	2.78	2.70	.115	40.0
104.50	2.86	2.68	.101	40.1
128.8	2.92	2.68	.092	40.0
163.5	2.98	2.67	.084	40.0
233.5	3.12	2.64	.062	39.2
319.4	3.19	2.64	.050	39.5
392.4	3.25	2.62	.041	39.7
1499	3.52	2.60	.002	-
1725	3.51	2.58	0	-
			Average	40.6

TABLE IV (Cont'd)

Time (min.)	app. m.-moles N_2 evolved	app. $\underline{M}$ ketone	app. $\underline{M}$ HN_3	$k_3 \times 10^5$ (sec.$^{-1}$ moles^{-2} liters^2)

C: Runs in Chloroform (μ=1.15) and Ethylidene Chloride (μ=2.05)

1-5: CH_3CHCl_2 : $CHCl_3$ = .1 : 3.03 $C_2H_5SO_3H$ = .517 $\underline{M}$ v = 6.38 ml.

0	0	3.20	.549	-
8.57	2.36	2.82	.180	50.0
14.37	2.49	2.81	.160	48.9
43.0	2.76	2.77	.118	49.9
76.1	2.83	2.75	.106	46.7
96.1	2.91	2.74	.094	46.8
122.5	2.99	2.73	.082	46.2
226.1	3.16	2.70	.054	45.4
309.0	3.26	2.69	.038	44.7
1277	3.50	2.65	.002	-
1372	3.51	2.65	0	-
			Average	47.3

D: Runs in Nitrobenzene (u=4.24) and Chloroform (u=1.15)

1-6: $C_6H_5NO_2$: $CHCl_3$ = .75 : 3.28 $C_2H_5SO_3H$ = .517 $\underline{M}$ v = 6.38 ml.

0	0	3.13	.549	-
42.23	2.71	2.78	.126	46.6
68.0	2.84	2.75	.104	46.4
79.2	2.88	2.74	.099	46.4
106.5	2.97	2.73	.085	45.5
139.2	2.99	2.73	.081	46.5
151.1	3.08	2.71	.062	44.5
193.2	3.16	2.70	.054	43.3
1080	3.49	2.65	.003	-
1148	3.51	2.65	0	
			Average	45.6

5-0: $C_6H_5NO_2$: $CHCl_3$ = 1 : 3.03 $C_2H_5SO_3H$ = .517 $\underline{M}$ v = 6.38 ml.

0	0	3.13	.549	-
144.8	3.05	2.65	.072	37.8
322.8	3.28	2.63	.035	37.2
357.1	3.31	2.62	.032	34.4
491.2	3.37	2.71	.023	34.8
521.1	3.39	2.60	.019	32.9
1351	3.49	2.58	.003	-
1419	3.51	2.58	0	-
			Average	35.4

TABLE IV (Cont'd)

Time (min.)	app. m.-moles N_2 evolved	app. M ketone	app. M HN_3	$k_3 \times 10^5$ ($sec.^{-1}$ $moles^{-2}$ $liters^2$)

E: Runs in $CHCl_3$ (μ=1.15), CH_2Cl_2 (μ=1.57) and CH_2ClCH_2Cl (μ=1.8)

2-4: $CHCl_3$: CH_2Cl_2 : CH_2ClCH_2Cl = 2.28 : 1 : .75
$C_2H_5SO_3H$ = .517 M v = 6.38

0	0	3.13	.550	-
3.42	1.98	2.82	.237	25.6
6.90	2.18	2.79	.206	24.4
15.75	2.38	2.76	.174	23.6
201.6	2.97	2.72	.082	21.6
1345	3.36	2.61	.021	25.1
1514	3.41	2.59	.012	23.9
1769	3.44	2.59	.008	25.2
1849	3.44	2.59	.008	25.6
2798	3.50	2.58	.001	-
2860	3.49	2.58	0	-
			Average	24.4

3-3: $CHCl_3$: CH_2Cl_2 : CH_2ClCH_2Cl = 2.28 : .75 : 1
$C_2H_5SO_3H$ = .517 M v = 6.38 ml.

0	0	3.14	.551	-
18.77	2.52	2.74	.155	34.4
30.85	2.63	2.72	.138	33.5
68.55	2.76	2.71	.117	32.9
88.03	2.79	2.70	.113	33.1
111.50	2.81	2.69	.095	33.2
371.12	3.19	2.63	.051	31.8
1323	3.48	2.59	.005	-
1412	3.51	2.58	0	-
			Average	33.3

F: $CHCl_3$ (μ=1.15), CH_2Cl_2 (μ=1.57) and $C_6H_5NO_2$ (μ=4.24)

5-3: $CHCl_3$: CH_2Cl_2 : $C_6H_5NO_2$ = 2.28 : .75 : 1
$C_2H_5SO_3H$ = .517 M v = 6.38 ml.

0	0	3.14	.551	-
129.85	2.95	2.67	.110	34.5
181.55	3.06	2.66	.070	32.8
203.20	3.26	.039	2.62	29.2
398.3	3.32	2.61	.030	28.6
546.9	3.37	2.61	.022	28.5
624.3	3.38	2.61	.020	30.3
1425	3.49	2.59	.004	-
1630	3.51	2.58	0	
			Average	30.6

TABLE IV (Cont'd)

Time (min.)	app. m.-moles N_2 evolved	app. $\underline{M}$ ketone	app. $\underline{M}$ HN_3	$k_3 \times 10^5$ ($sec.^{-1}$ $moles^{-2}$ $liters^2$)
2-6: $CHCl_3$: CH_2Cl_2 : $C_6H_5NO_2$ = 2.28 : 1 : .75 $C_2H_5SO_3H$ = .517 $\underline{M}$ v = 6.38 ml.				
0	0	3.14	.551	-
20.30	2.51	2.74	.157 -	39.8
38.62	2.65	2.72	.135	37.5
54.4	2.73	2.71	.122	35.8
67.8	2.79	2.70	.112	34.6
105.8	2.86	2.69	.102	34.6
143.6	2.99	2.67	.081	30.4
532	3.30	2.62	.033	-
763	3.61	2.58	0	-
			Average	35.6
G: $CHCl_3$ (μ=1.15), CH_2ClCH_2Cl (μ=1.8) and $C_6H_5NO_2$ (μ=4.24) $C_2H_5SO_3H$ = .517 $\underline{M}$ v = 6.38 ml.				
3-6: $CHCl_3$: CH_2ClCH_2Cl : $C_6H_5NO_2$ = 2.28 : 1 : .75				
0	0	3.14	.550	-
6.60	2.15	2.80	.214	37.3
14.45	2.36	2.76	.180	36.0
22.58	2.48	2.75	.162	35.2
41.25	2.62	2.72	.140	34.4
78.3	2.75	2.71	.119	34.0
133.2	3.04	2.66	.074	33.6
348	3.13	2.64	.060	34.2
445	3.19	2.64	.050	35.6
1356	3.48	2.59	.004	-
1472	3.51	2.58	0	-
			Average	35.0
5-4: $CHCl_3$: CH_2ClCH_2Cl : $C_6H_5NO_2$ = 2.28 : 1 : .75 $C_2H_5SO_3H$ = .517 $\underline{M}$ v = 6.38 ml.				
0	0	3.13	.550	-
20.13	2.72	2.71	.120	48.7
47.8	2.82	2.69	.108	51.8
78.2	2.94	2.67	.089	51.0
162.7	3.07	2.65	.068	52.1
235.1	3.23	2.62	.044	52.1
764	3.47	2.59	.007	-
1474	3.51	2.58	0	-
			Average	51.1

TABLE IV (Cont'd)

Time (min.)	app. m.-moles N_2 evolved	app. $\underline{M}$ ketone	app. $\underline{M}$ HN_3	$k_3 \times 10^5$ ($sec.^{-1}$ $moles^{-2}$ $liters^2$)

H: $CHCl_3$ (μ=1.15), $C_6H_5NO_2$ (μ=4.24) and CH_3CHCl_2 (μ=2.05)

4-6: $CHCl_3$: $C_6H_5NO_2$: CH_3CHCl_2 = 2.28 : .75 : 1
$C_2H_5SO_3H$ = .517 $\underline{M}$ v = 6.38 ml.

0	0	3.13	.550	-
28.6	2.69	2.72	.128	33.8
38.6	2.75	2.70	.119	35.6
69.8	2.84	2.67	.105	33.8
168.5	3.10	2.65	.064	36.2
248.5	3.15	2.64	.056	34.7
474	3.34	2.61	.027	37.3
525	3.36	2.61	.023	37.8
616	3.39	2.60	.019	38.2
1153	3.48	2.59	.005	-
1351	3.51	2.58	0	-
			Average	35.9

I: $CHCl_3$ (μ=1.15), $C_6H_5NO_2$ (μ=4.24) and C_6H_6 (μ=1)

$CHCl_3$: $C_6H_5NO_2$: C_6H_6 = 2.28 : .75 : 1
$C_2H_5SO_3H$ = .474 $\underline{M}$ v = 6.38 ml.

0	0	3.14	.550	-
25.30	2.54	2.74	.152	40.7
95.0	2.87	2.68	.100	39.5
165.6	3.11	2.65	.062	38.0
297	3.24	2.63	.043	40.0
497	3.39	2.60	.018	-
1900	3.51	2.59	0	-
			Average	39.6

TABLE V

Determination of the Order of the Schmidt Reaction on Acetophenone in Chloroform, Ethanesulphonic Acid Catalyst

Time (min.)	app. m.-moles N_2 evolved	app. $\underline{M}$ ketone	app. $\underline{M}$ HN_3	$k_3 \times 10^5$ ($sec.^{-1}$ $moles^{-2}$ $liters^2$)
	($C_2H_5SO_3H$) = .66 $\underline{M}$ v = 5.34 ml.			
0	0	1.87	.616	-
22.50	1.108	1.71	.401	1.78
43.55	1.412	1.65	.361	1.75
75.00	1.584	1.63	.330	1.72
128.0	1.683	1.61	.312	1.71
176.6	1.846	1.59	.279	1.68
1027	2.645	1.45	.127	1.65
1426	2.812	1.43	.095	1.73
3965	3.216	1.35	.015	1.68
4382	3.231	1.35	.012	-
6 weeks	3.290	1.26	0	-
			Average	1.71

TABLE V (Cont'd)

Summary of Other Runs on Acetophenone

B: $C_2H_5SO_3H$ = .956 M v = 6.40 ml.

Time (min.)	app. m.moles N_2 evolved	app. M ketone	app. M HN_3	$k_3 \times 10^5$ ($sec.^{-1}$ $moles^{-2}$ $liters^2$)
0	0	3.13	3.73	1. (Average)

C: $C_2H_5SO_3H$ = 1.132 M v = 5.34 ml.

0	0	1.88	.660	1.6 (Average)

D: $C_2H_5SO_3H$ = .949 M v = 6.38 ml.

0	0	3.13	.548	2. (Average

TABLE VI

Determination of the Order of the Schmidt Reaction on Diisopropyl Ketone in Chloroform; Ethanesulphonic Acid Catalyst

Time (min.)	app. m.moles N_2 evolved	app. M ketone	app. M HN_3	$k_3 \times 10^{-5}$ (sec.$^{-1}$ moles^{-2} liters^2)
Run A	$C_2H_5SO_3H$ = 1.09 M		v = 5.56 ml.	
0	0	1.80	.634	-
3.50	2.47	1.33	.188	41.2
5.30	2.57	1.31	.120	40.7
7.62	2.70	1.30	.146	40.1
13.30	2.89	1.26	.111	39.4
21.27	3.06	1.23	.081	38.7
43.47	3.12	1.22	.070	46.3
130.42	3.49	1.15	.003	-
165.63	3.51	1.15	0	-
			Average	41.1
Run B	$C_2H_5SO_3H$ = 1.067 M		Isopropylisobutyramide = .1853 M v = 5.68 ml.	
0	0	1.76	.604	-
20.05	1.67	1.46	.309	3.12
51.57	2.04	1.40	.244	3.02
260.05	2.60	1.29	.144	2.98
386.5	2.81	1.27	.108	3.06
1695	3.39	1.16	.008	-
2351	3.42	1.16	0	-
			Average	3.04

DISCUSSION OF EXPERIMENTAL RESULTS

Determination of the Order

Qualitative observation of the Schmidt reaction in aqueous and non-aqueous systems showed that the rate of the Schmidt reaction was increased by increasing the concentration of the acid catalyst, ketone, or hydrogen azide. Therefore the orders for the acid, ketone, and hydrogen azide, respectively, should each be greater than zero. Accordingly, the most likely values were considered to be first or second order for each. Since the acid in the Schmidt reaction functions only as a catalyst and is not used up, its concentration is essentially constant (however, see p. 100). This means that runs made at the same acid concentration may be compared directly with one another, but the effect of the acid catalyst may not thereby determined. Runs at different acidities, however, can be compared only if the effect of the acid is determined and taken into account. For uniformity, the role of acid concentration as found from comparison of runs at different acidities will be inserted in the comparison of rate constants from different runs at the same acidity.

The acidity function may appear in the rate expression as molarity (moles/l.), as the activity, and as the acidity function, h_o. This acidity function, h_o, was introduced by Hammett.[132] It is related to the Ho acidity function of Hammett and Deyrup in the same way that the concentration of hydrated hydrogen ions in water solutions is related to pH,

$$Ho = -\log. h_o$$

$$\text{and} \quad h_o = a_{H^+} \frac{f_B}{f_{BH^+}} \quad . \quad 132,133$$

Both h_o and Ho measure the tendency of a solution to donate a proton to an unchanged base. By using compounds whose absorption of light changes with conversion to the conjugate acid, various workers have been able to determine the values of Ho in various solvents[133,134] and the value of H-, the corresponding acidity function which measures the tendency of a solution to donate a proton to a singly-negatively charged base.[135] Certain workers have indicated that the values of Ho given in the literature for higher acid concentrations may be only apparent Ho values measuring the ability of the solution to donate several possible acidic entities;[136,137] however, the studies here were made at low enough concentrations of acid that it may safely be assumed that the h_o and Ho do, indeed, measure the tendency to donate a proton only.

The h_o function has been used here because it may be inserted directly in the rate expression. Its use in this manner is exactly equivalent to the correlations of Ho and log k present in the literature.[133]

A table is presented below giving the activities and h_o functions of aqueous hydrochloric acid and sulphuric acid solutions, calculated from data for Ho[99] and the activity coefficients.[138,139]

Hydrochloric Acid

Molarity	Activity	$h_o = 10^{-Ho}$
1.0	.809	1.045
2.0	2.02	4.16
3.0	3.96	12.0
4.0	7.04	18.1

Sulphuric Acid (pure)

Molarity	Activity	h_o
1.0	.130	1.14
2.0	.248	5.36
3.0	.423	16.95
4.0	.684	39.1

No values for the activity or h_o function are known for ethanesulphonic acid.

This table may be summarised as follows: If the acid effect is a function of the molarity, there should be an equal correction for all acids; if a function of the activity, the reaction should be accelerated much more by introducing higher hydrochloric acid concentrations than higher sulphuric acid concentrations; if a function of h_o, then the reaction should be accelerated much more by introducing higher concentrations of sulphuric acid than hydrochloric acid.

Qualitatively, it is found that only use of the h_o function fits the experimental data. Inclusion of the first power of the h_o value gives near-congruent curves graphically and the same rate constant both graphically and analytically, while other powers do not. The Schmidt reaction is therefore proportional to the first power of the h_o function, which measures the tendency of an acid to donate a proton to a neutral compound.

The experimental data may be treated either analytically or graphically. Plotting of the appropriate function of the concentration against time should give a straight line, the slope of which is the reaction rate constant. From the function giving a straight line the overall order of the reaction may be determined. The functions corresponding to the lower integral orders for two reactants are summarised below. (The constants are corrected for the catalyst concentration.)

Ordinate	Reaction Order
$\frac{1}{c}\left(\frac{1}{b-a}\right)\log\left(\frac{b-x}{a-x}\right)$	1,1
$\frac{1}{c}\left(\frac{1}{b-a}\right)\left[\frac{1}{a-x}+\left(\frac{b}{b-a}\right)\log\left(\frac{b-x}{a-x}\right)\right]$	2,1
$\frac{1}{c}\left(\frac{1}{b-a}\right)^3\left[\frac{(a-b)(b+a-2x)}{(a-x)(b-x)}-2\log\left(\frac{b-x}{a-x}\right)\right]$	2,2

Here 'c' is the ability of the solution to donate a proton as expressed by h_o, 'b', the concentration of ketone, 'a', the concentration of hydrogen azide, and 'x', the concentration of ketone and azide reacted, as shown by the nitrogen evolution.

Analytical treatment involves direct calculation of the rate constant from a suitable number of experimental points covering the entire period of observation. The variation due to experimental error must be small enough to allow any drift to be distinguished which indicates that the rate-law chosen does not yield a true constant. The formulas for the rate constants with different orders of reaction are summarised

below. Again the constants are corrected for catalyst concentration. The symbols have the same significance as in the resume above.

Order — k - Formula

1,1

$$k = \frac{\left(\frac{1}{c}\right)\left(\frac{1}{b-a}\right)\log\left[\left(\frac{a-x_1}{b-x_1}\right)\left(\frac{b-x_2}{a-x_2}\right)\right]}{t_2 - t_1}$$

when $t_1 = 0$

$$k = \frac{\left(\frac{1}{c}\right)\left(\frac{1}{b-a}\right)\log\left[\left(\frac{b-x}{a-x}\right)\left(\frac{a}{b}\right)\right]}{t}$$

2,1

$$k = \frac{-\frac{1}{c}\left(\frac{1}{b-a}\right)\left[\frac{x_2 - x_1}{(a-x_1)(a-x_2)}\right]\left(\frac{b}{b-a}\right)\log\left[\frac{(b-x_2)(a-x_1)}{(a-x_2)(b-x_1)}\right]}{t_2 - t_1}$$

when $t_1 = 0$

$$k = \frac{-\frac{1}{c}\left(\frac{1}{b-a}\right)\left[\frac{x}{(a-x)\,a}\right]\left(\frac{b}{b-a}\right)\log\left[\left(\frac{b-x}{a-x}\right)\left(\frac{a}{b}\right)\right]}{t}$$

2,2

$$k = -\frac{1}{c}\left(\frac{1}{b-a}\right)^3\left[\frac{(a-b)(b+a-2x_2)}{(a-x_2)(b-x_2)} - \frac{(a-b)(b+a-2x_1)}{(a-x_1)(b-x_1)} + 2\log\left[\frac{(b-x_1)(a-x_2)}{(b-x_2)(a-x_1)}\right]\right]$$

when $t_1 = 0$

$$k = -\frac{1}{c}\left(\frac{1}{b-a}\right)^3\left[(a-b)\left\{\frac{b+a-2x}{(a-x)(b-x)} - \frac{b+a}{ab}\right\} + 2\log\left[\left(\frac{b}{a}\right)\left(\frac{a-x}{b-x}\right)\right]\right]$$

The experimental data taken for runs in aqueous solutions may be very simply converted into m-moles of nitrogen formed, by application of the gas laws.*

$$x\ (\text{m-moles}) = \left(\frac{v}{22.4}\right)\left(\frac{273}{T}\right)\left(\frac{p'}{760}\right),$$

---

* The use of the perfect gas laws for nitrogen at pressures near one atmosphere is not subject to error of significant magnitude in this study.

where v = volume of nitrogen in cc.
T = the temperature of the air jacket surrounding the collected gas
p' = barometric pressure - water vapor pressure at temperature T .

The amount of each reactant remaining at any time may be obtained by simply subtracting the moles of nitrogen evolved from the starting quantities.

The concentration of the reactants in non-aqueous solutions may not be found so simply because the vapor pressure of the reaction mixtures cannot be accurately estimated. Nevertheless, the correct order for such a reaction may still be determined by finding what may be called 'pseudo rate constants' for the reaction. These "pseudo-constants" are empirical preliminary values obtained by ignoring vapor-pressure corrections. They may be determined approximately from the apparent volume of nitrogen evolved at the completion of the reaction and the apparent amount evolved at any particular time. The volume at completion may be assumed to be equivalent to the number of m-moles of hydrogen azide inserted into the reaction mixture, since it has been found that all of the hydrogen azide is removed from the solution by way of the Schmidt reaction. The number of m-moles of nitrogen left to be evolved at any time is proportional to the difference between the apparent volume at the time of measurement and the apparent total evolved volume. The assumption made above gives a way of estimating this proportionally constant and thus of finding the rate constant.

In general such a procedure will give a "pseudo-constant" which is a small factor times the real reaction rate constant,

$k_\psi = \psi^y k$, because of the error introduced in the evaluation of the proportionality constant by ignoring vapor-pressure corections. For reactions which are first order with respect to each reactant, the correction factor between the two rate expressions is 1; but for reactions of other order, the two constants are not equal (see Appendix). This mode of treatment thus precludes accurate comparison of rate data in different solvent systems unless the reaction happens to be first order with respect to each constituent.

The pseudo-rate constants may be calculated either graphically or analytically, in the same manner as the regular constants. The general method is outlined below.

$$\psi\gamma = \psi\left(\begin{matrix}\text{m-moles} \\ N_2 \text{ not yet evolved}\end{matrix}\right) = \frac{(v_f - v)}{22.4}\left(\frac{273}{T}\right)\left(\frac{p}{760}\right)$$

Where v, and T have the same significance as in the aqueous solution. Here p is the barometric pressure. The actual correction factor that should be applied is thus $\frac{p''}{p} \simeq \frac{(HN_3)_o}{y_o}$, where p"=corrcted vapor pressure. (v_f) is the volume of nitrogen measured at the completion of the reaction.

The apparent amount of 'potential nitrogen' left in the solution, would be the same as the apparent amount of hydrogen azide. The corresponding apparent amount of ketone may be found by adding to the value 'y' the difference between the original amounts of ketone and azide.

On the basis of these considerations, values for rate constants have been calculated for each of the runs listed in the Tables and may be consulted there. The rate expression

used is $\frac{d(N_2)}{dt} = k_3 (HN_3)$ (ketone) h_o, which is the only one found to give reasonably constant values for k_3.

Temperature Effects

The Schmidt reaction is strongly exothermic, and, as to be expected, is extremely sensitive to changes in temperature. The consequences of this are seen in runs I-A, I-B, and II-E. Initial overheating in runs I-A and I-B is responsible for high values of the rate constants. It will be noticed that when the rate constant for run I-A is calculated from the middle or the end of the run where normal temperatures prevail, rate constants more nearly agreeing with reactions I-B, C, D are obtained. The rate constant is diminished by a factor of 2.5 in run I-B which was run at 22° C. instead of the usual 25°.

The high value in run I-F undoubtedly resulted from inability of the thermostatting conditions to carry away the large heat of reaction when the reaction proceeds so fast.

Dependence on Acidity

Comparison of those runs which are free from temperature variations shows that use of the h_o function gives satisfactory agreement among the rate constants, but use of the activity does not. Use of the activity in comparing the runs I-B and I-D, for instance, would give rate constants that differed by a factor of 1 1/2; use of molarity in comparing those two runs would give rate constants that differed by a factor of 2 1/2. Values for the rate in 6 M hydrochloric acid (IF) can

be estimated from the rate constants of runs in lower concentrations of acid (IA-ID) on the basis of the several acidity functions - h_o, activity, or molarity. The experimentally determined constant unfortunately could not be measured with accuracy due to the much greater speed at the high acidity. However, the approximate value differs by a factor of 70 from that estimated from activity, and by a factor of 18 from that measured by molarity. The rate constant estimated from the h_o differs by only a factor of 4 from the approximate measurement. The lack of applicability of activity in comparing the runs in sulphuric acid is also evident. Use of activity or molarity in comparing runs II-C and II-E would each produce rate constants differing by a factor of about 1 1/2. Moreover, the h_o function is the only function by which the rate constants with different acid catalysts may be compared. Using the h_o function, the values of the rate constants in sulphuric and hydrochloric acids are essentially the same (mean $k_3 = 6.10^{-4}$ moles^{-2} l.^{2} sec.$^{-1}$). Using the activity, the rate constants from sulphuric acid runs are about eight times as great, using the molarity, about half as great, as those from hydrochloric acid runs.

Since the h_o functions for ethanesulphonic acid solutions are unknown, the molarity of this acid was used in calculating the rate constants in the non-aqueous solutions. Evidently, in the acid range in which the rate studies were undertaken, the h_o function is roughly proportional to the molarity for ethanesulphonic acid in chloroform, since satisfactory agreement was obtained between the rate constants at different

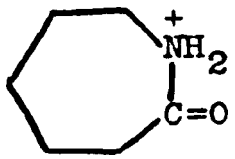
acidities in these solutions, such as in runs III-A, B, C.

The fact that the h_o function is a factor in the rate-constant implies that one of the preliminary steps of the Schmidt reaction involves proton donation to the substrate by the solution, and that a proton is not returned to the solution to replace it until after the rate-determining step in the reaction (p. 34). Furthermore, this preliminary step must be dependent on only the proton-donating power of the solution, and not on a special characteristic of the acid. Therefore, in the cases studied, the Schmidt reaction goes by a specific lyonium-acid catalysis as opposed to general acid catalysis or general proton-acid catalysis.[99,100]

Effect of Amides

In no case was the introduction of amides found to accelerate the Schmidt reaction. Introduction of a small amount of ϵ-caprolactam had very little effect on the strongly acidic hydrochloric acid solutions (run I-C). In some of the sulphuric acid runs, notably run II-E, there is a decided drift toward a lower rate constant as the ketone is transformed into ϵ-caprolactam. In the non-aqueous solutions, introduction of rather large amounts of isopropylisobutyramide or ϵ-caprolactam had a decided retarding effect on the rate of the reaction. For example the rate constants for runs III-D, E in which amides were present are about one-tenth for the corresponding rate constants for III-A, B, C in which no amides were present. ϵ-Caprolactam is very soluble in hydrochloric and sulphuric acids, presumably due

to salt formation. An estimate of k_b defined by the equation $B + H^+ = BH^+$ may be made by comparing ϵ-caprolactam with dimethylformamide and dimethylacetamide. These compounds are stronger bases than acetone.[101,105] By analogy ϵ-caprolactam should be a stronger base than cyclohexanone. Extrapolating the data of Gordy[105,140] in this manner yields an estimate of $2.5 < K_b < 20$ (as defined by the equation above); k_b (cyclohexanone) = 10^{-2}. These constants mean that in aqueous solutions both cyclohexanone and ϵ-caprolactam actively compete with water for protons. ϵ-Caprolactam (or isopropylisobutyramide), whether present in the solution as product of the reaction, or introduced into the solution initially, will act in this way, lowering the h_o of the solution. In solutions where there is more ϵ-caprolactam than acid, the effective proton donor would be the conjugate of ϵ-caprolactam,



Such a species would, of course, be a much weaker acid than hydrochloric, sulphuric, and ethanesulphonic acids, and would generate solutions of lower h_o value.

Effect of Solvents

Changing the dipole moment of the solvent in the non-aqueous solutions seemed to have little effect on the rate constants. For instance, the substitution of 2.5 ml. of nitrobenzene (μ = 4.24) (run IV 5-6) for the same amount of

chloroform (μ = 1.15) (run III-B) in a Schmidt reaction resulted in no significant change in the rate constant. Likewise, substitution of carbon tetrachloride (μ = 0) for nitrobenzene did not make a change in the rate constant. This as in contrast to the results of Chapman's studies on the Beckmann rearrangement, in which he found that addition of small amounts of polar substances very greatly increased the speed of the rearrangement of oxime-esters.

$$\begin{matrix} R \\ R \end{matrix}\!\!>\!C = N\!-\!OTs \longrightarrow R - C = \overset{+}{N} - R + OTs^{-} .$$

The difference in the two effects probably results from the fact that the rearrangement step of the Schmidt reaction does not involve a change in the number of ions, but the rearrangement step of that Beckmann rearrangement does.

Recapitulation

The preceding results, and the comparisons and conclusions from them may be summed up as follows:

In all cases studied, the rate law was found to be

$$\frac{d(N_2)}{dt} = k_3 h_0 (HN_3) (\text{ketone}).$$

The rate constant calculated on this basis was of the order of 5 x 10^{-5} for aqueous solutions of cyclohexanone (.161 M to 1 M) which ranged in hydrogen azide concentration from .316 M to 1.22 M in sulphuric acid solutions (h_0 = 3.83 to 10.72) and from .0528 to .105 M in 1.5-6 M hydrochloric acid solutions (h_o = 2.21 to ca. 50).

Use of acid concentration or activity instead of h_o did not give satisfactory constants in aqueous solutions. The

rate of reaction was affected by the presence of amides, the expected product of the reaction, to the extent to be expected due to the reduction in total acidity which they bring about. It was unaffected by small amounts of cupric and chromic ions, which might also have been expected to have possible catalytic activity.

In non-aqueous solutions, ethanesulphonic acid was used as a catalyst in concentrations from .5 M to 1.88 M. (An experiment with the indicators 2-nitro-4-chloroaniline and 2,4-dinitroaniline showed that 1.52 M ethanesulphonic acid changed the color of 2-nitro-4-chloroaniline, but not of 2,4-dinitroaniline. This would correspond to an Ho of about 1.3 ± .6.) The concentration of ketone (cyclohexanone) ranged from .83 M to 3.33 M, while that of the hydrogen azide ranged from .333 M to .584 M. The rate constant, calculated on the basis of molarity of ethanesulphonic acid, was of the order of 10^{-4}. The rate of reaction is here, too, probably proportional to the h_o value. Since the h_o values for ethanesulphonic acid solutions have not been determined, it was impossible to determine the proportionality exactly. The h_o value is apparently nearly proportional to the concentration of ethanesulphonic acid in the dilute non-aqueous solutions, just as it is in dilute aqueous solutions.

Runs with cyclohexanone were made in non-aqueous solutions using carbon tetrachloride, chloroform, methylene chloride, ethylene chloride, ethylidene chloride and nitrobenzene, having dipole-moments ranging from 0 (carbon tetrachloride) to 4.24 debye units (nitrobenzene). In this variation in



solvents, little change was noticed in the rate constant.

Implications Concerning Mechanisms

On the basis only of the results summarised above, it is possible to eliminate a great many of mechanisms for the Schmidt reaction proposed in the literature. The orders expected for the various mechanisms already discussed for ketones and aldehydes (p. 21) are listed here.

Mechanism	Identification	Order
Schmidt	NH - Direct Addition	$(HN_3)^1(\text{ketone})^0(\text{acid})^0$
	NH - Oxime Formation	$(HN_3)^1(\text{ketone})^0(\text{acid})^0$
	NH_2^+ - Direct Addition	$(HN_3)^1(\text{ketone})^0(\text{acid})^1$
	NH_2^+ - Oxime Formation	$(HN_3)^1(\text{ketone})^0(\text{acid})^1$
Oliveri-Mandala	Heterocycle Intermediate	$(HN_3)^1(\text{ketone})^1(\text{acid})^0$
Hurd	Active HN_3 ketone	$(HN_3)^1(\text{ketone})^1(\text{acid})^1$
Smith	Hydroxycarbonium ion (Dehydration)	$(HN_3)^1(\text{ketone})^1(\text{acid})^1$
Newman and Gildenhorn	Hydroxycarbonium ion (No dehydration)	$(HN_3)^1(\text{ketone})^1(\text{acid})^1$
Sherk	Hydroxycarbonium ion (No dehydration)	$(HN_3)^1(\text{ketone})^1(\text{acid})^1$

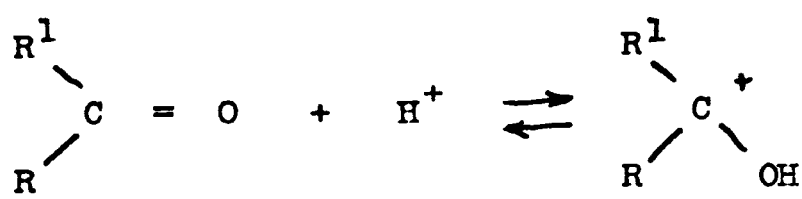
Those rate-laws (Schmidt and Oliveri-Mandala) which do not involve all three constituents may be excluded immediately by consideration of the qualitative dependence of the rate on all three components. Therefore, of the mechanisms that have been proposed, only that of Hurd involving "activated" hydrogen azide and those involving the hydroxy-carbonium ion (Sherk, Newman, Smith) need now be considered.

These mechanisms will now be discussed further in the

light of the non-kinetic experimental evidence that has since been obtained. The mechanism advanced by Hurd was shown to be inadequate by Newman, who pointed out that Hurd's "activated" form of hydrogen azide was merely one of the canonical forms in which the hydrogen azide molecule may be written. A real activated (triplet) state of the molecule is highly unlikely as an intermediate because of the high energy required; furthermore, treatment with sulphuric acid could not bring this about.

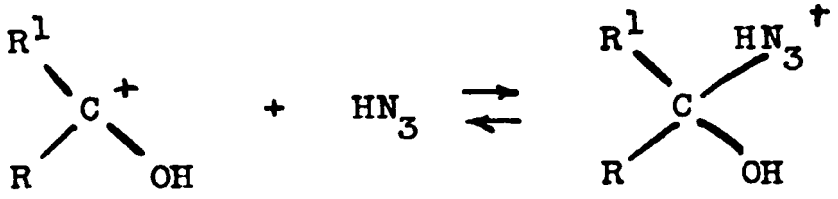
Since all of the hydroxy-carbonium ion mechanisms (and their modifications) involve the first power of the acid catalyst, ketone, and hydrogen azide, the measured rate law confirms their possible validity. Furthermore, the rate studies can give some insight into the importance and relative speed of the various steps in the reaction. In addition, the kinetic data should delimit the type of alternative mechanism that may be proposed.

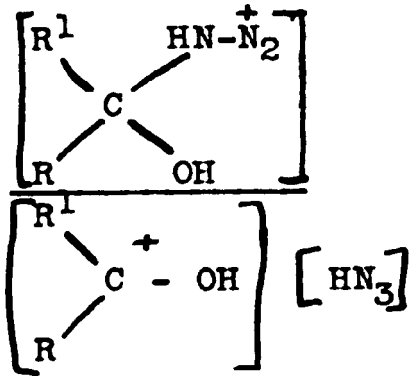
The first two steps of all the hydroxy-carbonium ion mechanisms are essentially the same.

1) 

$$K_1 = \frac{\left[\begin{array}{c} R^1 \\ \diagdown \\ C^+ \\ \diagup \quad \diagdown \\ R \qquad OH \end{array}\right]}{\left[\begin{array}{c} R^1 \\ \diagdown \\ C = O \\ \diagup \\ R \end{array}\right] [H^+]}$$

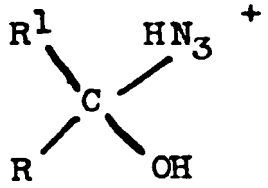
A rapid reversible equilibrium.

2) 

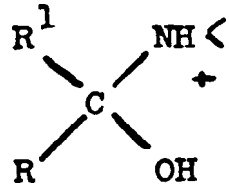
K_2 = 

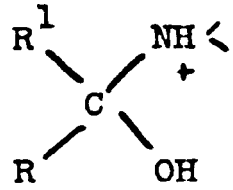
A rapid reversible equilibrium.

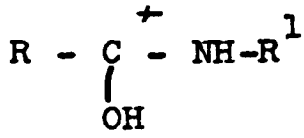
The mechanism of Sherk assumes prelirinary loss of nitrogen, followed by migration of one group to the unsaturated nitrogen thus formed.

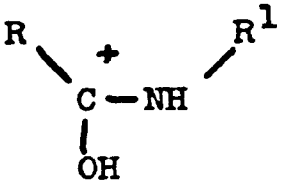
3d) 

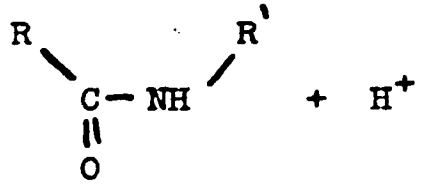
rate-determining; irreversible.



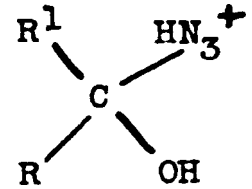
4d) 



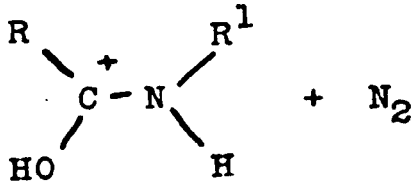
5d) 

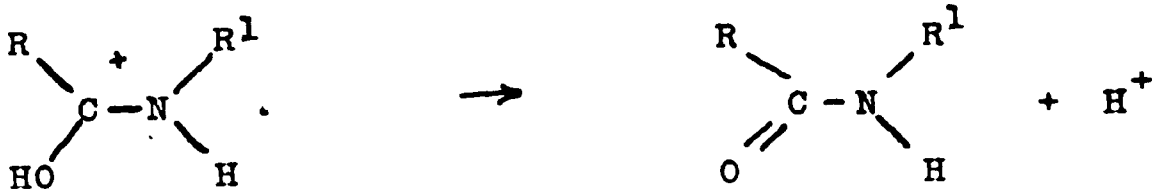


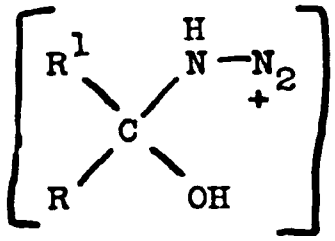
The mechanism due to Newman assumes rearrangement without dehydration, followed by loss of a proton to form the amide.

3a) 

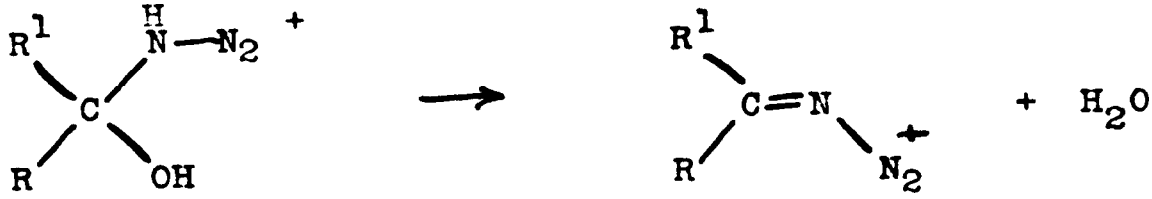
rate-determining; irreversible.

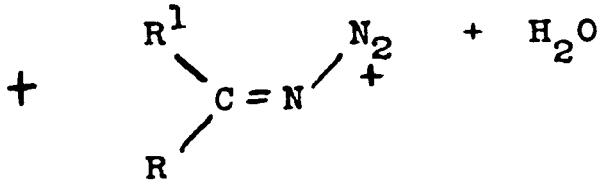


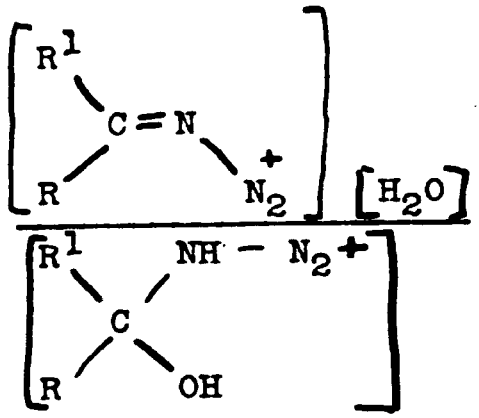
4a) 

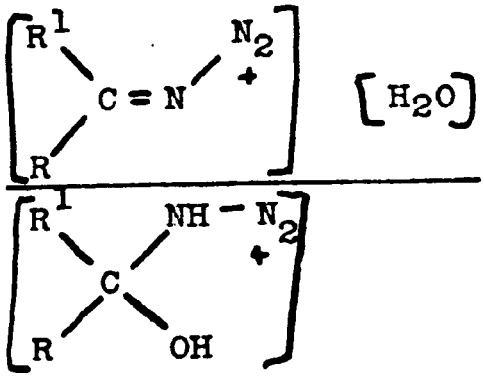
$$\frac{d(N_2)}{dt} = k_N$$ 

The mechanism of Smith assumes dehydration to an intermediate capable of geometrical isomerism before rearrangement.

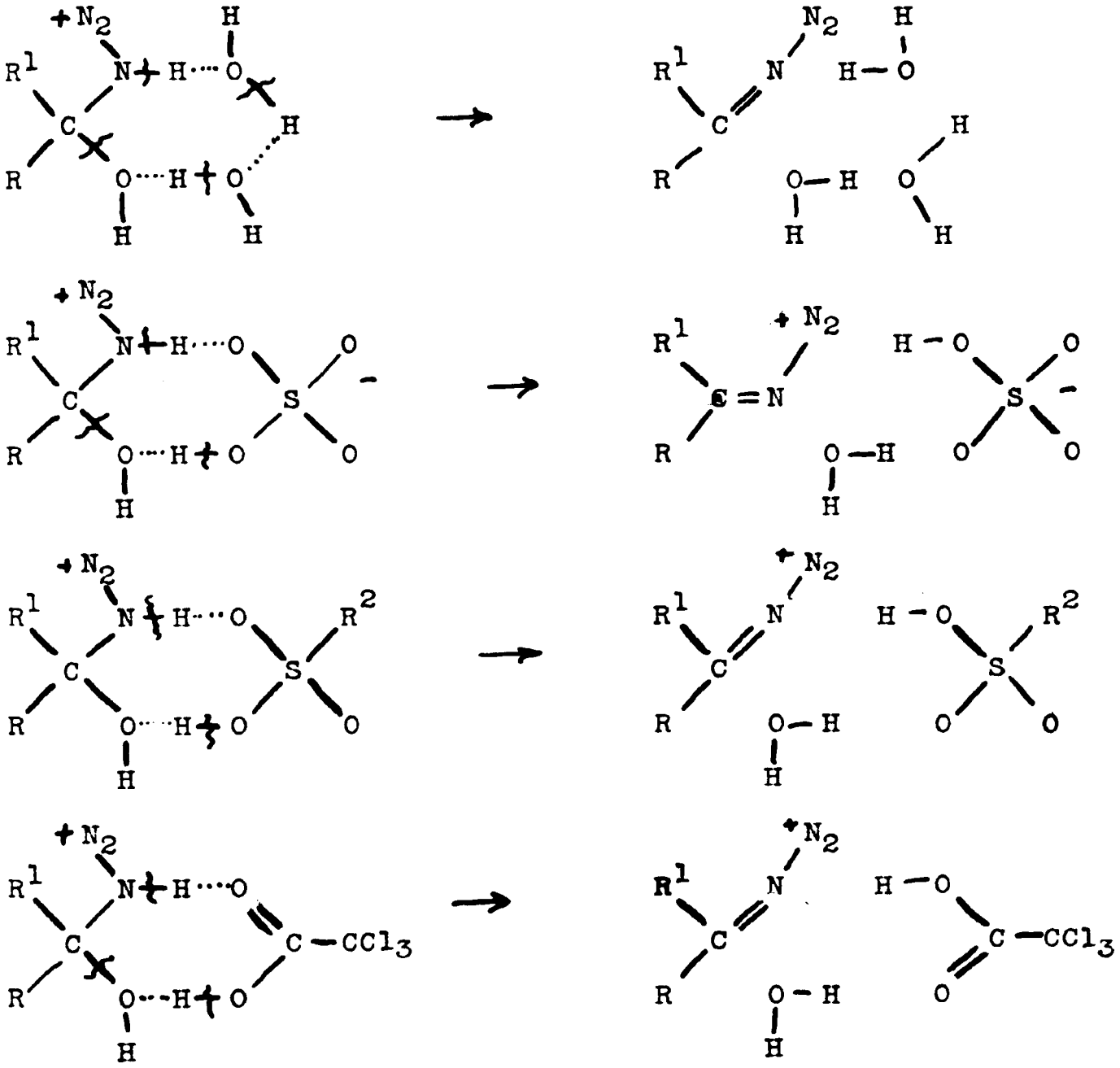
3b) 



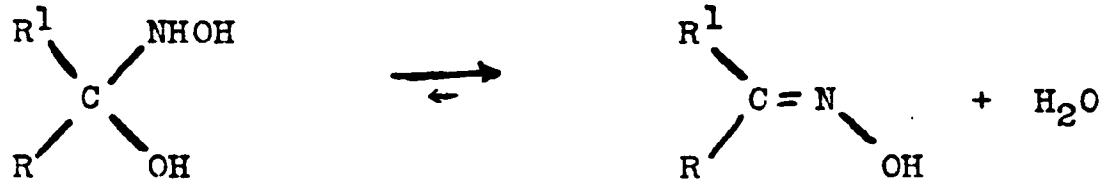
$$K_{31} =$$ 

$$K_{32} =$$ 

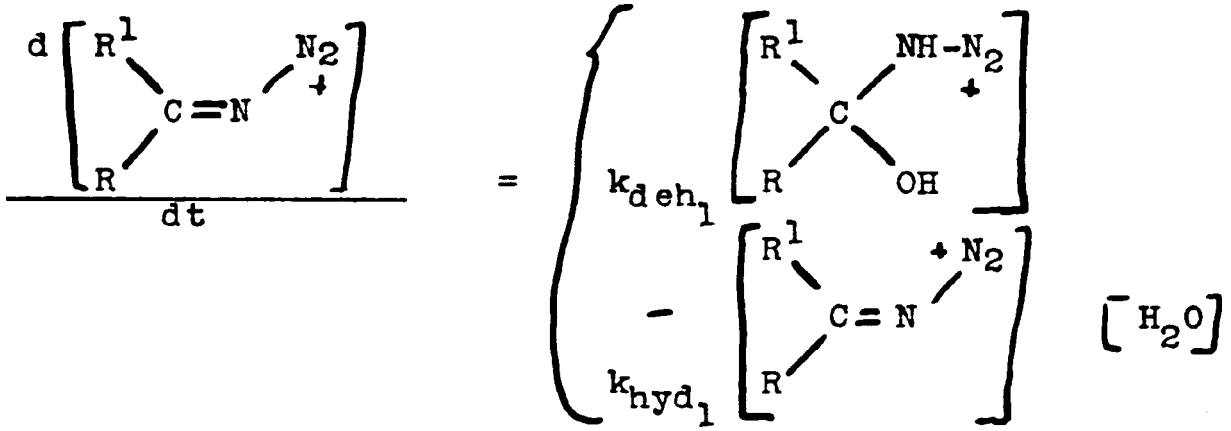
For symmetrical ketones $K_{31} = K_{32}$. For unsymmetrical ketones and for aldehydes the ratio K_{32}/K_{31} is the ratio of the syn- to the anti- R^1 forms when equilibrium is reached. It seems reasonable to assume that the dehydration process would be a rapid and reversible one, facilitated by any hydroxylic compound in a cyclic acid-base catalysed path.



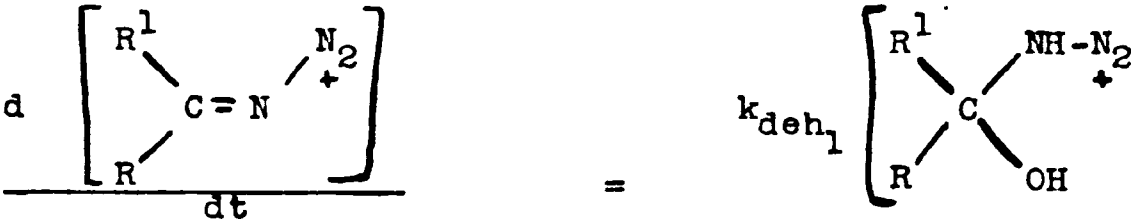
It also seems probable from the behavior of aldehydes in the Schmidt reaction that, as in oxime formation, the dehydration process goes practically to completion,



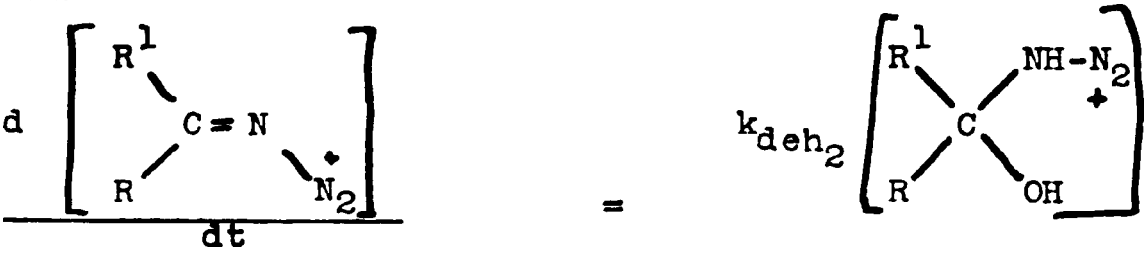
Under these conditions, although the reaction is actually reversible, kinetically it will appear irreversible. This may be expressed mathematically as



If the reaction, though reversible, is very near completion, the equation reduces to



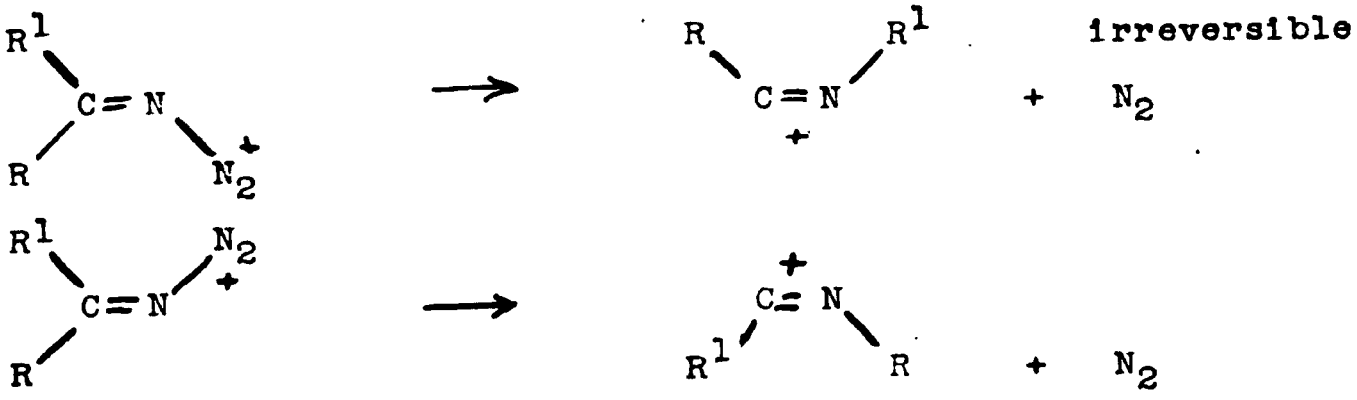
and

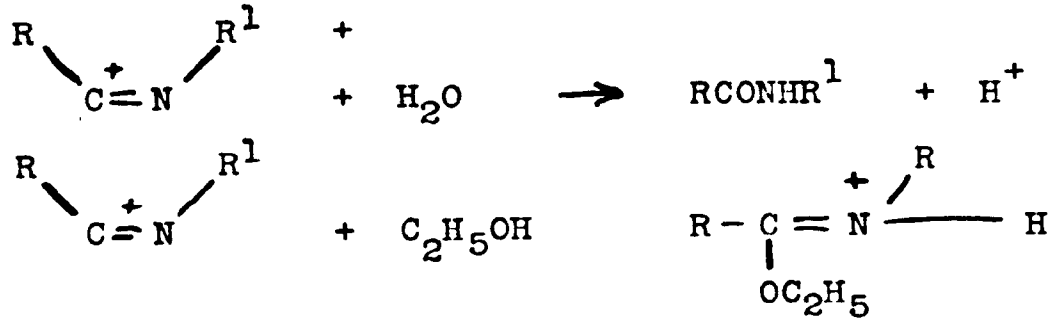


Now it is quite likely that the rate of this relatively fast dehydration depends on the other hydroxylic molecular species

in solution. In such a situation, the ratio of the two isomers formed would be the ratio of the rate constants: syn R^1/anti R^1 = k_{deh_1}/k_{deh_2}. The ratio of isomers then would be a function of the nature of the solution. Such a process would provide an explanation of the variation in the product ratios with concentration of acid alternative to that based on interconvertability of the syn- and anti- forms.[58] Interconversion of the geometric isomers probably proceeds through hydration and dehydration, although alternative paths for interconversion similar to those of oximes are possible.

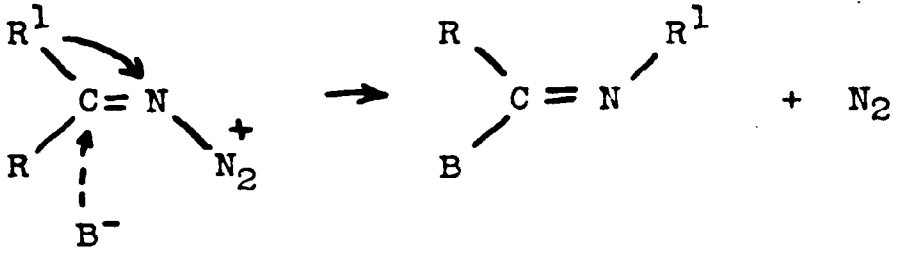
The fourth step in the mechanism suggested by Smith involves irreversible rearrangement, followed by reaction with a nucleophilic species to make an amide, or the appropriate derivative.

4b) 

5b) 

The rearrangement is probably the slow, rate-determining step, since it involves rupture of a carbon-carbon bond.

An alternative path for this fourth step involves rearrangement of the imino-carbonium ion simultaneously with attack by the neucleophilic species.

4c) 

This would imply that the rate of rearrangement would be proportional to the concentration of the attacking nucleophilic species.

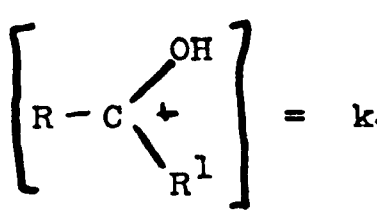
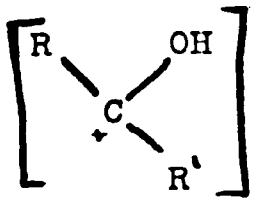
$$\frac{d\left[\begin{matrix} R \diagdown & & R^1 \diagup \\ & C=N & \\ B \diagup & & \end{matrix}\right]}{dt} = k_r \left[\begin{matrix} R^1 \diagdown & & \\ & C=N & \\ R \diagup & & \overset{+}{N_2} \end{matrix}\right] [B^-]$$

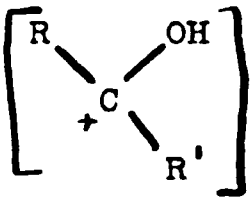
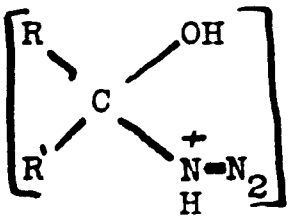
$$\frac{d\left[\begin{matrix} B \diagdown & & \\ & C=N & \\ R^1 \diagup & & R \end{matrix}\right]}{dt} = k_r \left[\begin{matrix} R^1 \diagdown & & N_2 \\ & C=N & \overset{+}{} \\ R \diagup & & \end{matrix}\right] [B^-]$$

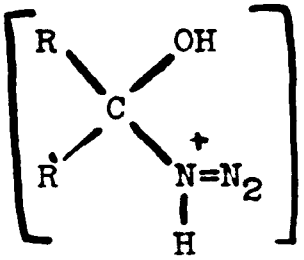
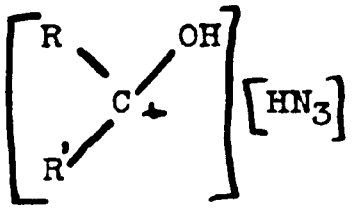
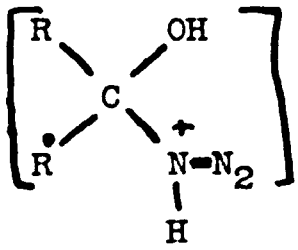
The results of this detailed kinetic picture of the preceding mechanisms for the Schmidt reaction may be summarised by the following equations:

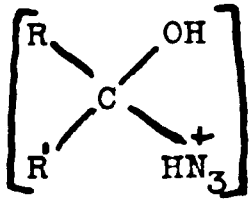
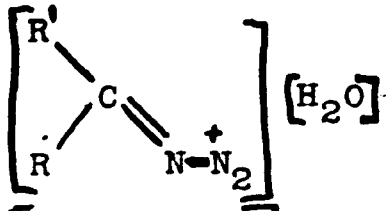
I) Dehydration - imino-carbonium mechanism:

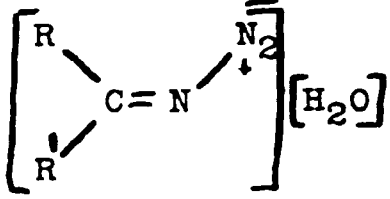
1) $$\frac{d}{dt}\left[R_2CO\right] = -k_1(R_2CO)(H^+) + k_{-1}\left[\begin{matrix} R \diagdown & & OH \diagup \\ & C^+ & \\ R \diagup & & \end{matrix}\right]$$

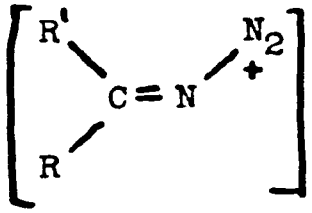
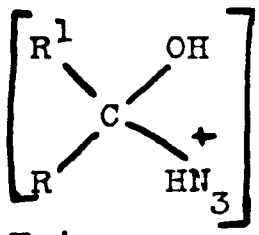
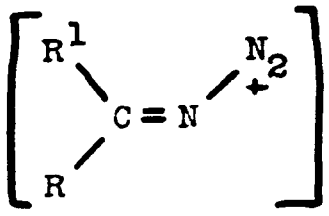
2) $\frac{d}{dt}$  = $k_1(R_2CO)(H^+)$ - k_2 

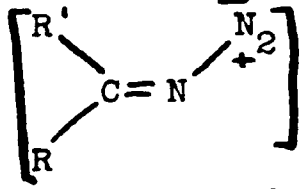
$-k_{-1}$  + k_{-2} 

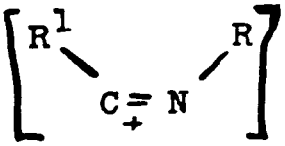
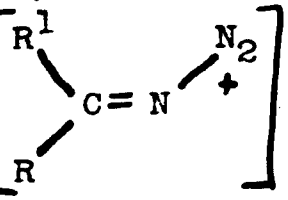
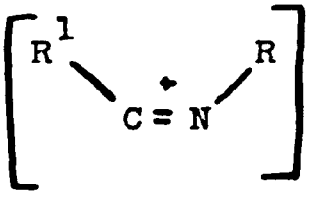
3b) $\frac{d}{dt}$  = k_2  - k_3 

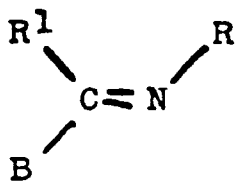
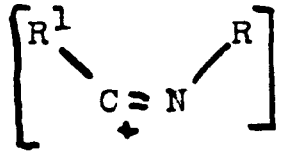
$-k_{-2}$  + k_{-31} 

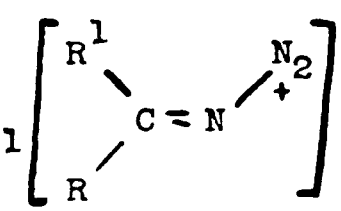
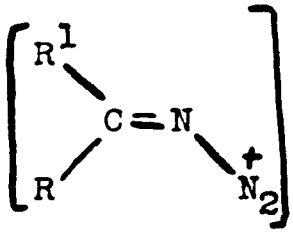
+ k_{-32} 

4b) $\frac{d}{dt}$  = k_{31}  - k_{41} 

$-k_{-31}$  etc.

5b) $\frac{d}{dt}$  = k_{41}  $-k_{51}$  (B^-)

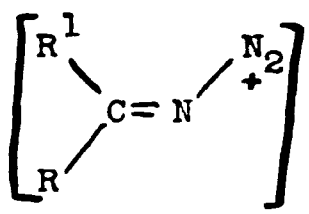
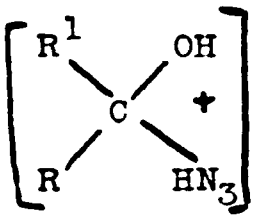
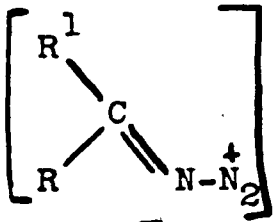
6b) $\frac{d}{dt}$  $= k_{51}$  (B)

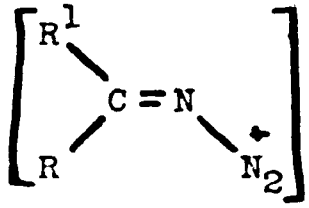
N-b) $\frac{d}{dt}(N_2) = k_{41}$  $+ k_{42}$ 

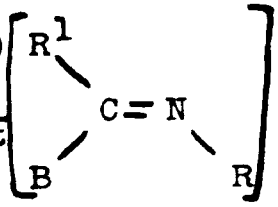
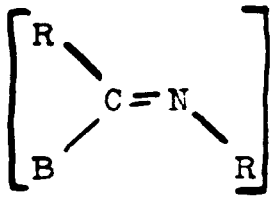
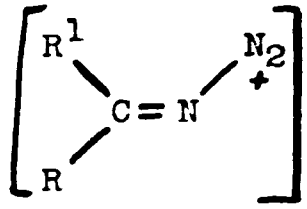
Assuming no side reactions

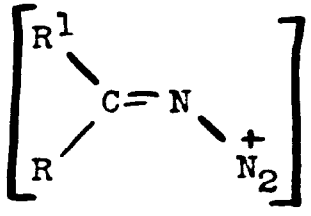
II) Push-pull (concerted displacement) Mechanism.

The equations 1-3 are the same as for the preceding mechanism.

4c) $\frac{d}{dt}$  $= k_{31}$  $- k_{41}$  (B)

$-k_{-31}$ 

5c) $\frac{d}{dt}$  $= -k_{51}$  $+ k_{41}$  (B)

N-c) $\frac{d}{dt}(N_2) = k_{41}$  (B)

III) Newman Mechanism.

The equations 1-2 are the same as those on the preceding page.

3a) $\frac{d}{dt}\left[\begin{array}{c} R^1 \quad OH \\ \diagdown\ /\ \diagup \\ C \\ \diagup\ \diagdown \\ R \quad N\text{-}N_2^+ \\ \quad\ H \end{array}\right] = k_2 \left[\begin{array}{c} R^1 \\ \diagdown \\ C\text{-}OH^+ \\ \diagup \\ R \end{array}\right][HN_3] - k_3 \left[\begin{array}{c} R^1 \quad OH \\ \diagdown\ /\ \diagup \\ C \\ \diagup\ \diagdown \\ R \quad N\text{-}N_2^+ \\ \quad\ H \end{array}\right] - k_{-2} \left[\begin{array}{c} R^1 \quad OH \\ \diagdown\ /\ \diagup \\ C \\ \diagup\ \diagdown \\ R \quad N\text{-}N_2^+ \\ \quad\ H \end{array}\right]$

4a) $\frac{d}{dt}\left[R-\overset{\overset{OH}{|}}{\underset{\downarrow}{C}}-NHR^1\right] = k_3 \left[\begin{array}{c} R^1 \quad OH \\ \diagdown\ /\ \diagup \\ C \\ \diagup\ \diagdown \\ R \quad N\text{-}N_2^+ \\ \quad\ H \end{array}\right] - k_4 \left[R-\overset{\overset{OH}{|}}{\underset{\downarrow}{C}}-NHR^1\right] + k_{-4}\left[R-\overset{\overset{O}{\|}}{C}-NH-R^1\right]$

N-a) $\frac{d}{dt}[N_2] = k_3 \left[\begin{array}{c} R^1 \quad OH \\ \diagdown\ /\ \diagup \\ C \\ \diagup\ \diagdown \\ R \quad N\text{-}N_2^+ \\ \quad\ H \end{array}\right]$

IV) Mechanism of Sherk, et al.

The equations 1-2, and 3 are the same as those for the preceding mechanisms.

4d) $\frac{d}{dt}\left[\begin{array}{c} R^1 \quad NH< \\ \diagdown\ /\ \diagup^+ \\ C \\ \diagup\ \diagdown \\ R \quad OH \end{array}\right] = k_3 \left[\begin{array}{c} R^1 \quad OH \\ \diagdown\ /\ \diagup \\ C \\ \diagup\ \diagdown \\ R \quad N\text{-}N_2^+ \\ \quad\ H \end{array}\right] - k_4 \left[\begin{array}{c} R^1 \quad NH \\ \diagdown\ /\ \diagup^+ \\ C \\ \diagup\ \diagdown \\ R \quad OH \end{array}\right]$

5d) $\frac{d}{dt}\left[\begin{array}{c} R \quad\quad R^1 \\ \diagdown\ \ /^+ \\ C=N \\ \diagup\ \diagdown \\ HO \quad\quad H \end{array}\right] = k_4 \left[\begin{array}{c} R^1 \quad NH< \\ \diagdown\ /\ \diagup^+ \\ C \\ \diagup\ \diagdown \\ R \quad OH \end{array}\right] - k_5 \left[\begin{array}{c} R \quad\quad R^1 \\ \diagdown\ \ /^+ \\ C=N \\ \diagup\ \diagdown \\ HO \quad\quad H \end{array}\right] + k_{-5} \left[\begin{array}{c} R \\ \diagdown \\ C-NHR^1 \\ \diagup \\ O \end{array}\right]$

N-d)

$$\frac{d}{dt}(N_2) = k_2 \left[\begin{array}{ccc} R^1 & & OH \\ & C & \\ & & HN\text{-}N_2 \end{array} \right]^+$$

The mechanisms proposed by Newman and Sherk do not satisfactorily account for the fact that ratios of isomers obtained in the Schmidt reaction do not vary as the migration aptitudes in the Beckmann rearrangement, as would be implied from the azidohydrin rearrangement. This problem also arises in considering the change of the ratio of nitrile to formamide in the Schmidt reaction on aldehydes with different concentrations of acid catalysts.

The other two mechanisms satisfy this requirements, as discussed earlier. An attempt will be made in this section to further justify these mechanisms and to point out the contrasting characteristics.

The Basis for the Postulated Ionic Species

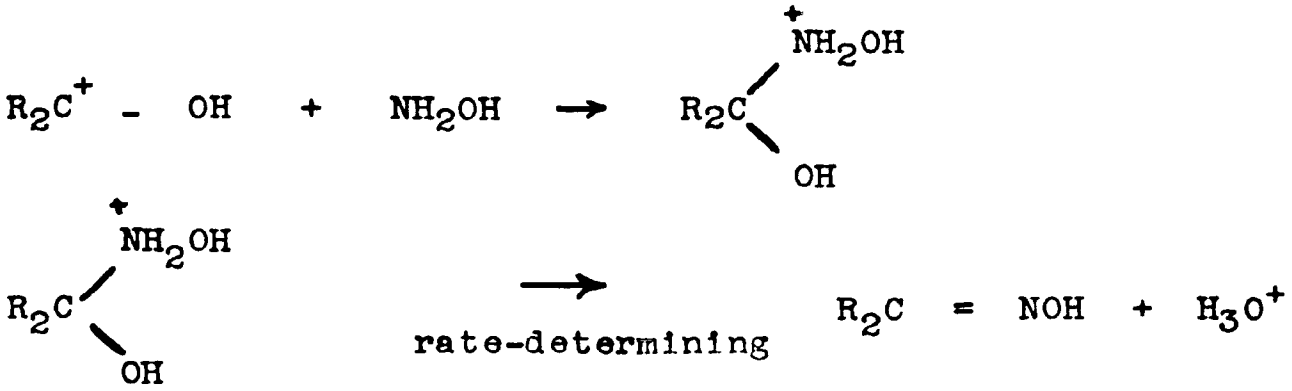
Formation of a hydroxy- or oxo-carbonium ion, from ketones, aldehydes, or carboxylic acids, the first step in several of the proposed mechanisms, has been substantiated by ultraviolet[102,103,104] and infra-red[101] spectroscopic evidence, by cryoscopic studies,[140,141] and by kinetic studies of other reactions of these carbonyl compounds in acid solution (p.28). These measurements show that the concentration of the carbonium ion is proportional to the concentration of the solvated hydrogen ion and the concentration of ketone, aldehyde, or carboxylic acid.

Most carbonium ions, once formed, have a very transient lifetime. However, special structural features like those in oxycarbonium ions, may stabilize them considerably. These ions usually react as primary Lewis acids, as secondary Lewis acids, or they rearrange. The decomposition of the carbonium ion back into the original ketone, aldehyde, or acid and the solvated proton (or other Lewis acid) is an example of the reaction as a secondary Lewis acid.

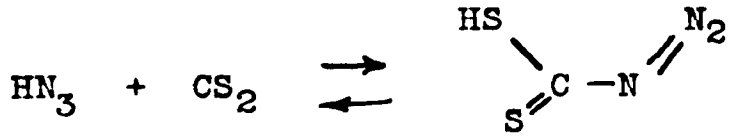
The commonly known rearrangements of hydrocarbons under the influence of acid catalysis offer a good example of the last-mentioned property of the carbonium ion.[142,143] (any rearrangement proceeds so that the new arrangement of atoms and groups of atoms is thermodynamically more stable than the old arrangement. This greater stability may be due to a more favorable pattern of groups left in the molecule after the rearrangement and/or the formation of a very stable separate molecule or ion during the rearrangement.)

Carbonium ions react as primary Lewis acids in those reactions which do not involve dissociation or displacement. Examples of this type of reaction are the etherification of carbonium ions by alcohols (p.28), the Friedel-Crafts reaction[144] of oxocarbonium ions, and the formation of semicarbazones, hydrazones, and related compounds from aldehydes and ketones in acidic solutions (p.28). For example, the accepted mechanism for the formation of oximes, based on kinetic studies, is the following:

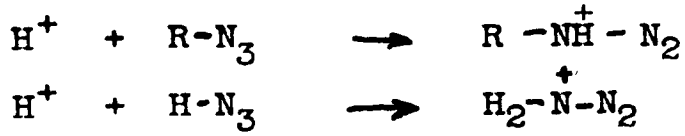
$$H^+ + R_2CO \rightleftharpoons R_2C^+ - OH$$



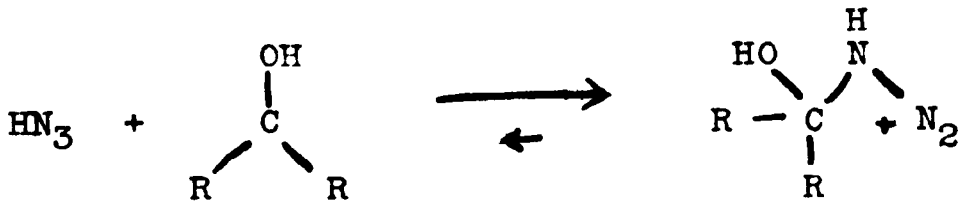
The action of hydrogen azide as a base (nucleophilic or electrodotic reagent) in the Schmidt reaction is suggested by the behavior of this compound toward carbon disulphide;[145]



and by the extremely rapid decomposition of hydrogen azide in strongly acid solutions, although as the undissociated acid in solution or as the anion it is quite stable in solution. Alkyl and aryl azides, with the same type of structure, likewise undergo decomposition in acid solution. Moreover, base-weakening groups increase the stability of azides to acid.[147] The initial step of acid-catalysed decomposition has been formulated as follows:[148]



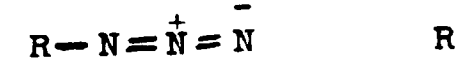
Hydrogen azide should be attacked even more energetically by the more powerfully electrophilic (acidic) carbonium ion than by reagents such as carbon disulphide and hydrated protons. Such an attack by a hydroxycarbonium ion might be indicated as follows:



Here, as in the simple decomposition of azides in acid solutions, decomposition has been postulated by the loss of nitrogen to form an electron-deficient particle, which subsequently undergoes rearrangement. Such a mechanism would imply that the relative extent of migration would be governed by the migration aptitudes of the groups attached to the original carbonyl group. It would also imply that the substitution of methyl azide for hydrogen azide would yield N-methylamides from ketones.

An experiment of this type has been made by treating benzophenone with methyl azide in concentrated sulphuric acid solution. The only product, isolated in low yield, was benzanilide, the normal product of the Schmidt reaction. No compounds containing methyl groups could be obtained except some undecomposed methyl azide.[9,59] However, alkyl azides have recently been found to undergo a Schmidt-type reaction with benzaldehyde, yielding N-alkylbenzamides.[149]

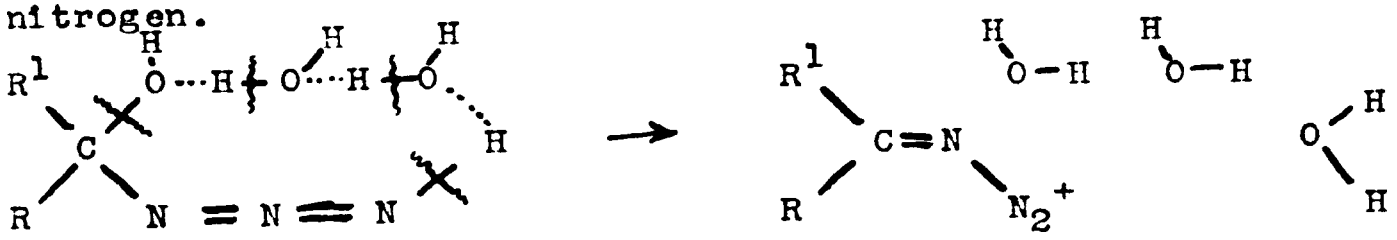
It is not possible to establish which nitrogen atom in hydrogen azide and other azides is the most basic, although the terminal nitrogens seem to be more nucleophilic than the center one. This might be expected from consideration of hydrazoic acid as "ammononitric acid" in the nitrogen system,[150] and from consideration of the principal canonical forms of hydrogen azide and the organic azides.



Irrespective of whether the proton adds preferentially to the nitrogen already substituted or not, rapid equilibrium between the resulting tautomers should be possible.

$$R-N=\overset{+}{N}=N-H \rightleftharpoons R-NH-\overset{+}{N}\equiv N$$

Since the energy barrier for the liberation of molecular nitrogen from a 1,3-disubstituted intermediate must be very large, it seems reasonable that the decomposition of azides in acid solution goes through the unsymmetrical intermediate. This would also be true to any mechanism for the Schmidt reaction in which rearrangement occurred while a hydrogen remained on one of the nitrogen atoms. In mechanisms for the Schmidt reaction which involve a dehydration step, the dehydration may also occur by removal of the proton from the terminal nitrogen.



The Iminodiazonium Ion

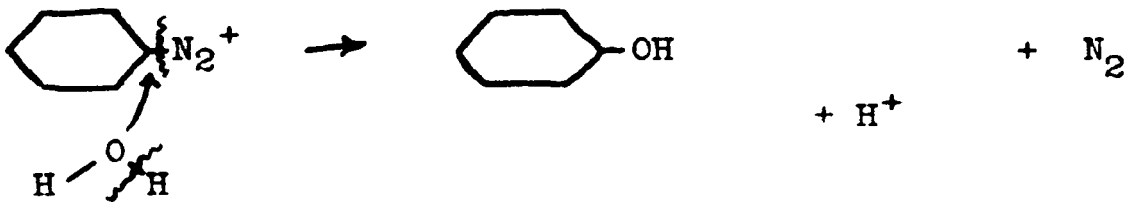
The next step in the two dehydration mechanisms involves a ketiminodiazonium ion. It should also be possible to prepare such an ion by the more familiar method - treatment of a suitable amine with nitrous acid. Hydrazine is known to give hydrogen azide on treatment with nitrous acid in the cold.[151] Analogously, hydrazones should give a corresponding product when treated with nitrous acid in the cold under non-hydrolysing conditions. This product should retain its original geometric configuration, since in such a reaction

the carbon-nitrogen double bond is not disturbed.



Following this reasoning, Pearson found that treatment of benzophenone hydrazone with nitrous acid at 0° in concentrated sulphuric acid gave benzanilide, the product of the Schmidt reaction on benzophenone.[152] It therefore seems reasonable that a ketimino-diazonium ion is, indeed, an intermediate in the Schmidt reaction. The iminodiazonium ion should be capable of existing in geometrically isomeric forms analogous to those of oximes and hydrazones. The nitrogen-nitrogen double bonds do not necessarily contribute to the geometrical isomerism. As in the case of oximes and hydrazones, one form would be generated faster than the other from unsymmetrical ketones, and one form, not necessarily the same one, will be more stable thermodynamically. The two forms would be capable of interconversion in the same ways that <u>syn</u>- and <u>anti</u>-oximes are interconverted: through the intervention of a catalyst or by a reversal of the path by which they were formed. The possibility of the formation of two geometrical isomers from an unsymmetrical ketone is the essential point of both the dehydration mechanisms, for it allows the ratio of the two isomers to determine the ratio of amides in the same way that the ratio of two oximes prepared from an unsymmetrical ketone determines the ratio of amides resulting from a Beckmann rearrangement.

The relative stability of a diazonium ion, such as the ketiminodiazonium intermediate, depends on the nature of the groups attached to it. As a general rule, all diazonium compounds are thermodynamically unstable with respect to loss of molecular nitrogen. The decomposition may be divided into those in which nitrogen is lost by intermolecular or intramolecular displacement, and those in which molecular nitrogen is lost unimolecularly, followed by further reaction of the residual cation. In the displacement reactions, displacement always occurs by attack of a nucleophilic group at the atom bearing the diazonium nitrogens, with simultaneous ejection of them as N_2. The energy of the reaction may be divided into the energy of formation of molecular nitrogen and the energy provided by the satisfaction of the deficiency in electrons in the diazonium group by the elctrons of the displacing base. Most reactions of aromatic diazonium ions fall into this class, of which an example is the production of phenol from benzene-diazonium chloride.



One possible mechanism for the decomposition of azides in strong acid is of this type,

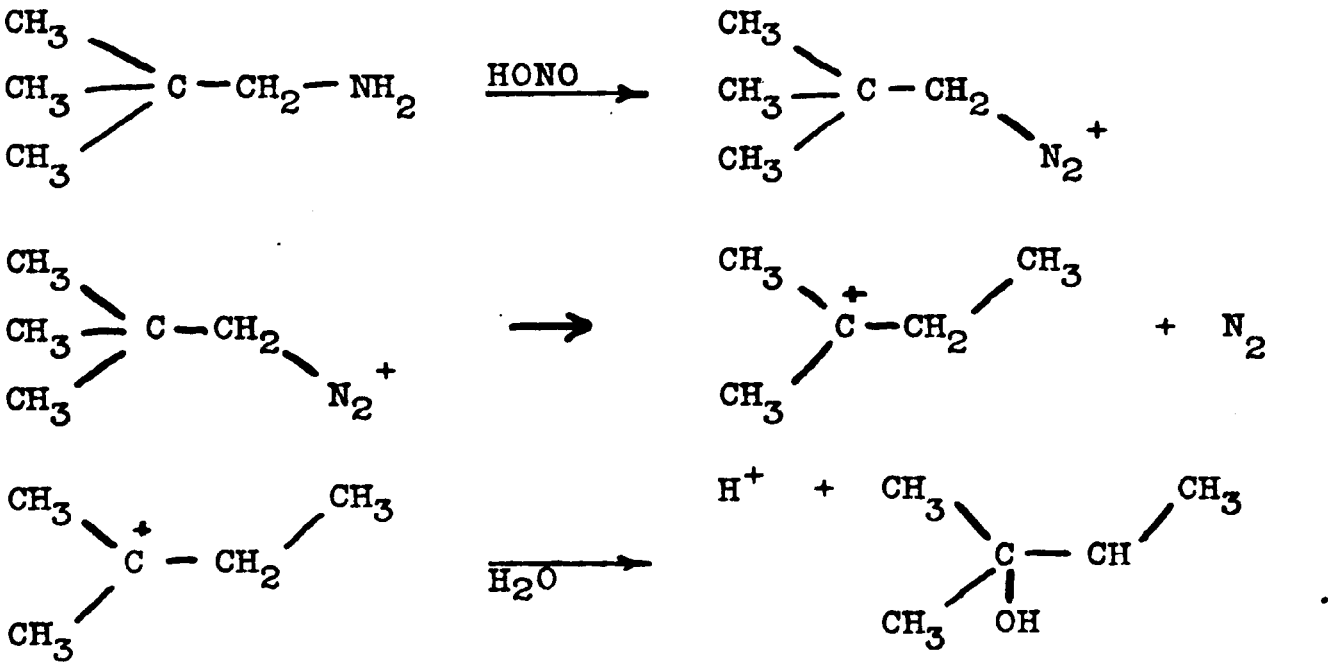
$$H-NH-N_2^+ + X^- \rightarrow H-NH-X + N_2$$

$$R-NH-N_2^+ + X^- \rightarrow R-NH-X + N_2$$.[147]

Internal displacements on diazonium ions are of the same

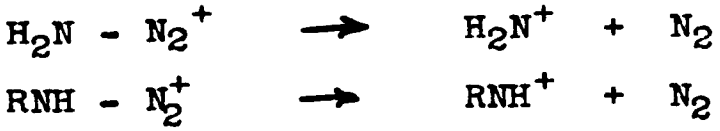
nature except that they involve a rearrangement wherein a group in the same molecule migrates from an adjacent atom to bearing the diazonium nitrogens. The driving force of the rearrangement consists of the energy of formation of molecular nitrogen less the energy necessary to create a new electron-deficient species.

The reaction of neopentylamine with nitrous acid to produce t-amyl alcohol[153] is an example of this type,

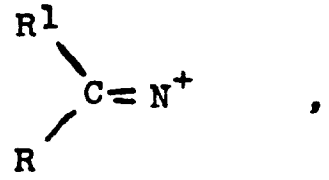


Those reactions which proceed by initial dissociation of the diazonium ion into molecular nitrogen leave an ion containing an electron-deficient atom as the other product.

This type of reaction sometimes occurs when displacement is impossible,[154] as appears to be the case in the conversion of l-apocamphylamine to l-apocamphyl alcohol. Azides may decompose in this manner in concentrated acid solutions. Preliminary dissociation of this type cannot be a factor in the

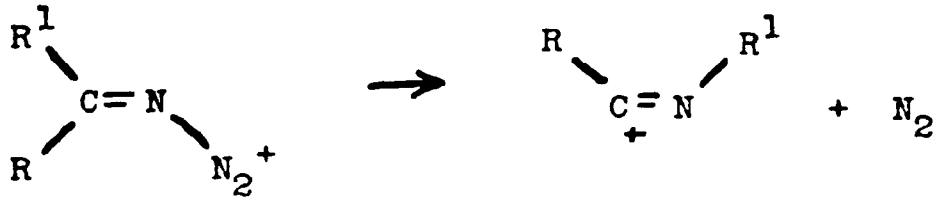


Schmidt reaction, because the resulting intermediate,



would be symmetrical, allowing an equal probability of migration to the nitrogen; this is not in accord with the experimental results from unsymmetrical ketones. Furthermore, displacement of the nitrogens of the diazonium ion by an external base cannot be a step in the Schmidt reaction because such a step would not lead to an iminocarbonium ion.

The formation of isoamylenes from neopentylamine as another product of nitrosation[155] can be considered as analogous to the rearrangement step in the single displacement process suggested for the Schmidt reaction.

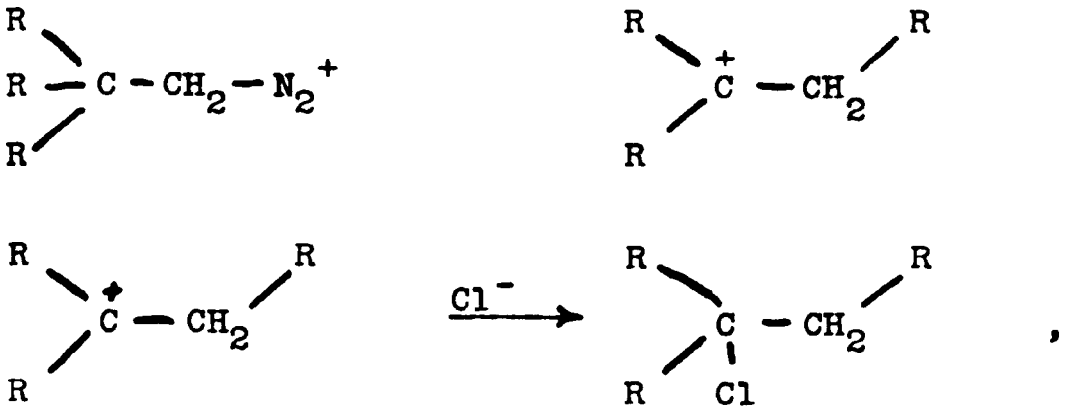


The second step in the neopentylamine reaction does not occur in the Schmidt reaction on ketones because the iminocarbonium ion has no properly situated proton which it might lose. However, the reaction on aldehydes, may undergo such a step.

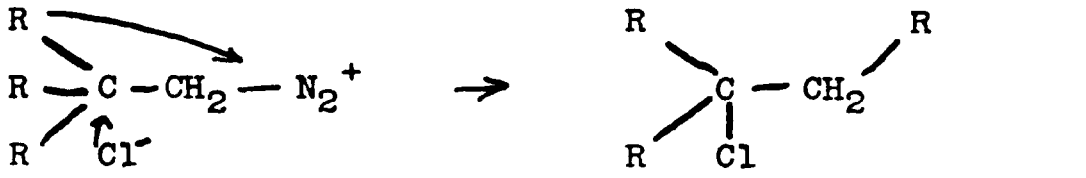


The production of alkyl chlorides by the diazotisation of alkyl amines with nitrous acid in the presence of large

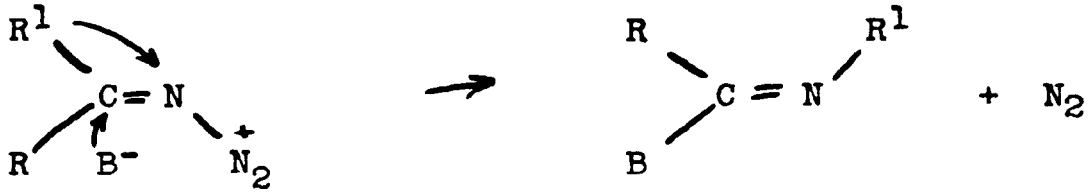
amounts of chloride ion[156] may, like the Schmidt reaction, be formulated by a single displacement mechanism.



or by a 'push-pull' mechanism,

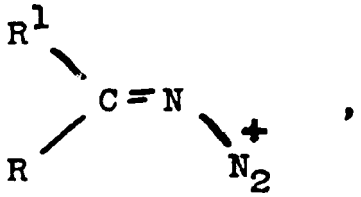


cf.

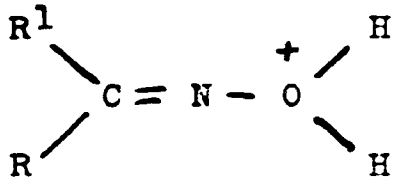


Here, as in the Schmidt reaction, the concerted displacement path may require a lower energy of activation, since the base (chloride ion) assists in the migration of the alkyl group with its electrons.

The iminodiazonium ion,



resembles the ketiminoxonium intermediate,

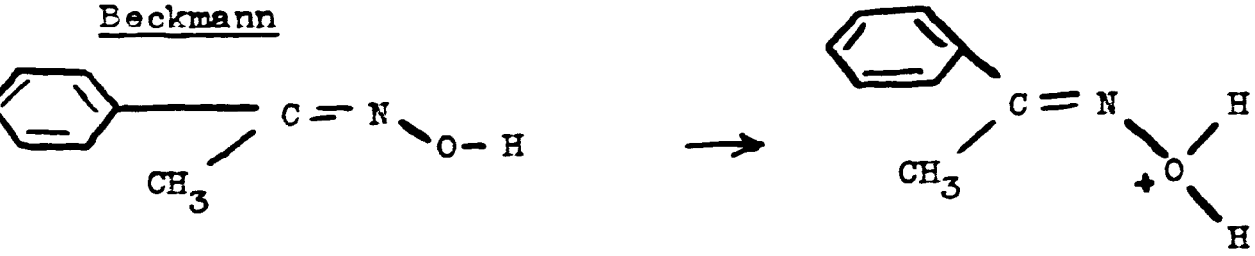


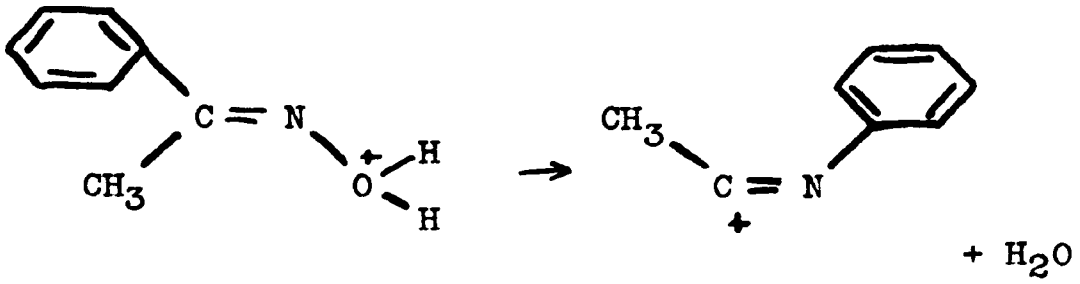
in the Beckmann rearrangement very closely. This Beckmann intermediate was first suggested by G. M. Bennett for the first stage of the acid-catalysed Beckmann rearrangement in non-aqueous solutions.[157] This mechanism was shown by Chapman[157] to apply to Lachman 's studies of the Beckmann rearrangement in aqueous hydrochloric acid.[158,159] This matter will be discussed further in connection with the iminocarbonium ion (p.126).

Further evidence for this iminoxonium intermediate in the Beckmann rearrangement is found in Hammett's discovery that the rate of the Beckmann rearrangement of benzophenone oxime concentrated sulphuric acid as measured by Lobry de Bruyn[160] is proportional to the h_o function (-log Ho).[133] The similarity between the iminodiazonium intermediate of the Schmidt reaction and the iminoöxonium intermediate of the Beckmann is indicative of the close relationship between these two reactions.

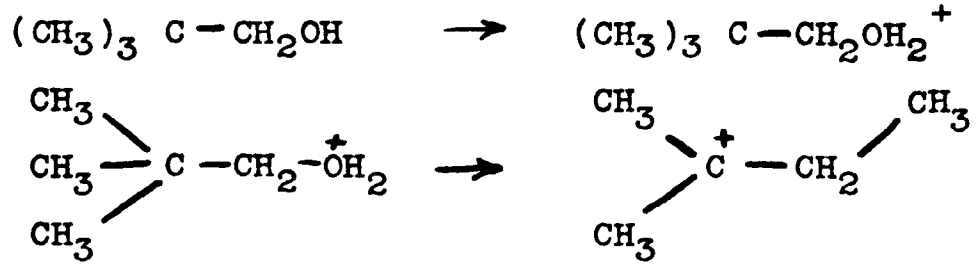
The Schmidt reaction is related to the Beckmann rearrangement in the same way as the rearrangement of aliphatic diazonium ions is related to the rearrangement of neopentyl alcohol in concentrated sulphuric acid.[161]

Beckmann

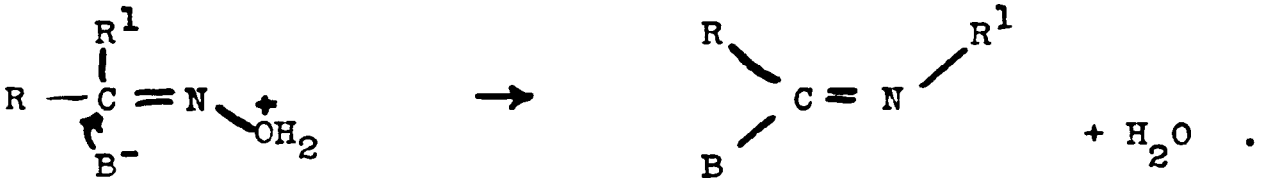




cf. Neopentyl alcohol



All of these rearrangements may, like the Schmidt reaction and the rearrangement of aliphatic diazonium ions, alternatively proceed by a 'push-pull' concerted displacement mechanism in which nucleophilic attack on the carbon bearing the migrating group lowers the activation energy in the transition state. In the case of the acid-catalysed Beckmann rearrangement, it is formulated thus:



The rearrangement of neopentyl alcohol with hydrobromic acid to give t-amyl bromide may be represented as follows:



Imino-Carbonium Ion

The initial product of rearrangement in the single

displacement version of the imino diazonium mechanism is an iminocarbonium ion, $R^1 - N = \overset{+}{C} - R$ (or $R^1 - \overset{+}{N} \equiv C - R$). This is the same type of ion initially formed in the acid-catalysed hydrolysis of cyanides and isocyanides.

$$R - C \equiv N + H^+ \longrightarrow R - C^{+} = NH$$

$$R - N = C + H^+ \longrightarrow R - N = \overset{+}{C}H \quad .$$

Salts of these ions have been isolated and analysed.[162,163]

Iminocarbonium ions similar to those of the Schmidt reaction appeared to have been formed during alkylation of cyanides by tertiary-butyl alcohol, isobutylene,[164,165,166] or formaldehyde[167,168] in concentrated sulphuric acid. Under the conditions of the alkylation, the iminocarbonium ion reacts with the elements of water to give amides. Isobutylene thus gives N-t-butylacetamide when treated with acetonitrile and sulphuric acid.

$$(CH_3)_2C = CH_2 \xrightarrow{H^+} (CH_3)_3\ C^+$$

$$(CH_3)_3\ C^+ + CH_3CN \longrightarrow (CH_3)_3\ C - N = \overset{+}{C} - CH_3$$

Likewise iminocarbonium ions appear to be produced from isonitriles in the Passerini reaction (the reverse of the "second order" Beckmann rearrangement[169]). The protonated aldehyde acts as the Lewis acid.

$$R - NC + CH_3\text{-}COOH + \phi - CH = O \qquad R - NH - \overset{O}{\overset{\|}{C}} - \overset{O}{\overset{|}{CH}} - \phi \qquad \overset{O}{\overset{\|}{O - C - CH_3}}$$

Cryoscopic studies of anilides have shown that they do not yield stable imino-carbonium ions in concentrated sulphuric acid.[170] Moreover, it seems improbable that even aliphatic amides form iminocarbonium ions under the conditions

of the Schmidt reaction, since amides can not be made to react with hydrogen azide under these conditions.[1,2]

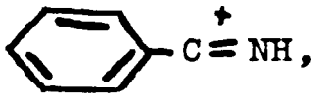
The hydrolysis intermediates of nitriles and carbylamines,

$R-C^{+}=NH$ and $R-N\overset{+}{=}CH$,

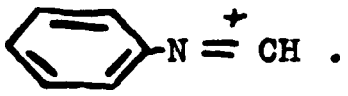
are actually the same species as would be predicted to be formed by the Schmidt reaction on the corresponding aldehydes, From benzaldehyde, for instance,



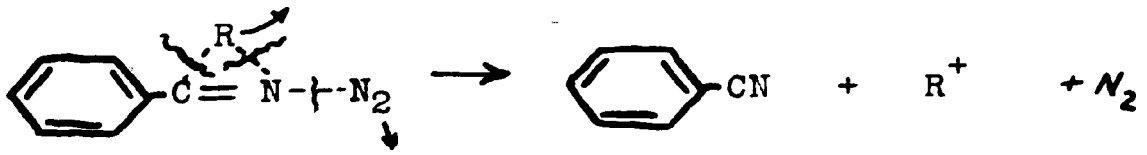
the intermediate leading to nitrile formation is



and the intermediate leading to formamide formation is

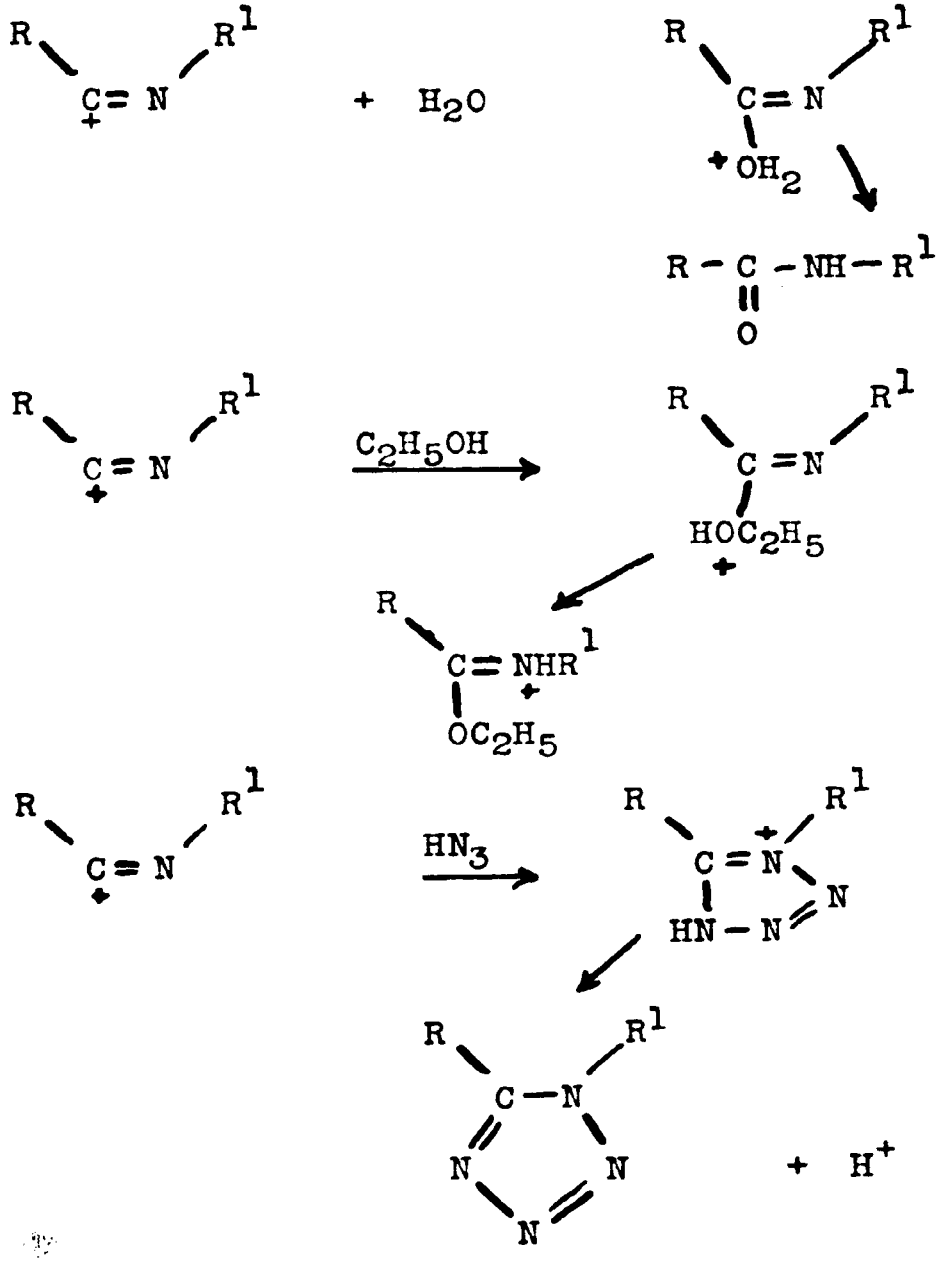


However, 'second order' reactions, such as the formation of nitriles from aldehydes need not go all the way to the iminocarbonium ion; double cleavage may occur in the transition state.



Such a process might partially account for the variation in yields of nitrile and formamide with different acid concentrations.

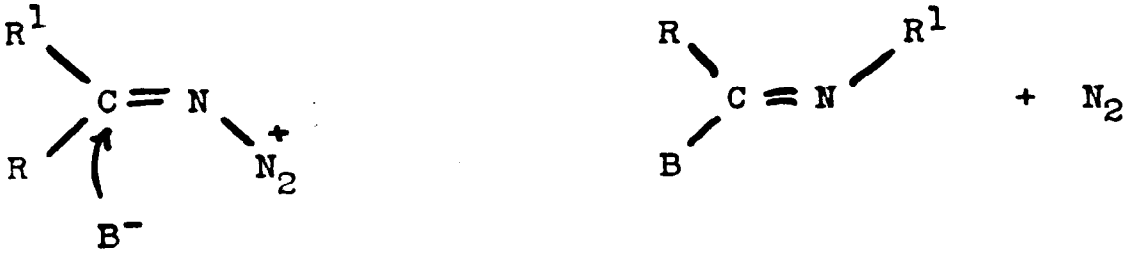
Iminocarbonium ions, once formed in the Schmidt reaction on ketones, may have only a transient existence due to their reactivity. Bases may attack the imino carbonium ion giving assorted derivatives.



This type of reaction accounts for the different products

when various reagents are introduced into the Schmidt reaction.

The alternative to rearrangement followed by stabilisation of the carbonium ion in discrete steps is a simultaneous process involving both of these steps. Attack by a base on the carbon adjacent to the nitrogen (potential carbonium ion) might assist the rearrangement by lowering its activation by lowering its activation energy. The deficiency resulting on the carbon from which the group is migrating could be compensated by the attacking base.



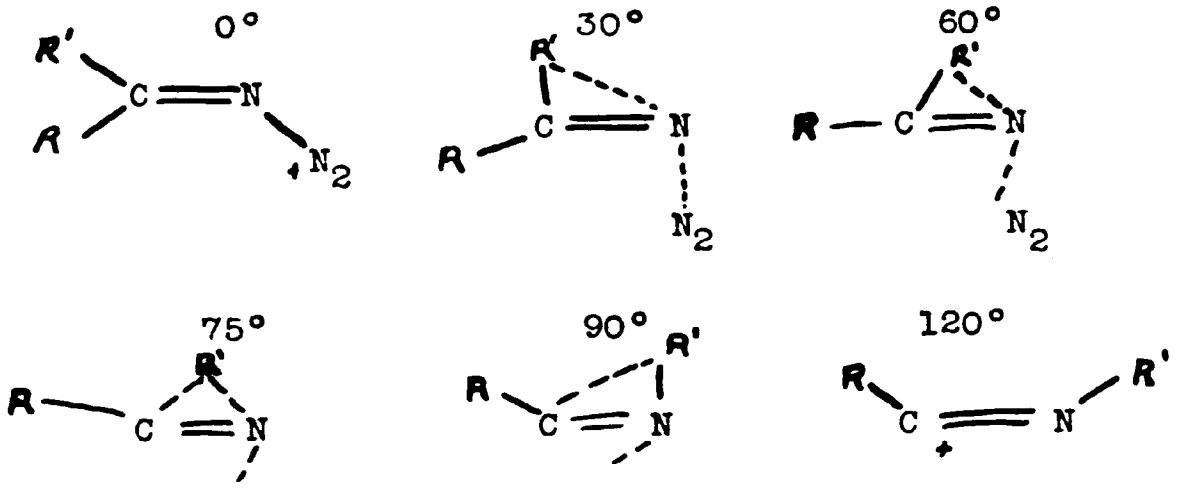
The same compounds would result from this participation as in the single displacement mechanism followed by basic attack.

This alternative process would yield the same apparent rate law as the single displacement dehydration process in solutions containing moderate amounts of hydroxylic species. Under anhydroxylic conditions, where a detectable difference in the rate-law would be expected, tetrazole formation becomes prominent, making rate measurements unreliable.

Mechanics of the Rearrangement

The process of migration during the rearrangement may be visualised rather simply by using transition state theory, (theory of absolute reaction rates).[77] The bond between the

migrating group and the carbon atom to which it is attached gradually stretches and weakens while binding gradually increases between the nitrogen atom and the migrating group. Simultaneously the binding between the retained nitrogen atom and the nitrogen atoms which leave weakens, leaving the positive charge on the iminocarbonium ion.



This interpretation is a modification of the three-center transition state suggested by Shilov[171] for the Beckmann and other rearrangements. It is known that the group migrating to the nitrogen atom in the rearrangement never becomes free of the molecule, since no migrating group has been found which either isomerises or loses its optical asymmetry.[172] Trans-migration has been assumed by analogy to the Beckmann rearrangement, where trans-migration has been confirmed by much independent chemical evidence.[173,174,175,176,177] Trans-migration is much more probable stereochemically.[178] The displacement attack on the nitrogen atom is the same type of attack which occurs in Walden inversions. Inversion of the nitrogen, of course, can not be detected. The orientation

of the non-migrating group with respect to the double bond may also be shifted; but, likewise, can not be detected. In the concerted displacement mechanism, preliminary attack by the base may come from above or below the carbon-nitrogen double bond, shifting as it nears the plane of the bond (and rearrangement proceeds) to the side opposite to that from which the migrating group is leaving. No ultimate asymmetry is introduced by this process, however.

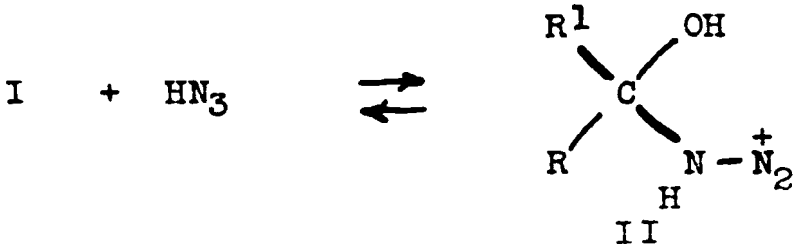
SUMMARY

The Schmidt reaction of hydrogen azide and ketones in the presence of an acid catalyst has been here examined kinetically with cyclohexanone, diisopropyl ketone and acetophenon. Aqueous solutions of hydrochloric and sulphuric acids and solutions of ethanesulphonic acid in several organic solvents were used. The rate in all cases could be expressed by $\frac{d(N_2)}{dt} = K_3\,(\text{ketone})(HN_3)h_o$. It was shown that, as had already been qualitatively established, temperature effects are large. The acid employed in the Schmidt reaction only affected the rate of reaction in so far as it determined the proton-donating intensity (h_o) of the solution. Amides, the expected products of the Schmidt reaction, did not affect the rate except in so far as they lowered the h_o of the solution. Metallic ions in small amounts did not affect the rate of the reaction. The lack of change in rate constant with change in the dipole moment of the solvent indicates the rate-determining step in the Schmidt reaction (presumably the rearrangement) does not involve a change in the number of ions.

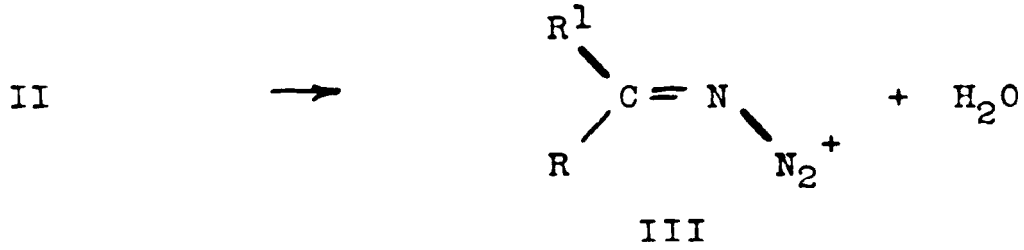
On the basis of these results, and by comparison with non-kinetic information on the Schmidt and other reactions, two mechanisms for the Schmidt reaction, both involving a dehydration step, have been found satisfactory.

I. Single-Displacement Mechanism.

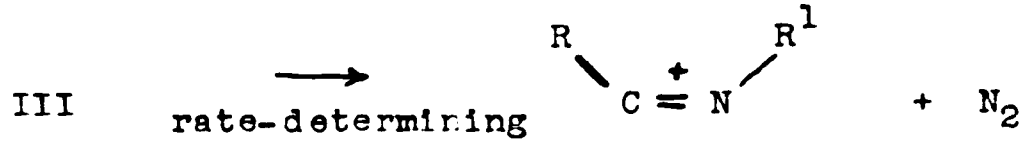
(1) $H^+ + R^1(R)C{=}O \rightleftharpoons R^1(R)\overset{+}{C}{-}OH$ (I)

(2) 

II

(3) 

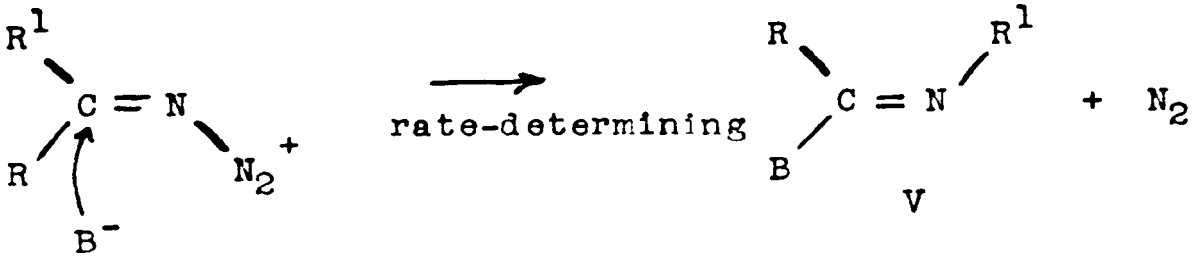
III

(4) 

(5) 

II. Concerted-Displacement Mechanism.

The first three steps are the same.

(4) 

V

If B^- is H_2O, V is the conjugate acid of the amide.

APPENDIX

Discussion of Vapor Pressure Correction and Ψ - Rate Constants

In any reaction which depends on only one varying component, the rate equation is

$$\frac{dx}{dt} = k\,(a - x)^n .$$

When x is determined from the volume of gas evolved, it will not be known accurately unless the vapor pressure of the solution under study is known accurately. However, if the volume of the gas is corrected only for temperature and pressure, the apparent value for x thus obtained, will always be a constant (the vapor correction) times the real value of x. Insertion of this apparent value of x for the real value in rate calculations does not give consistent results for any rational rate-law. If instead, the apparent value of $y = (a - x)$ be used, satisfactory rate constants may be obtained. The apparent value of y may be found by measuring the difference between the apparent value of x at the completion of the reaction and apparent value of x at any time during the reaction. Thus $y_{app.} = (x_f - x_{app.}) = (v_f - v)\left(\frac{273}{T}\right)\left(\frac{p}{760}\right)$. Now $y_{app.}$ will differ from the true y by the vapor pressure correction ; $y_{app.} = y\psi$. Since $dy = d(a - x) = -dx$, the differential equation may be written, $\frac{dy}{dt} = ky^n$. If y be used instead, this becomes $\frac{d(\psi y)}{dt} = -k_\psi(\psi y)^n$, and $\psi\frac{dy}{dt} = +\psi^n(-k_\psi y)^n$. It will be seen that the rate constant derived by this substitution is ψ^{n-1} times the correct rate constant. Thus, for first order reactions, $\psi^{n-1} = 1$, and the pseudo rate constant found in this way is the same as the

real rate constant. For higher orders the two constants will be related by a constant parameter for each solution of different vapor pressure. This treatment then enables the true order of the reaction to be found, even though there is an unknown vapor pressure correction.

In systems in which the rate of reaction depends on two varying components, the rate equation is

$$\frac{dx}{dt} = k\,(a - x)^n\,(b - x)^m \,.$$

When a and b, the concentrations of the two substrates, are different, the rate equation may be cast into the form

$$\frac{dy}{dt} = -k\,y^n\,(b - a + y)^m \,,$$

where y is defined in the same way as above. If y is also formulated in the same way, the pseudo-rate equation will be

$$\frac{d\psi y}{dt} = -k_\psi(\psi y)^n\,(b - a + \psi y)^m$$

$$\psi\frac{dy}{dt} = -\psi^n\,k_\psi y^n\,(b - a + \psi y)^m \,.$$

The relationship between k_ψ and k is then,

$$k = \frac{k_\psi}{\psi^{n-1}}\;\frac{(b - a + \psi y)^m}{(b - a + y)^m}$$

$$k = \frac{1}{\psi^{n-1}}\;k_\psi\left\{\frac{(1 + \frac{y}{b - a})^m}{(1 + \frac{y}{b - a})^m}\right\}$$

Using the binomial expansion

$$\left[\frac{1}{1 + (\frac{y}{b - a})}\right]^m = \left[1 - \frac{y}{b - a} - \frac{y^2}{(b - a)^2} - \frac{y^3}{(b - a)^3}\right]^m ;$$

this becomes,

$$\left(\frac{1}{1 + \frac{y}{b - a}}\right)^m \simeq 1 - \frac{y}{b - a} \,,$$ on dropping higher terms in $\frac{y}{b - a}$.

Then $k = k_\psi \frac{1}{\psi^{n-1}} (1 + \frac{\psi y}{b - a})^m (1 - \frac{y}{b - a})^m$

Expanding both terms by the binomial theorem, and again dropping higher terms in $\frac{\psi y}{b - a}$ and $\frac{y}{b - a}$,

$$k = k_\psi \frac{1}{\psi^{n-1}} (1 + m \frac{\psi y}{b - a} + \cdots) (1 - \frac{my}{b - a}) .$$

Multiplying the factors and again dropping the higher terms in $\frac{y}{b - a}$,

$$k = k_\psi \frac{1}{\psi^{n-1}} \left[1 + \frac{my}{b - a} (\psi - 1) + \right] .$$

This implies that the true rate constant will be a constant parameter times the apparent rate constant, minus a small correction factor. This factor was disregarded in the rate calculations, and may account for small drifts in the non-aqueous solutions occurring when the amount of ketone used was small.

BIBLIOGRAPHY

1. K. F. Schmidt, Z. angew. Chem., 36, 511, (1923)
2. K. F. Schmidt, Acta acad. Aboensis, Math. et Phys., (2), 38, 1924) [C. A., 19, 3248,(1925)]
3. K. F. Schmidt, Ber., 57, 704 (1924)
4. cf. T. Curtius and J. Rissom, J. pr. chem., (2), 58, 261, (1892) 161, 261 (1898)
5. J. von Braun, Ann., 490, 100, (1931)
6. J. von Braun and E. Anton, Ber., 64, 2865, (1936)
7. Schattner, thesis, Heidelberg, 1929
8. J. von Braun and A. Heymons, Ber., 63, 502, (1950)
9. L. H. Briggs, G. C. De Ath, and S. R. Ellis, J. Chem. Soc., 1942, 61
10. K. F. Schmidt and S. Strzygowski, Germ. Pat. 500,435 [Frdl., 17, 2612, (1932)]
11. K. F. Schmidt and S. Strzygowski, U. S. Pat. 1,926,756 [C. A., 27, 5752, (1933)]
12. M. Oesterlin, Z. angew. Chem., 45, 536, (1932)
13. R. Fusco and S. Rossi, Gazz., 81, 511, (1951)
14. H. Schecter and J. C. Kirk, J. Am. Chem. Soc., 73, 3087, (1951)
15. D. W. Adamson, J. Chem. Soc., 1939, 1564
16. K. F. Schmidt, Germ. Pat. 427,858 [Frdl., 15, 221 (1928)]
17. K. F. Schmidt, U. S. Pat. 1,564,631 [C. A., 20, 423, (1926)]
18. L. Ruzicka, M. W. Goldberg, and M. Hurbin, Helv. Chim. Acta., 16, 1335, (1933)
19. M. A. Spielman and F. L. Austin, J. Am. Chem. Soc., 59, 2658, (1937)
20. K. F. Schmidt, Germ. Pat. 439,041 [Frdl., 15, 333 (1930)]

21. K. F. Schmidt, U. S. Pat. 1,599,493 [C. A., 20, 3460, (1926)]

22. K. F. Schmidt, Brit. Pat. 250,897 [C. A., 21, 1272, (1927)]

23. K. F. Schmidt and P. Zutauern, Germ. Pat. 455,585 [Frdl., 16, 2862 (1931)]

24. K. F. Schmidt and P. Zutauern, U. S. Pat. 1,637,661 [C. A., 21, 3057, (1927)]

25. K. F. Schmidt and P. Zutauern, Germ. Pat. 488,447 [H. Wolff in "Organic Reactions", Vol. 3, John Wiley and Sons, New York, 1946, p.318]

26. K. F. Schmidt and P. Zutauern, U. S. Pat. 1,889,323 [C. A., 27, 1361, (1933)]

27. K. F. Schmidt, Germ. Pat. 544,890 [Ref. 25, p. 311]

28. K. F. Schmidt, Germ. Pat. 606,615 [C. A., 29, 3690^3, (1935)]

29. K. F. Schmidt, U. S. Pat. 2,029,799 [C. A., 30, 1950^6 (1936)]

30. S. E. Janson and W. J. Pope, Chem. and Industry, 51, 316, (1932)

31. S. E. Janson and W. J. Pope, Proc. Roy. Soc., London, A154, 53, (1936)

32. E. R. Buchman, A. O. Reims, T. Skei, and M. J. Schatter, J. Am. Chem. Soc., 64, 2696, (1942)

33. H. Arnold, Ber., 76, 777, (1943)

34. L. H. Briggs and G. C. De Ath, J. Chem. Soc., 1937, 456

35. V. Prelog and K. Božičević, Ber., 72, 1103, (1939)

36. V. Prelog, E. Cerkovnikov, and G. Ustricev, Ann., 535, 37, (1938)

37. V. Prelog, N. Šoštarić, and E. Guštav, Ann., 545, 247, (1940)

38. V. Prelog, S. Heimbach, and A. Režek, Ann., 545, 231, (1940)

39. V. Prelog, S. Heimbach, and Seiwerth, Ber., 72, 1319, (1939)

40. V. Prelog and B. Schönbaum, Ann., 545, 256, (1940)

41. V. Prelog and R. Seiwerth, Ber., 72, 1638, (1939)

42. E. Cerkovnikov and V. Prelog, Ber., 74, 1648, (1941) C. A., 37, 125, (1943)

43. J. von Braun and W. Pinkernelle, Ber., 67, 1056, (1934)

44. J. von Braun, Ber., 67, 218, (1934)

45. T. Cosciug, Wien. Chem. Ztg., 46, 145 (1943), C. A., 38, 4575, (1944)

46. L. Ruzicka, M. W. Goldberg, M. Hurbin, and H. A. Boecknoogen, Helv. Chim. Acta, 16, 1323, (1933)

47. L. Ruzicka, M. Kobelt, O. Haflinger, and V. Prelog, Helv. Chim. Acta., 32, 544, (1949)

48. Ref. No. 25, entire chapter.

49. V. A. Petrow, J. Chem. Soc., 1946, 200-3

50. L. Ruzicka, C. F. Seidel, W. Brugger, Helv. Chim. Acta, 30, 2168-98, (1947)

51. J. R. Dice and P. A. S. Smith, J. Org. Chem., 14, 179-93, (1949)

52. N. Campbell, W. K. Leadill, and J. F. K. Wilshire, J. Chem. Soc., 1951, 1404

53. D. V. Nightingale and R. M. Brooker, J. Am. Chem. Soc., 72, 3339, (1950)

54. C. Schuerch, Jr., and E. H. Huntress, J. Am. Chem. Soc., 71, 2233, (1949)

55. C. Schuerch, Jr. and E. H. Huntress, J. Am. Chem. Soc., 71, 2238, (1949)

56. C. S. Schuerch, J. Am. Chem. Soc., 70, 2293 (1948)

57. P. A. S. Smith and T.-Y. Yu, J. Org. Chem., in press (1952)

58. W. E. McEwen, W. E. Conrad, and Calvin A. Vanderwerf, J. Am. Chem. Soc., 74, 1168 (1952)

59. P. A. S. Smith, J. Am. Chem. Soc., 70, 320, (1948)

60. P. A. S. Smith and J. P. Horwitz, J. Am. Chem. Soc., 72, 3718 (1950)

61. G. Caronna, Gazz., 71, 481 (1941)

62. G. Caronna, Gazz., 79, 326, (1949)

63. G. Caronna, Gazz., 79, 603, (1949)

64. G. Caronna, Gazz., 80, 211, (1950)

65. E. F. M. Stephenson, J. Chem. Soc., 1949, 2620

65a. A. G. Caldwell and L. P. Walls, J. Chem. Soc., 1952, 2156

66. G. Caronna, Gazz., 80, 675, (1950)

67. J. K. Sanford, F. T. Blair, J. Arroya and K. W. Sherk, J. Amer. Chem. Soc., 67, 1941, (1945)

68. Handbook of Chem. and Phys., 27th ed., 1943, Chemical Rubber Publishing Co.

69. P. A. S. Smith, unpublished observation

70. G. N. Lewis, Valence and the Structure of Atoms and Molecules, Chem. Cat. Co., New York, 1920, 142

71. L. H. Briggs and J. C. Lyttleton, J. Chem. Soc., 1943, 421

72. J. von Braun and W. Keller, Ber., 65, 1677, (1932)

73. R. M. Herbst, C. W. Roberts and E. J. Harvill, J. Org. Chem., 16, 139, (1950)

74. J. S. Mihina and R. M. Herbst, J. Org. Chem., 15, 1082, (1949)

75. Ref. 25, p. 328

76. K. F. Schmidt, Ber., 58, 2413, (1925)

77. H. Eyring and M. Polanyi, Z. physik. Chem., 12B, 279, (1931)

78. H. E. M. Specht, A. W. Browne, and K. W. Sherk, J. Am. Chem. Soc., 61, 1083, (1939)

79. E. Oliveri-Mandalà, Gazz. chim. ital., 55, 271, (1925)

80. A. Angeli in Ahren's Sammlung chem. u chem.-tech. Vorträge, 13, prof. Ferdinand Enke, Stuttgart, 1908

81. A. A. Morton, "The Chemistry of Heterocyclic Compounds", McGraw-Hill Book Co., New York, 1946

82. L. I. Smith, Chem. Rev., 23, 193, (1938)

83. F. Schlotterbeck, Ber., 40B, 479, (1907)

84. J. Stieglitz, Am. Chem. J., 29, 49 (1903)

85. T. Curtius, J. prakt. chem., (2) 50, 275 (1894)

86. F. C. Whitmore, "Organic Chemistry", 1st ed., D. Van Nostrand and Co., New York, 1937, p. 305

87. D. T. Hurd, in Gilman's "Treatise on Organic Chemistry", John Wiley and Sons, New York, 1st ed., 1938, p. 700

88. F. S. Kepping, J. Chem. Soc., 65, 480, (1894)

89. L. H. Briggs and J. W. Lyttleton, J. Chem. Soc., 1943, 421

90. P. A. S. Smith, Thesis, "Reaction Mechanisms Involving the Radical NH", Univ. of Michigan, 1944, pp. 16-17.

91. R. N. Keller and P. A. S. Smith, J. Am. Chem. Soc., 66, 1122, (1944)

92. J. B. Conant and P. D. Bartlett, J. Am. Chem. Soc., 61, 1083, (1939)

93. F. H. Westheimer, J. Am. Chem. Soc., 56, 1162, (1934)

94. A. Oläander, Z. physik. Chem., 129, 1, (1927)

95. M. S. Newman and H. Gildenhorn, J. Am. Chem. Soc., 70, 317, (1948)

96. M. S. Newman, J. Am. Chem. Soc., 63, 2431, (1941)

97. S. C. Bunche with J. B. Cloke, 33M, Abstracts of the Meeting of the American Chemical Society, 1951

98. E. Fitzgerald and A. Lapworth, J. Chem. Soc., 93, 2163, (1908)

99. L. P. Hammett, "Physical Organic Chemistry", McGraw-Hill Book Co., Inc., New York, 1940, Chap. VII-IX.

100. R. P. Bell, "Acid-Base Catalysis", Oxford University Press, London, 1941

101. W. Stanford and S. C. Gordy, J. Chem. Physics, 8, 170, (1940)

102. L. A. Flexser, L. P. Hammett, and A. Dingwall, J. Am. Chem. Soc., 57, 2103, (1935)

103. L. A. Flexser and L. P. Hammett, J. Am. Chem. Soc., 60, 885, (1938)

104. L. Zucker and L. P. Hammett, J. Am. Chem. Soc., 61, 2785, (1939)

105. W. Stanford and S. C. Gordy, J. Chem. Phys., 9, 204, (1941)

106. M. H. Earing with J. B. Cloke, 81L, Abstracts of 117th Meeting of the American Chemical Society, 1950

107. L. P. Hammett, Chem. Rev., 16, 67, (1935)

108. A. W. Chapman and C. C. Howis, J. Chem. Soc., 1933, 806

109. A. W. Chapman, J. Chem. Soc., 1934, 1550

110. A. W. Chapman and F. A. Fidler, J. Chem. Soc., 1936, 448

111. L. P. Kuhn and A. H. Corwin, J. Am. Chem. Soc., 70, 3370, (1948)

112. H. Eyring and F. Daniels, J. Am. Chem. Soc., 52, 1472-86, (1930)

113. H. Eyring and F. Daniels, J. Am. Chem. Soc., 52, 1486-92, (1930)

114. T. Curtius, J. prakt. Chem., (2) 38, 396, (1888)

115. G. Bredig and P. F. Ripley, Ber., 40, 4015, (1907)

116. J. N. Brønsted and H. C. Duus, Z. physik, Chem., 117, 299, (1925)

117. G. Bredig and W. Fraenkel, Z. Electrochem., 11, 525, (1905)

118. J. N. Brønsted and R. P. Bell, J. Am. Chem. Soc., 53, 2478, (1931)

119. D. D. van Slyke, J. Biol. Chem., 9, 275, (1911)

120. e.g. F. Pregl, "Quantitative organische Mikroanalyse", 4th ed., Julius Springer, Berlin, 1935, p. 204

121. J. Hausser and P. T. Muller, Bull. soc. chim., (3) I, 721, (1891)

122. A. Hantzsch, Ber., 33, 2517, (1900)

123. J. C. Cain and F. Nickoll, J. Chem. Soc., 81, 1412, (1902)

124. J. Reilly and W. N. Rae, "Physico-chemical Methods", D. Van Nostrand Co., Inc., New York, 2nd ed., 1948, v. 3., Kinetics Chapter

125. J. Reilly and D. Madden, J. Chem. Soc., 127, 2936, (1925)

126. e.g. reference 120, p. 84

127. C. Drucker, ed., "Ostwald-Luther: Hand-und Hilfsbuch zur Ausführung Physikochemischer Messungen", 5th ed., Akademische Verlagsgesellschaft m.b.H., Leipzig, 1931

128. L. F. Fieser, "Experiments in Organic Chemistry, Part II", John Wiley and Sons, New York, 2nd ed., 1941, p. 308

129. Ref. 128, p. 309

130. Ref. 127, p. 729

131. V. Meyer and A. Warrington, Ber., 20, 505, (1887)

132. Ref. 99, p. 271

133. L. P. Hammett and P. J. Deyrup, J. Am. Chem. Soc., 54, 2721, (1932)

134. L. P. Hammett and M. A. Paul, J. Am. Chem. Soc., 56, 830, (1934)

135. N. C. Deno, J. Am. Chem. Soc., 74, 2039, (1952)

136. G. N. Lewis and J. Biegeleisen, J. Am. Chem. Soc., 65, 1144, (1943)

137. H. A. E. Mackenzie and E. R. S. Winter, Trans. Faraday Soc., 44, 159, (1948)

138. H. S. Harned and R. W. Ehlers, J. Am. Chem. Soc., 55, 2179, (1933)

139. H. S. Harned and W. J. Hamer, J. Am. Chem. Soc., 57, 27, (1935)

140. M. S. Newman, H. G. Kuivila, and A. B. Garrett, J. Am. Chem. Soc., 67, 704, (1945)

141. M. S. Newman, R. A. Craig, and A. B. Garrett, J. Am. Chem. Soc., 71, 869, (1949)

142. H. Meerwein and K. van Emster, Ber., 55, 2500, (1922)

143. P. D. Bartlett and I. Pockel, J. Am. Chem. Soc., 60, 1585, (1938)

144. C. Friedel and J. M. Crafts, Compt. rendu, 84, 1392, 1450, (1877)

145. G. B. L. Smith, F. Wilcoxon, and A. W. Browne, J. Am. Chem. Soc., 45, 2604, (1923)

146. E. Bamberger, Ann., 424, 252, (1921)

147. P. A. S. Smith and B. B. Brown, J. Am. Chem. Soc., 73, 2438, (1951)

148. K. W. Sherk, A. Houpt, and A. Browne, J. Am. Chem. Soc., 62, 329, (1940)

149. J. H. Boyer, unpublished results

150. E. C. Franklin, Chem. Rev., 14, 721, (1934)

151. T. Curtius, Ber., 23, 3023, (1890)

152. D. E. Pearson, J. Am. Chem. Soc., 71, 1895, (1949)

153. M. Freund and F. Lenze, Ber., 24, 2150, (1891)

154. P. D. Bartlett and L. H. Knox, J. Am. Chem. Soc., 61, 3184, (1939)

155. J. F. Norris and F. Cortese, J. Am. Chem. Soc., 49, 2640, (1929)

156. F. C. Whitmore and D. P. Langlois, J. Am. Chem. Soc., 54, 3442, (1932)

157. A. W. Chapman, J. Chem. Soc., 1935, 1223

158. A. Lachman, J. Am. Chem. Soc., 46, 1477, (1924)

159. A. Lachman, J. Am. Chem. Soc., 47, 260, (1925)

160. C. A. Lobry de Bruyn and Sluiter, Kgl. akad. wetenschappen, abdeling der wissen, 13, 813, (1904) [Ref. 133]

161. F. C. Whitmore and H. S. Rothbeck, J. Am. Chem. Soc., 54, 3431, (1932)

162. A. Gautier, Ann. chim., [4] 17, 176, (1869)

163. A. Gautier, Ann. chim., [4] 17, 222, (1869)

164. J. J. Ritter and P. P. Mineri, J. Am. Chem. Soc., 70, 4045, (1948)

165. J. J. Ritter and J. Kalish, J. Am. Chem. Soc., 70, 4048, (1948)

166. F. R. Benson with J. J. Ritter, J. Am. Chem. Soc., 71, 4178, (1949)

167. B. F. Faris, E. E. Magat, J. E. Reith, and L. F. Salisbury, 19L, Abstracts of the 117th Meeting of the American Chemical Society, 1950

168. L. B. Chandler, B. F. Faris, E. E. Magat, J. E. Reith, and L. F. Salisbury, 20L, Abstracts of the 117th Meeting of the American Chemical Society, 1950

169. P. A. S. Smith, quoted in R. H. Baker and D. Stanonis, J. Am. Chem. Soc., 73, 701, (1952)

170. M. S. Newman and N. C. Deno, J. Am. Chem. Soc., 73, 3652, (1951)

171. E. A. Shilov, Doklady Akad. Nauk. S. S. S. R., 30, 219-22, (1941)

172. A. Campbell and J. Kenyon, J. Chem. Soc., 1946, 125

173. J. Meisenheimer, Ber., 54, 3206, (1921)

174. J. Meisenheimer and H. Lange, Ber., 57, 282, (1924)

175. J. Meisenheimer, P. Zimmerman, V. von Kummer, Ann., 446, 205, (1925)

176. J. Meisenheimer, W. Theilacker, and D. Beisswenger, Ann., 495, 249, (1932)

177. L. E. Sutton and T. W. J. Taylor, H. Chem. Soc., 1931, 2190

178. W. H. Mills, Chemistry and Industry, 10, 750, (1932)