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PART I

The Effect of Structure on The Course of The Schmidt Reaction on Unsymmetrical Ketones

PART II

The Preparation of Some Substituted Succinic Acids

by

Jerome Philip Horwitz

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy in the
University of Michigan
1949

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PART I

A. Historical

In 1923 Karl Frederick Schmidt reported a reaction between carbonyl compounds and hydrazoic acid while studying the decomposition of hydrazoic acid by sulfuric acid.(63) His observation showed that benzene accelerated this decomposition and that the products obtained differed according to the temperature at which the reaction was carried out; at room temperature hydrazine sulfate was the chief product, whereas at a temperature of 60-70° aniline sulfate was formed in good yields. Acting on the hypothesis that during the decomposition of hydrazoic acid a free imide radical (NH) is formed which is capable of adding to a reactive group, Schmidt added benzophenone to the reaction mixture and obtained a quantitative yield of benzanilide.(62)

Since its inception, an imposing number of carbonyl compounds have been submitted to the Schmidt reaction which includes acids, aldehydes, quinones, lactones, anhydrides, esters and acid halides. The results to date have been tabulated and well summarized by Wolff.(76)

B. Mechanism of the Schmidt Reaction

The first attempted explanation of this reaction was offered by the author himself. Schmidt proposed a mechanism in which the hydrazoic acid is cleaved by strong mineral acid to nitrogen and the imide radical which may then react with benzene

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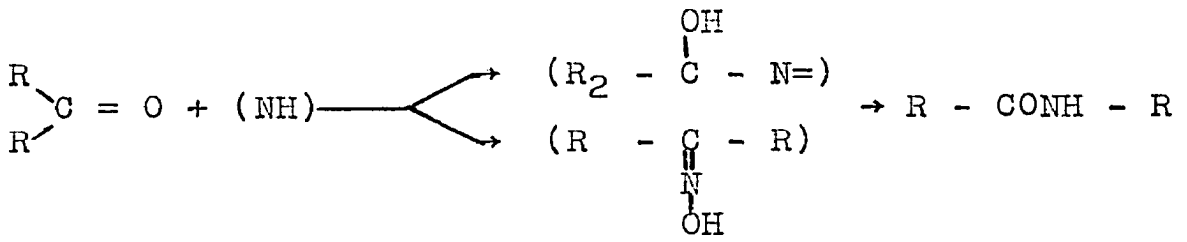
or water to produce aniline sulfate or hydroxylamine sulfate respectively. Polymerization, followed by disproportionation of the residue, produces hydrazine.

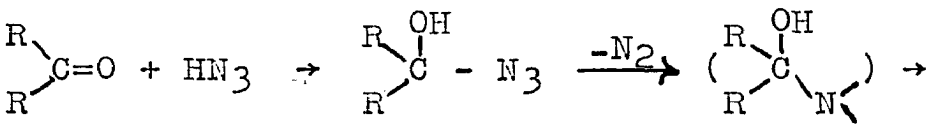
a) $HN_3 \xrightarrow{H_2SO_4} (NH) + N_2$

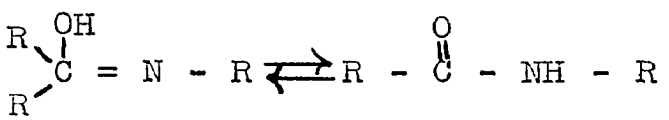
b) $4(NH) \rightarrow 2(H\text{-}N{=}N\text{-}H) \rightarrow N_2 + H_2N\text{-}NH_2$

In the presence of a carbonyl compound he further hypothesized that the radical added to the carbonyl group, followed by a rearrangement directly or by a Beckmann transformation



In 1925 Oliveri-Mandala[53] advanced a mechanism based on the addition of hydrazoic acid to the carbonyl group with subsequent elimination of nitrogen and rearrangement to the amide.





There is strong evidence to show that the mechanism as proposed by Schmidt is incorrect. If the imino radical is involved, the rate of reaction should be controlled by the rate of decomposition of hydrazoic acid. Schmidt, himself,

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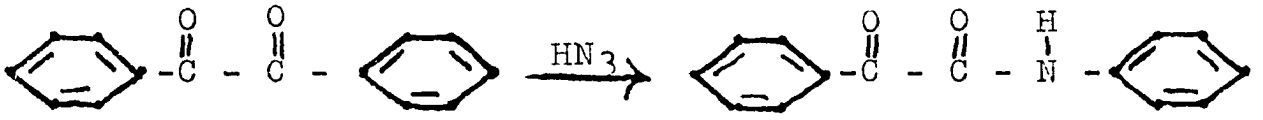
found, however, that the decomposition does not occur below 30° and even at 60-70° it is incomplete after five hours, whereas a number of ketones, e.g. cyclohexanone and benzylacetone, react vigorously at 0°. That the oxime is also not an intermediate as postulated by Schmidt is demonstrated by the fact that the oxime of α-hydrindone is unchanged by heating with concentrated sulfuric at 100°(36), whereas in the Schmidt reaction α-hydrindone is smoothly converted into hydrocarbostyril at 40°(11). Another rather conclusive piece of evidence that the oxime is not an intermediate in this reaction is the work of Spielman and Austin(70) on benzil. They showed where γ-dioxime is stable toward hydrazoic-sulfuric acid. Benzil itself reacts to give a mixture of the following amides:



I



III 30-60% II

in addition to tetrazoles.

Hurd(34) supplemented this approach by proposing the "activation" of hydrazoic acid (I) by concentrated sulfuric acid to the active form II which then adds to the carbonyl forming III. The transient adduct (III) loses nitrogen to

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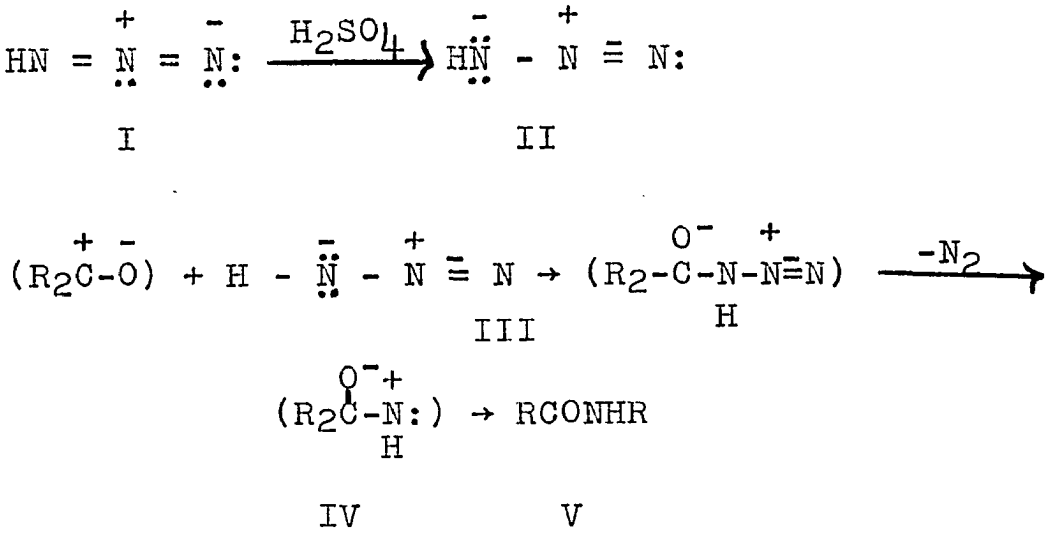
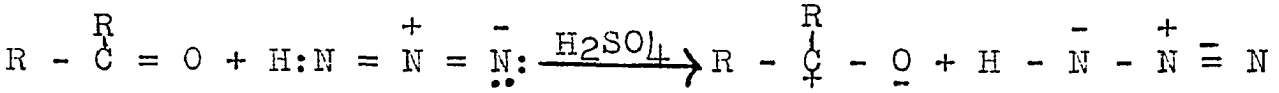
yield an unstable imino derivative (IV) which immediately undergoes a Beckmann type rearrangement and yields the amide (V).



This mechanism differed materially from that offered by Schmidt, not only because HN_3 rather than HN was considered as the addend, but also because it called for no oxime intermediate.

In interpreting their studies of substituted benzoic acids, Briggs and Lyttleton[12] professed complete agreement with the mechanism originally proposed by Hurd. However, they introduced one innovation that deserves mentioning.

These authors suggested that the sulfuric acid played a dual role, i.e. the activation of both the carbonyl group and hydrazoic acid by the strongly polar sulfuric acid.



Their work will be further discussed in a later section.

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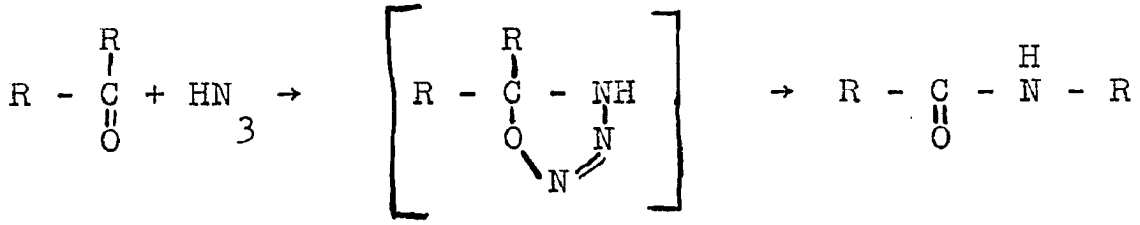
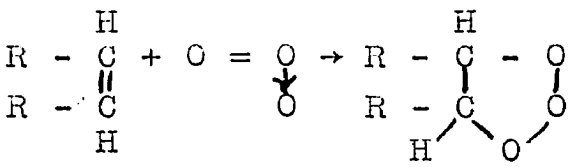
Morton[47] proposed the existence of an intermediate dihydroöxatriazole to represent the mechanism of the Schmidt reaction.



As stated by the author, the assumption of a transitory or incipient dihydroheterocyclic ring compound as an intermediate in this reaction was not intended to refute any electronic interpretation, but merely to provide a basis for correlating the behavior of diazomethane, hydrazoic acid and azides toward all double bonds. Morton reasoned that since ozone has a structure similar to hydrazoic acid and that the former adds to carbon-carbon double bonds to give what has been proposed as a 1,2,3-trioxole, by analogy, it would seem logical to assume that hydrazoic acid adds to the carbonyl groups in a similar fashion.



However, this trioxole structure for ozone addition is not currently accepted.

In 1945 a group of workers[58] proposed a mechanism for this reaction based on the experimental results obtained from the action of hydroxylamine-O-sulfonic acid on ketones. They stated that the mechanism of the Schmidt reaction with hydrazoic

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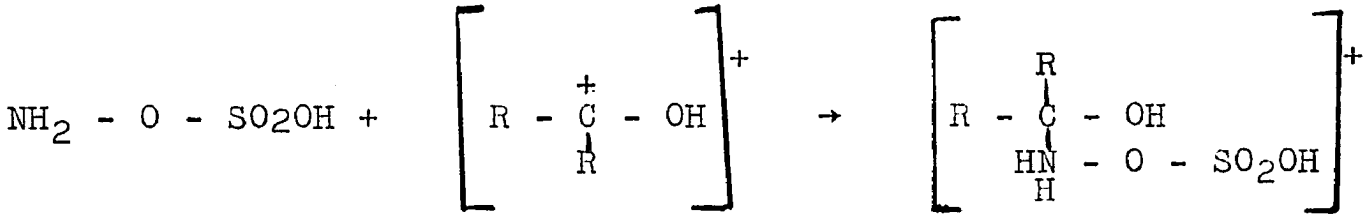
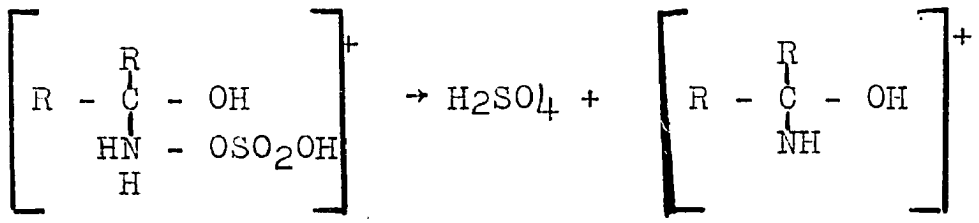
acid should be the same with the difference between the two reagents being one of degree rather than kind.

The first step of the reaction of hydroxylamine-O-sulfonic acid with ketones was postulated as being the addition of the acid to the conjugate acid of the ketone.



A shift of a proton from the nitrogen to the adjacent oxygen and the splitting off of a sulfuric acid molecule would then lead to the postulated residue for the Schmidt reaction.



They asserted further that the intermediate might change to the oxime or under more drastic conditions go directly to the mixed amides. The first case requires a shift of the OH group, while the latter requires the migration of the favored R group.

They indicated that some experiments had been performed in their laboratories involving different R groups and that the following was the order in tendency to migrate: p-anisyl > p-tolyl > phenyl > ethyl > isobutyl > methyl. The order is based, so state the authors, on the ease of polarization of the group by the positive nitrogen, i.e. the more polarizable of the two being the favored one.

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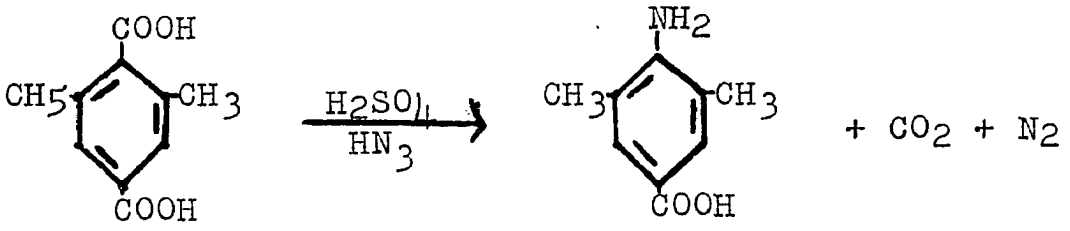
This work is most notable for the postulation of carbonium ion formation, for it marked the first step in what is currently believed to be the right direction. However, the remainder of the mechanism appears to be faulty in two respects. First, it fails to account for tetrazole formation which readily occurs in excess hydrazoic acid and second, the possibility of oxime formation appears to be excluded in the light of the experimental evidence previously cited.

In 1948 Newman[51] and Smith[68], working independently, arrived at a somewhat similar mechanism for the Schmidt reaction. Newman conceived of a carbonium ion mechanism from the fact that the hindered carboxyl group in 2,6-dimethylterephthalic acid reacted exclusively to yield 4-amino-3,5-dimethylbenzoic acid.



He had previously shown[49] that the sulfuric acid esterification of 2,4,6-trimethylbenzoic acid involved an oxocarbonium ion and therefore proposed that the Schmidt reaction should also take place by means of a similar intermediate, at least in the case of organic acids.

Since this thesis is primarily concerned with ketones, rather than acids, it is more pertinent at this stage to consider the mechanism advanced by Smith who developed his concept of the reaction from studies on experimental conditions

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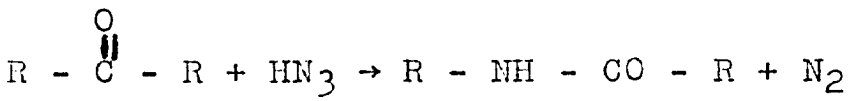
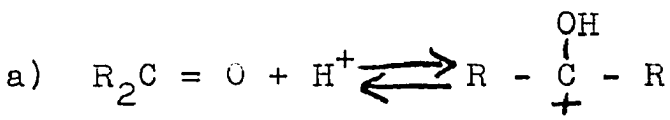
which gave rise to the highest yields with ketones.

The stoichiometry of the reaction with ketones is as follows:



Since the reaction is carried out with equimolecular quantities of catalyst which are strong Lewis acids, Smith proposed that the first step consists of carbonium ion formation from the carbonyl group and the acid catalyst. Newman refers to this particular carbonium ion as a hydroxycarbonium ion to differentiate between the large variety possible under various conditions:

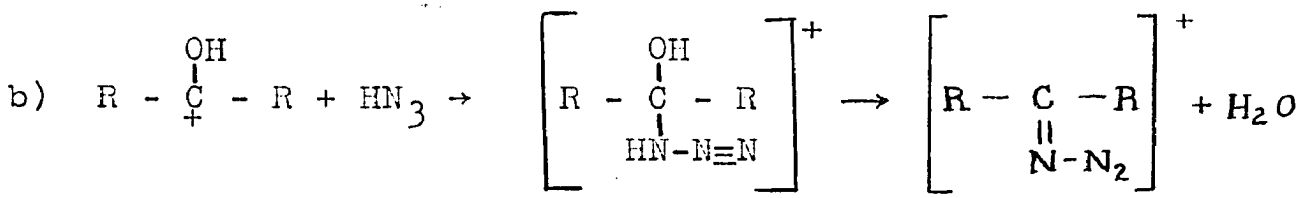
a)



I

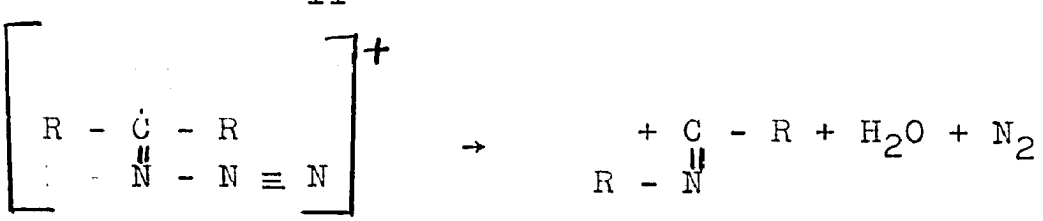
The hydroxycarbonium ion forms a transient adduct with hydrazoic acid (b) which loses water and undergoes a <u>trans</u> rearrangement with simultaneous loss of nitrogen.

b)



II

c)



III

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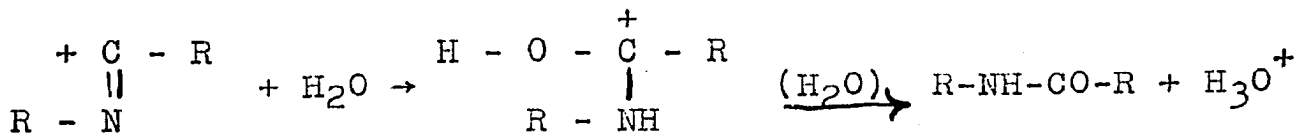
d) 

IV

From the suggested mechanism, Smith concluded that the occurrence of the Schmidt reaction is dependent upon both the extent to which the carbonyl group undergoes proton addition (a) and the polarizing power of the resulting hydroxycarbonium ion (I). Further, if the intermediate (II) has a finite existence, there should exist a geometrical effect influencing the "apparent migration aptitudes" of the two groups in unsymmetrical ketones.

C. Purpose of the Investigation

The purpose of this investigation was to determine the influence of electrical and steric factors on the ratio of isomeric amides produced by the Schmidt reaction on unsymmetrical ketones.

To study the electrical effect divorced as much as possible from steric effects, a series of para-substituted benzophenones was chosen; in such a series, great latitude in electrical properties is possible through variation of the para-substituent, without making an appreciable change in the steric environment of the carbonyl group. In addition, this choice would allow us to make the highly desirable comparison of the ratios of isomers produced in the Schmidt reaction with

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the ratios obtained from oximation and Beckmann rearrangement by Bachmann and Barton(2).

To study the steric effect in the Schmidt reaction with minimal disturbance from electrical influences, a series of aryl alkyl ketones was chosen in which the alkyl group was made successively more bulky by branching at the α-carbon.

It was expected that the theoretical insight into the Schmidt reaction gained by this study would at the same time be of considerable aid in assessing the utility of the Schmidt reaction in numerous cases where it might be considered as a tool in organic synthesis and degradation.

D. Discussion of Results

The composition of the mixtures of pairs of isomeric amides obtained from the Schmidt reaction on unsymmetrical ketones was determined by analysis of the mixtures of amines and acids obtained from them by hydrolysis. The amides from aryl alkyl ketones, which gave to rise to mixtures of aromatic and aliphatic amines and acids, required different treatment from the amides from the diaryl ketones; these two classes will therefore be discussed separately.

Hydrolysis of the mixed amides resulting from the Schmidt reaction on aryl alkyl ketones gave mixtures of benzoic acid with small fatty acids and of anilines with small alkylamines. The quantitative isolation of the small fatty acids is difficult and inaccurate because of their volatility and water-miscibility. Benzoic acid, on the other hand, is crystalline and easily isolated, identified, and weighed. Consequently, the amount of N-alkylbenzamide was calculated from the amount of benzoic acid isolated. The amounts of isomeric anilides were

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best calculated from the amount of aniline obtained, for it can be converted quantitatively into crystalline acetanilide, which is also easily isolated, identified, and weighed. By contrast, the alkylamines arising from the N-alkylbenzamides could not readily be separated from the aniline without erratic losses. The combined mole-per cent. yields of acetanilide and benzoic acid were high, and the amounts of these substances may therefore be taken as a reliable measure of the composition of the original amide mixtures.

A complication encountered only with the aryl alkyl ketones was partial hydrolysis of theamides during the Schmidt reaction. The aniline thus produced was recovered from the filtrates from the mixed amides as insoluble 2,4,6-tribromoaniline by treatment with bromine water; the quantities so obtained were not in excess of 15% of the amount of ketone initially taken. Not more than negligible traces of benzoic acid were ever obtained from the filtrates. The molar quantity of tribromoaniline was added to the amount of acetanilide obtained at a later stage in reckoning the ratio of isomeric amides produced.

For the analysis of the mixtures of aromatic amines and acids obtained from the para-substituted benzophenones the procedures of Bachmann and Barton[2] were used in part. In their methods, mixtures of benzoic acid with a para-substituted derivative are usually separated by the sharp solubility-difference in water. In cases where an insufficient difference exists, one of the components is converted into a different substance - terephthalic acid in the case of o-toluic acid - which does differ sufficiently in solubility from the other component. It was usually more reliable and convenient to determine the

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more soluble component of each mixture by difference, for the weight of the combined acids could be accurately determined. Bachmann and Barton confirmed the quantitative nature of these procedures by applying them to synthetic mixtures.

In most cases it was possible to confirm the results thus obtained independently by determining the mixtures of anilines. This was done by utilizing the usually much reduced solubility of a para-substituted acetanilide compared to acetanilide itself, but could not be accomplished with the mixtures of aniline with p-toluidine, however. The results of these independent determinations were in good agreement with those obtained from the analysis of the benzoic acid mixtures.

In the most unfavorable cases the absolute error in the ratios of isomeric amides may have been as high as 10%; for most of the mixtures, however, the error is believed to be less than half that figure.

1. Ketones

The ketones used in this investigation are given in Tables I and II. They were prepared in most cases according to methods described in the literature.

As previously stated, this work was designed to investigate both the steric and electric effects which might be operative in determining the ratios of mixed amides. The ketones in Table I differ in both bulk and electrical properties of the groups. Table II, however, lists a series of ketones in which the bulk near the carbonyl group stays constant while the electrical properties are altered by para-substituents.

Some additional ketones which were prepared but not used in this work will be reported elsewhere in conjunction with this

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study by Smith. The preparation of these ketones is presented in the experimental section and include β,β-dimethyl-α-tetralone, acetomesitone, pivalophenone and tertiary-butyl mesityl ketone.

Table I

Aryl-Aliphatic Ketones

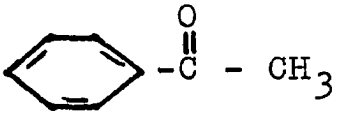
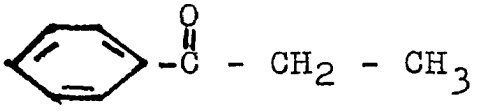
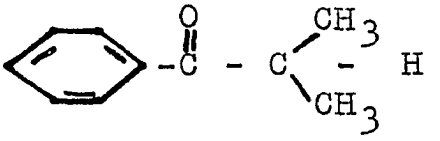
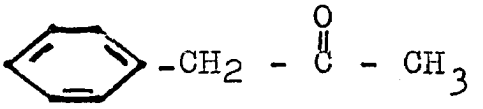
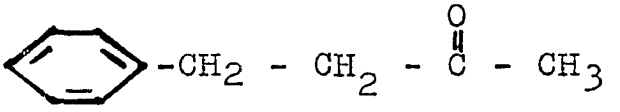
No.	Name	Formula
1	acetophenone	
2	propiophenone	
3	isobutyrophenone	
4	phenylacetone	
5	benzylacetone	

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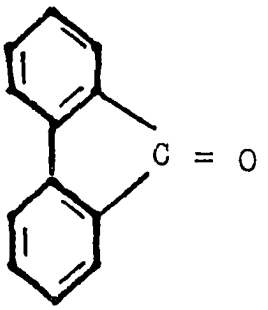
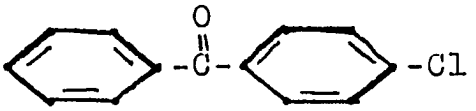
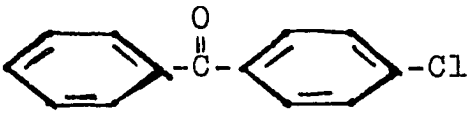
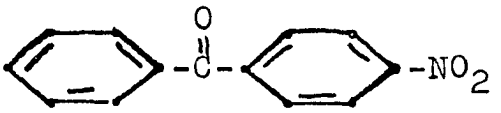
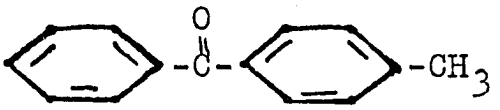
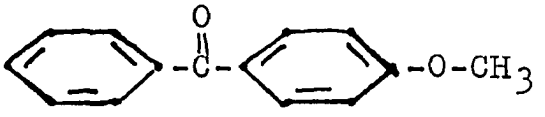
Table II

Aryl Ketones

No.	Name	Formula
1	fluorenone	
2	4,4'-dichlorobenzophenone	
3	p-chlorobenzophenone	
4	p-nitrobenzophenone	
5	p-methylbenzophenone	
6	p-phenylbenzophenone	
7	p-methoxybenzophenone	

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2. Schmidt Reaction

As already pointed out, the success of this investigation depended first upon the completeness of the reaction between the ketone and hydrazoic acid. Fortunately, the ground work for optimum experimental conditions had previously been laid by Smith.(68) He carried out a number of Schmidt reactions on different types of ketones in solvents of varying basicity and with catalysts of different acid strengths. The results of his study will be briefly summarized here as it played a fundamental role in this work.

First, Smith found that the more basic the carbonyl compound and the more acidic the reaction medium, the faster the reaction would go. He clearly pointed out that only a qualitative agreement might be expected since each carbonium ion has its own specific reaction rate. Further, his results showed that the more basic carbonyl compounds, such as the cycloalkyl and dialkyl ketones, would undergo the Schmidt reaction even in such basic solvents as water, alcohols and ether, but with the less basic aryl alkyl ketones the use of these solvents inhibited the reaction largely or completely. In this same work Smith showed that catalysts which were strong enough acids to bring about the Schmidt reaction with the more basic alkyl and aryl alkyl ketones were not necessarily effective with basic diaryl ketones. For example, while trichloroacetic acid proved to be effective for alkyl and aryl alkyl ketones, it was only partially so with benzophenones.

Since the carboxyl group of trichloroacetic acid does not exhibit a measurable tendency to form carbonium ions,(31)

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it serves as an excellent solvent for carrying out the Schmidt reaction on other carbonyl compounds. Thus, with the more basic carbonyl compounds this acid may act as both solvent and catalyst while the less basic aryl ketones require the addition of sulfuric acid as catalyst.

In summarizing, Smith recommended using the least strongly acid medium which would bring about the reaction in a reasonable time, as these conditions gave the purest products. This conclusion was further substantiated in our work with benzylacetone which gave only a 61% yield of mixed amides in sulfuric acid compared to the 87% yield in concentrated hydrochloric acid reported by Smith. Also, phenylacetone, whose yield in trichloroacetic acid was far below those obtained with similar ketones in this solvent, gave a 70% yield in concentrated hydrochloric acid.

Tables III and IV summarize the yield of "total Schmidt product" obtained with each ketone, along with the solvent and catalyst employed. The total Schmidt product consists in some cases of hydrolyzed product found in the reaction mixture.

Table III

Aryl Alkyl Ketones

No.	Name	Acid Catalyst	Solvent	Total Schmidt Product
1	Acetophenone	trichloroacetic	same	81%
2	Propiophenone	trichloroacetic	same	80%
3	Isobutyrophenone	trichloroacetic	same	57%
4	Phenylacetone	hydrochloric	same	70%
5	Benzylacetone	sulfuric	benzene	61%*

*Smith reported an 85% yield in trichloroacetic acid.

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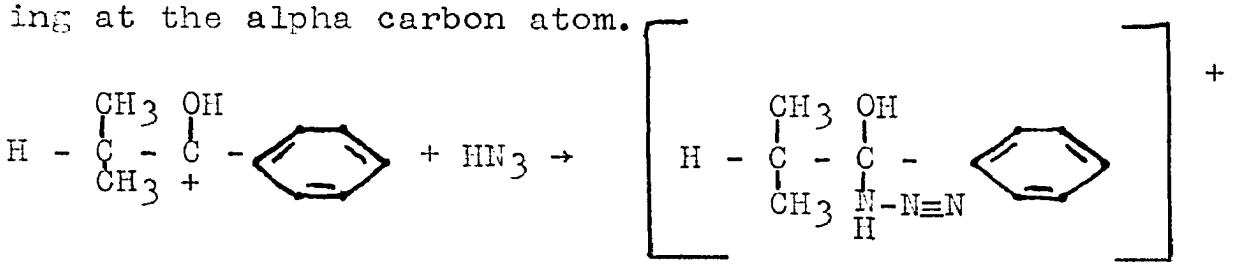
Table IV

Aryl Ketones

No.	Name	Acid Catalyst	Solvent	Total Schmidt Reaction
1	Fluorenone	sulfuric	same	99%
2	4,4'-dichloro-benzophenone	sulfuric	trichloroacetic	94%
3	p-chlorobenzo-phenone	sulfuric	trichloroacetic	94%
4	p-nitrobenzo-phenone	sulfuric	trichloroacetic	93%
5	p-methylbenzo-phenone	sulfuric	trichloroacetic	89%
6	p-phenylbenzo-phenone	sulfuric	trichloroacetic	97%
7	p-methoxybenzo-phenone	sulfuric	trichloroacetic	92%

From Table III it may be seen that isobutyrophenone gave an exceptionally low yield of mixed amides under the usual conditions. Even prolonged heating and excess sodium azide failed to change the yield appreciably, as 28% of unreacted ketone was recovered in the form of its 2,4-dinitrophenylhydrazone. This lower yield with isobutyrophenone may be attributed to the difficulty of forming the transient adduct from the corresponding carbonium ion and hydrazoic acid due to the increased branching at the alpha carbon atom.



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This would then explain the decreased rate of nitrogen evolution observed in the Schmidt reaction on isobutyrophenone as compared to the relatively unhindered aryl alkyl ketones.

The same phenomen has been observed by Smith[69] with pivalophenone and tertiary butylmesityl ketone. The former evolves nitrogen extremely slowly and the yield of "total Schmidt product" is of the same order of magnitude as that obtained with isobutyrophenone. Tertiary butylmesityl ketone not only appears completely inert toward hydrazoic acid, but even fails to give the usual reactions of the carbonyl group.

Oximation of this ketone failed to take place even in a sealed tube at 180°. This behavior suggests, as a first approximation, that the rate of nitrogen evolution may be considered a direct measure of the steric effect in the Schmidt reaction.

The Schmidt reaction on the aryl alkyl ketones was carried out with 15 g. (0.09 mol.) of trichloroacetic acid for each 0.01 mol. of ketone. This mixture was fused at a temperature of 55-60° and 2 g. (0.031 mol.) of powdered sodium azide was added all at once and the reaction mixture held at this temperature for the specified time by means of a Fischer "Autemp Heater". The diaryl ketones were subjected to the same treatment, but in addition, the reaction was catalyzed by 2 ml. (0.036 mol.) of concentrated sulfuric acid.

Fluorenone was found to give practically quantitative yields by using 20 ml. (0.36 mol.) of concentrated sulfuric acid at room temperature, but it gave only a 56% yield

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of phenanthridone (Smith[68]) in trichloroacetic acid. Apparently this lower yield in the weaker acid medium is due to the feeble basic properties of fluorenone.

After the completion of the reaction, as evidenced by the cessation of nitrogen evolution, the acid mixture was poured into water or on ice in the case where concentrated sulfuric acid is employed as solvent. The product was filtered or extracted, depending on the physical nature of the amides, washed with ammonium hydroxide, and finally treated with warm petroleum ether. This treatment usually was sufficient to give a product free from the acid solvent, catalyst, or unreacted ketone. However, in the majority of diaryl-ketones considerable trichloroacetic acid was occluded in the mixed amide crystals, and it was necessary to break up the lumps and digest with dilute ammonium hydroxide to get rid of the acid.

3. Hydrolysis and Separation of Products

a) Aryl Alkyl Ketones.- The substituted amides arising from the Schmidt reaction on aryl alkyl ketones were hydrolyzed by refluxing them with 100 ml. of 25% methanolic potassium hydroxide for twenty-four hours. The amines were then separated either by steam distillation or extraction and converted to solid derivatives which, in the majority of cases, were the N-acetyl derivatives since the aromatic amine was usually aniline. At the start of this work an attempt was made to collect the aliphatic amine in Kjeldahl-like fashion and back-titrate the excess acid. This, however, was

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discontinued when it was found that the titration data were erratic and did not correspond to the quantity of aromatic acid which was isolated. The latter was separated by acidifying the residue in the still-pot and extracting with ether.

The recovery of these products of hydrolysis ranged from 90 to 98% of the moles of mixed amides and hence the amounts of acid and amine could be used as an index to the relative extent of migration of the various groups.

Arranged in Table V are the series of aryl alkyl ketones used in this investigation along with the relative extent of migration of the substituents expressed in percent.

Table V

Relative Extent of Migration

Ketone R ----- C(=O) ----- R'		% R	% R'
phenyl	methyl	95	5
phenyl	ethyl	85	15
phenyl	isopropyl	51	49
benzyl	methyl	50	50
β-phenylethyl	methyl	95	5

It was mentioned in a previous section that if the intermediate $\left[R - \underset{\underset{N - N \equiv N}{\|}}{C} - R' \right]^{+}$ has a finite existence, there should be manifested at this stage a definite geometrical

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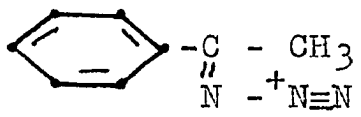
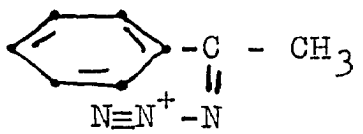
effect, the influence of which would be observable in the relative amounts of isomeric amides formed and measurable from the quantity of acid and amine isolated. In addition, since the ease of "trans" migration of a group with its bonding pair of electrons is a function of the "electron donating" character of this group, then the relative amounts of isomeric amides might also be influenced by the electronegativity of the migrating group. If the electric effect is dominant, then the order of migration should follow the order of polarizability of the "trans" group; namely, t-butyl > isopropyl > ethyl > methyl > phenyl.

The results of the study on the aryl alkyl ketone series established the order of preferential migration as t-butyl > isopropyl > phenyl > ethyl > methyl, which is clearly the order of decreasing hindrance near the carbonyl group, and does not correspond to any known gradation of electrical properties of the groups concerned.

In the azidocarbonium ion intermediate from acetophenone, the two geometrical isomers may be represented as follows:



(a)



(b)

The isomer with the nitrogen residue "syn" to the methyl group (a) should be favored from the standpoint of the relative size of the adjacent groups. This should result in phenyl migration, which corresponds to experiment. On the other hand, methyl migration, contrary to the observed result, would be favored from

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electrical considerations since the methyl group is the less electronegative of the two.

With the successive addition of methyl groups on the alpha carbon atom, the amount of phenyl migration decreases with a simultaneous increase in the proportion of alkyl migration until, with isobutyrophenone, the relative amounts of migration become approximately equal. This is in accordance with the steric effect already cited and with Smith's work on pivalophenone, which was found to undergo exclusive tertiary butyl migration in the Schmidt reaction.

Though benzylacetone gave the expected results in the Schmidt reaction, being completely analogous to acetophenone in migrational tendencies, phenylacetone exhibited a rather unusual behavior by giving a nearly equal proportion of isomeric amides. Whether this unanticipated result is due to an anomalous behavior on the part of the benzyl group or simply to the increased acidity of the alpha hydrogen adjacent to the aromatic ring cannot be answered at this time without further study.

It appears from the results obtained with benzylacetone that the interposition of two methylene groups between the carbonyl group and aromatic residue does not alter either the steric or electrical factors which control the migration tendencies of acetophenone.

b) Aryl Ketones.- The hydrolysis of most of the aryl substituted amides arising from the Schmidt reaction on the unsymmetrical aryl ketones was accomplished through the

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use of a mixture of glacial acetic and hydrochloric acids. The period of reflux varied from twenty-four to ninety-six hours, depending upon the solubility of the amide mixture in the hydrolytic reagents.

This method of hydrolysis appears to have a number of advantages over the methanolic potassium hydroxide procedure used for the previous series of amides. First, the hydrolysis periods were shortened considerably using a glacial acetic acid medium. Second, the mixed acids were isolated directly after pouring the mixture into water without first having to remove large amounts of silica which frequently is formed in alkaline hydrolysis. Finally, this method resulted in a great saving of the round-bottomed flasks, which were seldom able to withstand more than two alkaline reflux periods.

The usual hydrolytic conditions were modified for the amides resulting from para-methoxybenzophenone when it appeared that some demethylation had occurred in the normal course of the Schmidt reaction. It was found that para-anisic acid could be demethylated practically quantitatively (95%) even in the presence of an equivalent amount of benzoic acid by using a solution of 30% hydrogen bromide in glacial acetic acid in a sealed tube at 100°. These same conditions accomplished the hydrolysis of the corresponding anilide so that this procedure proved to be an ideal approach to the problem of analyzing for para-anisic acid in the presence of benzoic acid.

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After the completion of hydrolysis, the acetic acid mixture was poured into water, the solid acids filtered off, and the filtrate extracted with ether to remove the remaining aromatic acids.

The problem of analysis of the mixture of acids was, in each case, a separation of a para-substituted benzoic acid from benzoic acid itself. However, it was first necessary to dissolve these acids in a sodium carbonate solution to separate them from small amounts of neutral material, such as unhydrolyzed amide, since in some cases one of the acids was determined by difference.

Para-chlorobenzoic acid was separated from benzoic by virtue of the former's small solubility in cold water. When this same method was applied to a mixture of para-nitrobenzoic and benzoic acids, it was found that despite the small solubility of the para-nitrobenzoic acid in water, it always crystallized from water along with an appreciable amount of benzoic acid. This problem was circumvented by catalytically hydrogenating the mixture of acids and extracting the benzoic acid from a strongly acidic medium.

The separation of para-phenylbenzoic acid from benzoic acid provided some difficulty inasmuch as the sodium salt of this acid proved to be relatively insoluble, thus increasing the mechanical loss due to repeated handling. Despite a low recovery of the individual acids, the proportion of mixed amides calculated from this data agreed remarkably well with the values obtained from the amounts of amines isolated.

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The permanganate oxidation of para-toluic acid to the insoluble terephthalic acid, as described by Bachmann and Barton[2], was used to analyze the para-toluic and benzoic acid mixture.

The insolubility of para-hydroxybenzoic acid in carbon disulfide was used to separate this acid from benzoic acid. However, a small amount of benzoic acid always remained in the filter cake, and it was necessary to treat the latter with a small amount of benzene to remove the last traces of benzoic acid. Fortunately, the solubility of para-hydroxybenzoic in benzene is negligible.

After the acids were removed, the acetic acid solution was evaporated to dryness and then the residue of amine salts were taken up in a small amount of water. This aqueous solution was alkalyzed with potassium hydroxide and then extracted with benzene. After acetylating the benzene solution with acetic anhydride and then evaporating both the benzene and the excess acetylating reagent, it was then a comparatively easy task to effect a separation of the resulting anilides since the majority of the negatively substituted acetanilides are relatively insoluble in cold water.

While the method described above was very satisfactory for separating 4-acetamidobiphenyl and para-chloroacetanilide from acetanilide, the method obviously could not be applied to a separation of para-methylacetanilide from acetanilide itself. As a matter of fact, no method which might be termed quantitative was found to be applicable to this situation.

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The search for a desirable method of separation included bromination in various solvents, permanganate oxidation under various conditions and chromic acid oxidation.

A neutral potassium permanganate oxidation of a known mixture of acetanilide and para-methylacetanilide gave the most promise as a solution to the problem insofar as Ullman and Uzbachian[71] had reported that para-acettoluidide could be oxidized to para-acetamidobenzoic acid in 98% yield in neutral permanganate solution. However, only a 67% yield of para-acetamidobenzoic acid could be obtained when the oxidation was carried out on a known mixture of these anilides. Apparently, the presence of acetanilide has a detrimental effect on this rather selective oxidation. Consequently, the relative proportion of mixed amides had to be calculated solely from the amounts of terephthalic and benzoic acids obtained.

The separation of para-nitroaniline from aniline did not necessitate the conversion of these amines into their corresponding N-acetyl-derivatives since the basicity of para-nitroaniline is such that complete hydrolysis of its salt occurred when the acetic acid solution was poured into cold water. Treatment with alkali separated this amine from the para-nitrobenzoic and benzoic acids simultaneously precipitated.

No attempt was made to isolate para-aminophenol obtained from para-methoxybenzophenone since it readily undergoes an air oxidation[4] in both alkaline and acid solution followed

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by polymerization to give a substance reported as being $(C_6H_5ON)_x$. The amount of acetanilide obtained agreed fairly well with the amount of para-hydroxybenzoic acid isolated, however.

A summary of the results obtained with the series of aryl ketones in this study is presented in Table VI. The relative extent of migration was calculated from the amount of acids isolated and checked against the quantity of amines obtained. These values represent the average of several determinations and the mean was well within the experimental error of this work. However, the mechanical loss incurred as a result of repeated handling may cause the error to be, in some cases, as high as 10%.

The results presented in Table VI show that there is a remarkable recurrence of a fifty-fifty ratio in the relative extent of migration of the two groups regardless of the electrical nature of the para-substituent; i,e., whether it is of electrophilic or nucleophilic character.

If the products of the Schmidt reaction on ketones were strongly influenced by the electrical character of the migrating group, then these effects should be manifested in the migration tendencies of the two unsymmetrical groups with the para-nitrophenyl group and para-anisyl group representing the extremes of electrophilic and nucleophilic states.

The work of Briggs and Lyttleton[12] shows that electrical influences definitely affect the Schmidt reaction on meta substituted benzoic acids. These authors found that the rate of reaction between a meta substituted benzoic acid and

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hydrogen azide was inversely related to the strength of the acid. Specifically, the rates of reaction for these acids are the following: $CH_3 > H > OCH_3 > Cl > NO_2$, whereas acid strengths as measured by dissociation constants is the reverse order; viz, $NO_2 > Cl > OCH_3 > H > CH_3$.

While a meta substituent exerts an influence almost exclusively by induction and therefore may not parallel the case of the para substituent where the electrical effect is the algebraic sum of the mesomeric and inductive effects, it should be expected, nevertheless, that the relative extent of migration would present a totally different picture than the fifty-fifty ratio already observed if these forces played a dominant role in the Schmidt reaction on ketones.

Table VI

Relative Extent of Migration

R ------ C(=O) ------ R'		% R	% R'
phenyl	p-chlorophenyl	40	60
phenyl	p-nitrophenyl	49	51
phenyl	p-tolyl	46	54
phenyl	biphenyl	56	44
phenyl	p-methoxyphenyl	38	62

A comparison of the results obtained with the Schmidt reaction and the closely allied Beckmann rearrangement on the oximes of these same ketones is of interest inasmuch as both

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reactions may be roughly classified as Wagner-Meerwein rearrangements. These transformations, reduced to the simplest terms, involve an exchange of positions on two adjacent atoms by a hydrocarbon radical and a potentially anionic group.

In this connection, some of the results obtained by Bachmann and Barton[2] are summarized in Table VII. The ketones chosen are those which were investigated in our study and whose oximes were subjected to the Beckmann rearrangement by these authors.

Table VII

Proportion of Syn and Anti Stereoisomers

Ketone R ------ C(=O) ------ R'		% R - C(=N-OH) - R'	% R - C(=N-OH) - R'
phenyl	p-chlorophenyl	44	56
phenyl	p-nitrophenyl*	----	----*
phenyl	p-tolyl	48	52
phenyl	biphenyl	49	51
phenyl	p-methoxyphenyl	51	49

Bachmann and Barton calculated the percent of "syn" and "anti" stereoisomers from the amounts of aromatic acid isolated.

* Para-nitrobenzophenone was not used in the study of the Beckmann rearrangement by Bachmann and Barton.[2]

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These authors also recognized a fifty-fifty ratio of stereoisomeric oximes and concluded that the determining factor in the rearrangement of the oximes is the original orientation of the oximino-hydroxyl group, rather than the polarity of the para substituent.

Another important study relative to our investigation is the work of Chapman and co-workers[14,15,16,17] on the mechanism of the Beckmann rearrangement. In addition to his studies on the effect of the dielectric constant of the medium on the rearrangement of benzophenoneoxime picryl ether, Chapman made a very thorough investigation of para and di-para substituted benzophenoneoxime picryl ethers. From this work certain fundamental conclusions emerged concerning the effect of electric character on the Beckmann rearrangement. These will be briefly summarized.

The introduction of the electron-attracting groups into either group of a benzophenoneoxime retards the Beckmann transformation, whereas the electron-repelling groups accelerate it. Moreover, the introduction of a substituent into the migrating nucleus has a much greater effect on the rate of transformation than a similar substitution in a stationary nucleus. The picryl ether of <u>anti</u> para-nitrobenzophenone-oxime (<u>anti</u> to the nitro group) rearranged much more slowly than the corresponding para-chloro compound. The syn oxime picryl ether of para-nitrobenzophenone was recovered unchanged from all attempts to cause it to rearrange. On the

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other hand, when Chapman attempted to prepare the di-para anisyl-ketoxime picryl ether, the only product that could be isolated was para-anisoyl-para-aniside; evidently rearrangement had occurred at room temperature.

Before concluding this discussion of the relative influence of the steric and electrical effects, it seems apropos at this time to mention the studies of Bachmann and Moser[3] on the migration aptitudes of aryl groups in the rearrangements of symmetrical mixed pinacols. They found that the migration aptitudes in symmetrical, aromatic pinacols depended on the individual radicals themselves and not on the pinacol in which the group occurred. On the basis of phenyl as 1, the following order of relative migration aptitudes was obtained: anisyl, 70 or more; para-tolyl, 15; para-biphenyl, 11.5; and para-chlorophenyl, 0.66. On comparing results such as these with the results obtained in the Schmidt reaction on similarly substituted ketones, there appears to be little or no relation. However, in view of the very high migrational aptitude of the para-anisyl group, it is not surprising that this group exhibited a somewhat higher (61%) relative extent of migration in the Schmidt reaction compared to the other groups.

From our results and from the data on what appear to be related reactions, certain conclusions concerning the effects of structure on the products of the Schmidt reaction on ketones are forthcoming.

1) The steric effect appears to be the dominant factor in determining the relative amounts of isomeric amides obtained.

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2) It appears that the electrophilic or nucleophilic character of the migrating group has only a very minor influence on the proportion of isomeric amides.

3) The ratio of isomeric amides is governed by the orientation of the nitrogen chain in the transient adduct, the orientation being a statistical phenomenon in the absence of bulk effects in the neighborhood of the carbonyl group.

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PART II

The Preparation of Some Substituted Succinic Acids

A. Introduction

In the course of study on the Schmidt reaction, it was decided to include β,β-dimethyl-α-tetralone among the ketones to be examined. The method of preparation chosen was that previously used for the preparation of tetralone[44] itself, through the cyclization of γ-phenylbutyric acid.

The immediate problem was the selection of a convenient method for preparing unsymmetrical dimethylsuccinic acid to initiate the synthesis. A variety of mono- and disubstituted succinic acids and their methods of preparation had been reported, but many represent isolated reactions specific for the desired acid. Since our ultimate findings are of synthetic value, some of the earlier preparative methods deserve mentioning.

In 1861 Kekule[37] showed that reduction of mesaconic, citraconic and itaconic acids with sodium amalgam gave methylsuccinic acid. A year later Walden[74], pursuing a similar investigation, prepared a number of succinic acids by reducing the corresponding maleic or fumaric acid with 4% sodium amalgam.

In the same year, Simpson[67] reported a general method for preparing substituted succinic acid from vicinal dibromides and potassium cyanide, followed by hydrolysis of the dinitrile.

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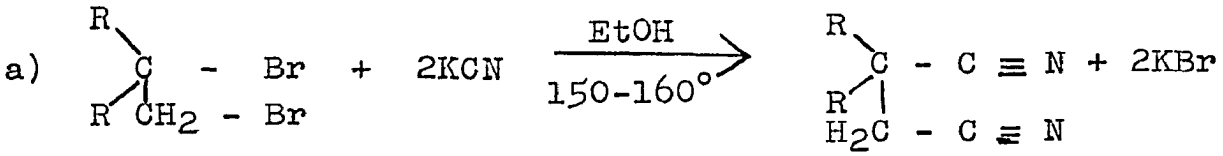
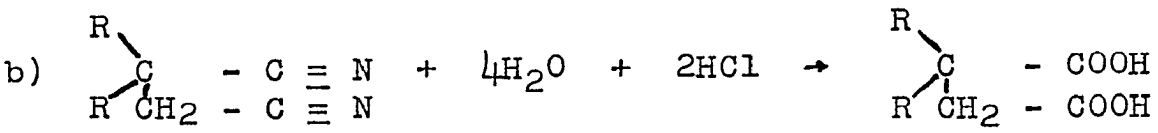
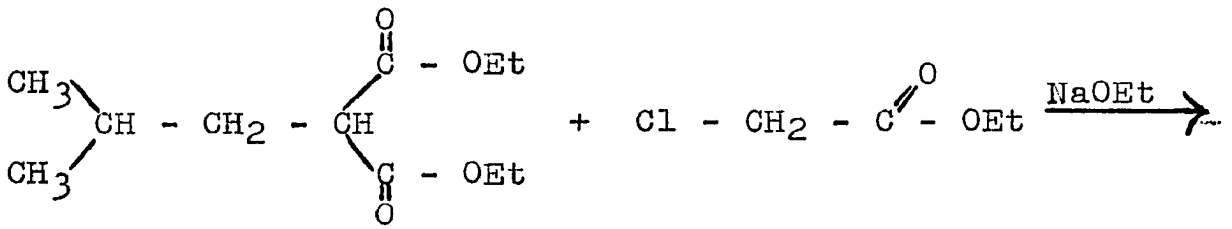
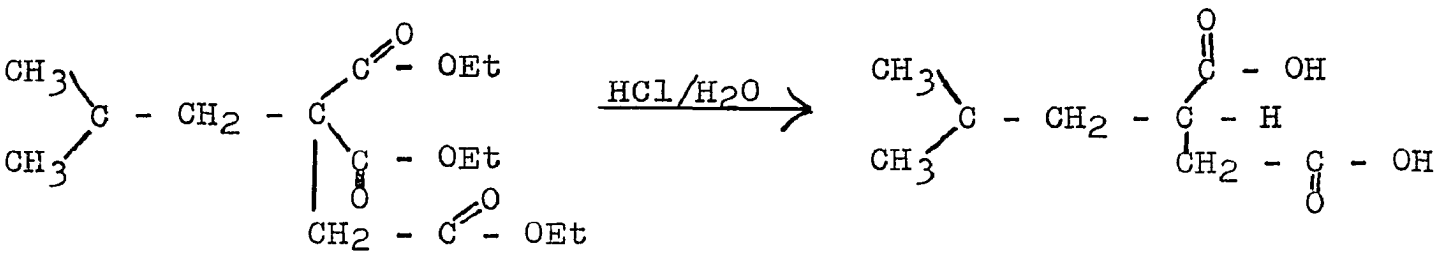
a) 

b) 

While this method is a general preparative method, it has the disadvantage of requiring a sealed tube for step (a). In 1898 Bentley and Perkin[8] prepared isobutyl succinic acid from ethyl isobutylmalonate and ethyl α-chloroacetate in the presence of sodium ethoxide.





Soon after the publication of the above reaction, there appeared in the literature a variety of modifications and applications of this reaction which offered a very convenient way of preparing all types of substituted succinic acids in reasonably good yields.

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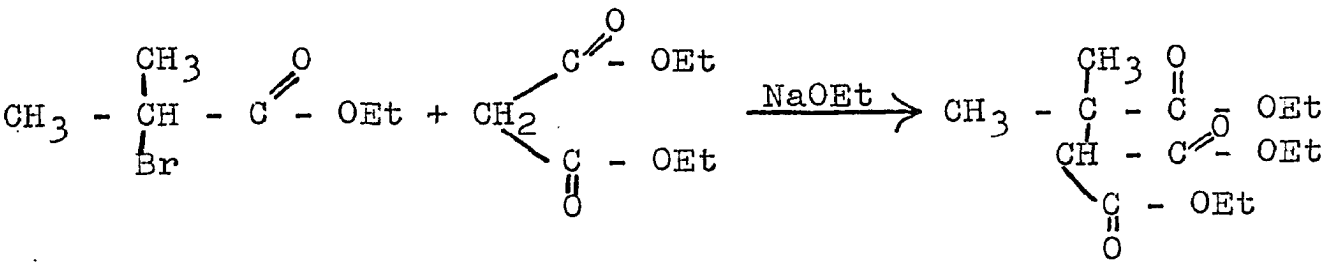
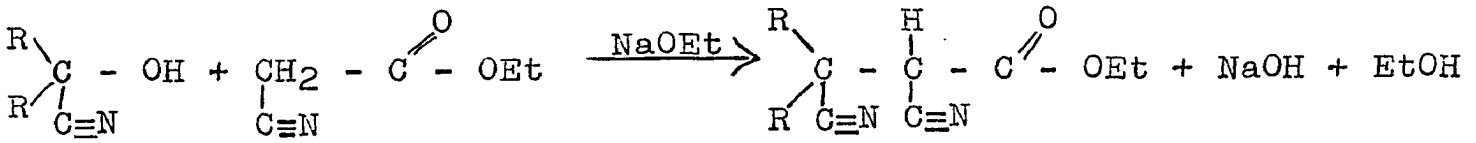


Shortly thereafter, Higson and Thorpe[31] showed that, in the presence of sodium ethoxide, a number of cyanohydrins could be condensed with ethyl α-cyanoacetate to give α,β-dicyano-β-substituted propionic esters in moderately good yields.



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Our attempt to repeat their work with acetone cyanohydrin resulted in a very low yield of the dinitrile-ester. This may be attributed, at least in part, to the sensitivity of acetone cyanohydrin to alkali, as a noticeable reduction of temperature occurred on addition of the sodio-cyanoacetic ester to the previously chilled acetone cyanohydrin. It has been shown[72] that traces of alkali bring about this decomposition and heat is absorbed in the process. To avoid having an excess of alkali present at any one time, Higson and Thorpe recommended the addition of sodium ethoxide to the pre-cooled mixture of cyanohydrin and ester. This resulted in a cumbersome operation as the base was in the form of a slurry, and it was necessary to dismantle a part of the

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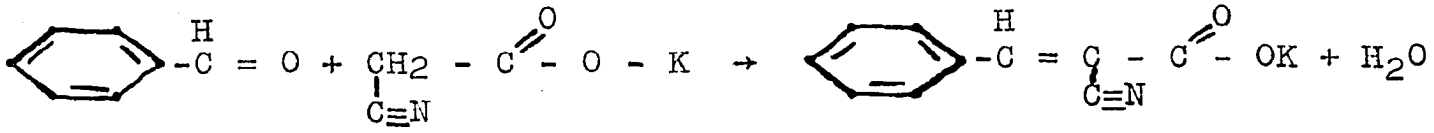
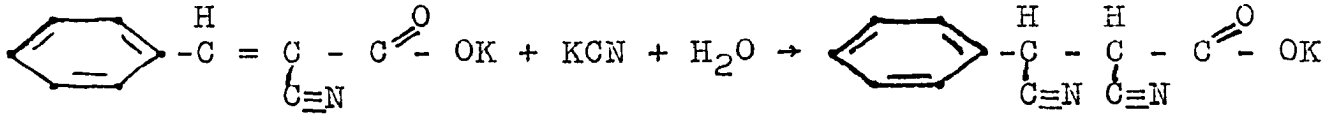
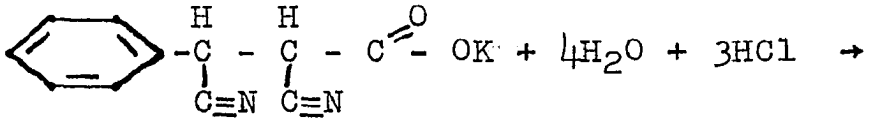
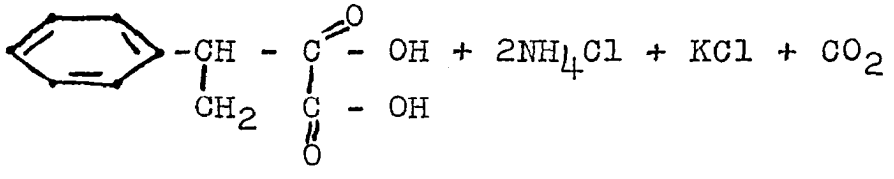
apparatus for each addition. Consequently, it was quite difficult to maintain the required temperature control during the addition.

Lapworth and McRae[38,39] succeeded in preparing not only mono- and dialkylsuccinic acids but also succinic acids containing an aromatic residue. This was accomplished by heating the carbonyl compound with potassium or sodium α-cyanoacetate, isolating the substituted α-cyanoacrylic acid and finally treating with an aqueous potassium cyanide solution.









The last general preparative method to be considered in this brief discussion is one which has appeared in steroid

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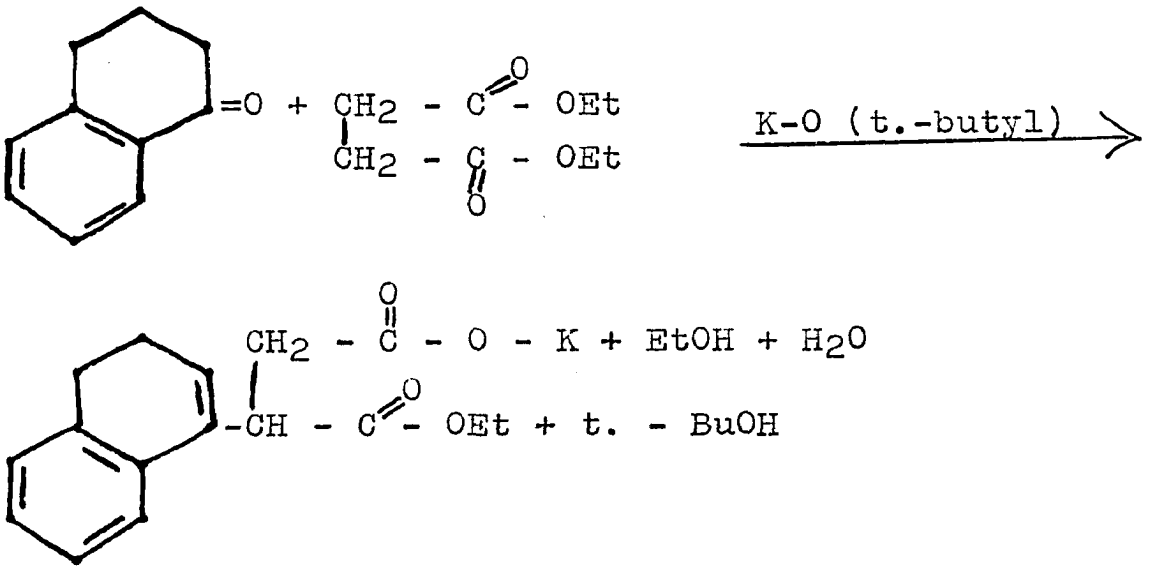
synthesis quite recently. Johnson and Peterson[35] modified the Stobbe reaction, using potassium tertiary butoxide to condense α-tetralone with ethyl succinate, obtaining dihydronaphthylsuccinic acid.



The same reaction was applied to 1-keto-tetrahydrophenanthrene.

Of the methods presented above, that of Lapworth seemed most convenient and applicable to the problem of preparing unsymmetrical dimethylsuccinic acid. However, this method necessitated the isolation of the β,β-dimethylacrylic acid before the potassium cyanide could be added.

Cope and his students[18,19] had been quite successful in condensing both aldehydes and ketones with ethyl α-cyanoacetate and ethyl malonate in the presence of a variety of salts, the most notable of which were the acetates of ammonia, piperidine and triethylamine, each in the presence of acetic acid.

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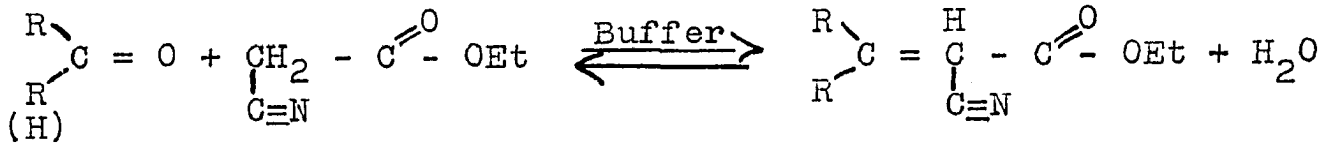

Further, these workers demonstrated that the equilibrium could be shifted to the right by removing the water formed as a result of the condensation by using a constant water separator on the reflux apparatus. A short time later Cope and Alexander[1] showed that this same equilibrium could be shifted by removing the unsaturated ester as it was formed by catalytic hydrogenation.

Weiner and Michael[75] had previously shown that the addition of potassium cyanide to alkylidene-α-cyano acetic and malonic esters in alcohol gave near quantitative yields.

In view of the success achieved by Cope and his co-workers in driving the condensation reaction to completion by removing one of the products and the apparent ease with which potassium cyanide adds to α,β unsaturated esters, it was decided to employ potassium cyanide to shift the equilibrium and in this manner produce the desired α,β-dicyanoester without having first to isolate the unsaturated intermediate. Thus acetone and ethyl α-cyanoacetate were condensed in the presence of pyridine acetate. Then, without isolating the ethyl β,β-dimethyl α-cyanoacrylate, ethyl alcohol and potassium cyanide were added to the reaction mixture, isolating only the ethyl α,β-dicyano-β methylbutyrate and subjecting it to hydrolysis and decarboxylation.

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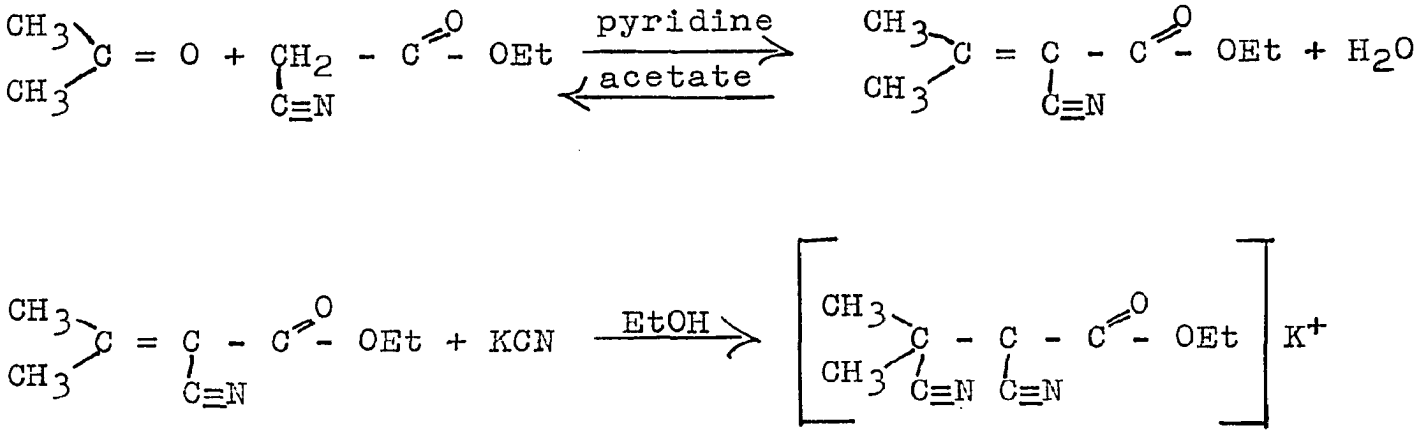

B. Discussion of Results

1. Aldehydes and Ketones.- The choice of carbonyl compound was governed by its availability so that the selection was more or less random. Each was purified by distillation before use.

2. Condensation.- Equimolecular quantities of aldehyde or ketone, ethyl α-cyanoacetate, acetic acid and pyridine were refluxed for one to two hours; in the case of propionaldehyde, it was found that the best yield was obtained after only a fifteen minute reflux period.

Although the yields in Table VIII are based on a tenth of a mole of starting material, it was found, in the use of acetone, that the yield of dicyanoester increased approximately 10% when the reaction was carried out on a one mole scale.

3. Addition of Potassium Cyanide.- After the reaction mixture had been refluxed for the required time, it was allowed to cool just to the point where it failed to reflux of its own accord. Ethyl alcohol was then introduced through the top of the reflux condenser. Immediately after the addition of alcohol, the condenser was momentarily removed to

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Table VIII

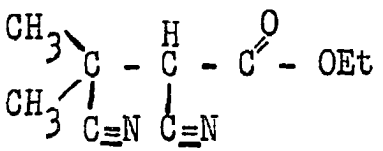
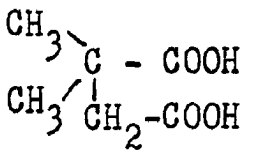
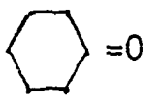
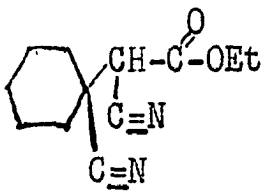
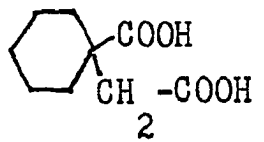
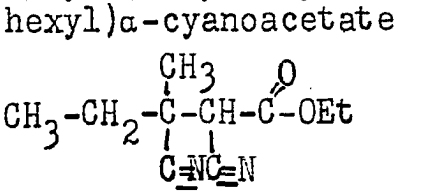
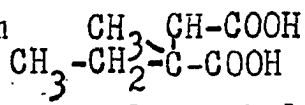
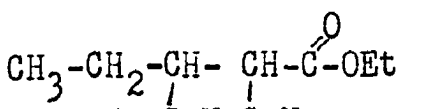
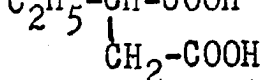
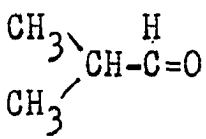
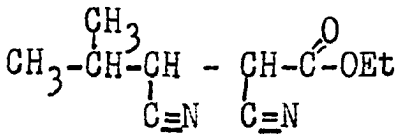
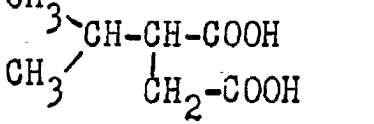
Carbonyl Compound	α,β-Dicyanoester	Yield	Higson-Thorpe Method	Boiling Point	Succinic Acid
1) $CH_3-\overset{O}{\overset{\|}{C}}-CH_3$	 ethyl α,β-dicyano-β methylbutyrate	70%	65-70%	141°/10 mm	 α,α-dimethylsuccinic acid
2)  =O	 ethyl (1-cyanocyclo-hexyl)α-cyanoacetate	75%	70%	177°-179°/10mm	 1-carboxycyclohexyl-acetic acid
3) $CH_3-\overset{O}{\overset{\|}{C}}-CH_2-CH_3$	 ethyl-α,β-dicyano-β-methylvalerate	49%	80%	145°-146°/10mm	 α,methyl-α-ethyl-succinic acid
4) $CH_3-CH_2-\overset{H}{\overset{\|}{C}}=O$	 ethyl α,β-dicyanoval-erate	53%	--	158°-160°/13mm	 ethyl succinic acid
5) 	 ethyl α,β-dicyano- -methylvalerate	67%	--	151°-155°/10mm	 isopropyl succinic acid

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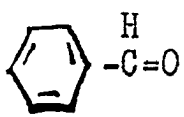
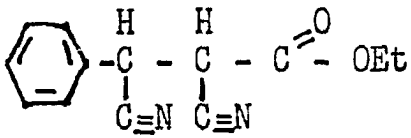
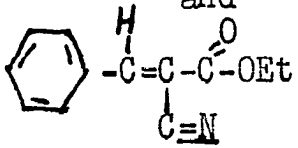
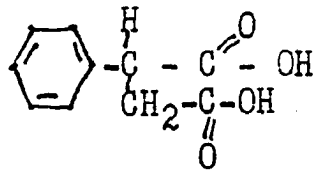
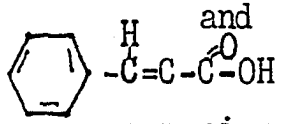
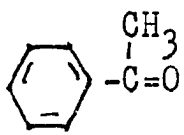
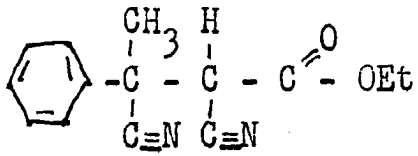
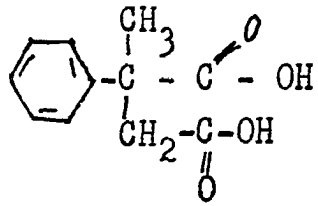
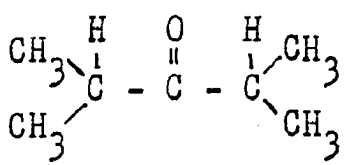
Table IX

Carbonyl Compound	Condensation Product	Yield	Boiling Point	Succinic Acid
1) 	 ethyl α,β-dicyanopropionate and  ethyl α-cyanocinnamate	*	145-158°/0.1mm.	 phenylsuccinic acid and  α-cyanocinnamic acid
2) 	 ethyl α,β-dicyano-β-phenylpropionate	16.5%	145-150°/0.1mm.	 α-phenyl,-α-methyl-succinic acid
3) 	No product	----	----	----

* No yield calculated.

add the potassium cyanide.

The temperature at which the potassium cyanide is added appears to be critical as addition at lower temperature reduced the yield materially. The optimum temperature in the case of the acetone reaction proved to be 70-75° which is just below the boiling point of ethyl alcohol itself.

The addition of potassium cyanide at this temperature causes a moderately vigorous reaction which subsides in twenty to forty-five minutes, depending on the scale of the reaction. In general, the mixture was allowed to come to room temperature after a brief reflux period, whereupon the potassio-salt crystallized out. Addition of dilute hydrochloric liberated the "free acid" in the form of a highly colored oil whose color varied from one carbonyl compound to the next.

The oil was extracted with ether, dried over anhydrous sodium sulfate and distilled under reduced pressure. In some cases the forerun was equal to or greater than the volume of desired product. The exact nature of these side products was not determined as it was not felt that further pursuit of this subject constituted progress toward the elucidation of the Schmidt reaction.

The results tabulated in Table VII show that the yields obtained in this reaction compare quite favorably with those of Higson and Thorpe in two of the three parallel cases. These authors based their yields on a quarter of a mole of

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cyanohydrin which is two and a half times the amount of ketone or aldehyde used in our reactions with the exception of acetone.

At the present time there appears to be no explanation - from experimental data - as to the reason why the yield with butanone was not in line with those of acetone and cyclohexanone. The reaction was run several times with variations in the reflux period without increasing the yields. However, on the basis of the 10% increase in yield with acetone when the amounts of reactants were increased to one mole, it seems safe to predict that a substantial gain should be realized with both butanone and propionaldehyde.

The dicyanoesters arising from propionaldehyde and isobutyraldehyde are new compounds, though the corresponding succinic acids are known.

When a condensation with diisopropylketone was attempted, an oil resulted which resisted prolonged hydrolysis and appeared to be the recovered ketone. Apparently, the steric effect of the two rather bulky isopropyl groups is large enough to inactivate this ketone toward both condensation and 1,4 addition.

Our results with benzaldehyde were somewhat disappointing in comparison to the 95% conversion of mandelonitrile into ethyl-α,β-dicyano-β-phenylpropionate reported by Higson and Thorpe. From the products isolated it appears that the addition of potassium cyanide was incomplete.

When treated successively with ethyl α-cyanoacetate and potassium cyanide, benzaldehyde gave rise to an oil collected

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at 145-158°/0.1 mm. After an extended hydrolysis period with excess hydrochloric acid, two organic acids, later identified as α-cyanocinnamic and phenylsuccinic from their respective neutral equivalents and melting points, were isolated in equal amounts (12%). The acids were separated from one another on the basis of a differential in water solubility, α-cyanocinnamic acid being very much less soluble.

As in previous cases, the forerun in the distillation of the mixed esters was not examined other than to note that it was quite large and, in addition, decomposition appeared to be taking place, as was evident from the gaseous material which accompanied the entire distillation. Thus, the small yield of both acids may be partly accounted for if this gaseous material, presumably hydrogen cyanide, is attributed to the decomposition of mandelonitrile which is known to be quite incapable of sustaining distillation even at greatly reduced pressure.

The results with acetophenone seemed to further the belief that the reaction is not applicable to those carbonyl compounds which are directly adjacent to an aromatic nucleus. For when this ketone was subjected to an hour's reflux with ethyl α-cyanoacetate and pyridine acetate, there was no trace of a compound distilling in the anticipated range. Instead, the distillate consisted wholly of a low boiling mixture which appeared to be starting material. However, when the reflux period was increased to eighteen hours, there was isolated in 16.5% yield a product which distilled at 145-150°/0.1 mm.

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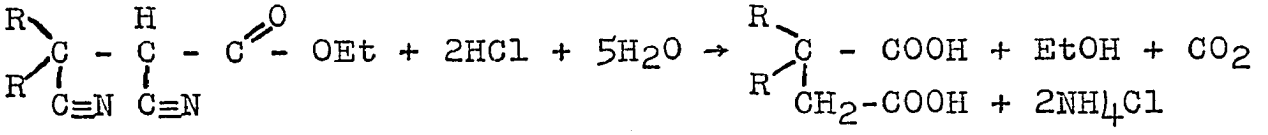
and gave on hydrolysis an acid melting at 157-158° whose neutral equivalent corresponded to that of α-methyl-α phenylsuccinic acid. This was ultimately confirmed by analyses of both the dicyanoester and acid.

4. Hydrolysis.- Concentrated hydrochloric acid was chosen to hydrolyze and decarboxylate these dicyanoesters. The time of reflux varied from five to eighteen hours.

The stoichiometry of the hydrolysis requires two moles of hydrochloric acid for each mole of ester, but it was found that excess acid was required due apparently to the loss of hydrogen chloride during refluxing.



Consequently, a ratio of nine moles of hydrochloric acid to one mole of the ester was chosen or approximately 4 ml. of acid to 1 g. of ester. It was frequently necessary, after several hours of refluxing, to add more acid when it appeared that a relatively large amount of material remained unhydrolyzed in the form of the original insoluble oil.

After the completion of hydrolysis, the acid mixture was cooled and the resulting solids filtered. At this stage it was found that the acids were badly contaminated with ammonium chloride. The relatively pure acids were extracted by successive treatment with ether and hot benzene. The insolubility of the majority of these acids in cold benzene provided an excellent method of obtaining the desired acid, free from any unhydrolyzed material.

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When the succinic acid contained a large alkyl substituent or an aromatic residue, however, the solubility in benzene appeared to be too great to permit its use as a crystallizing medium. This particular case is described in the experimental for 1-carboxycyclohexylacetic acid, where petroleum ether was added to the benzene solution of the acid to reduce the solubility of the acid.

For unsymmetrical dimethylsuccinic acid it was found that the hydrochloric acid filtrate contained 15% of the total organic acid isolated. Therefore, it was necessary to remove the solvent either by direct evaporation or distillation under reduced pressure, the latter being preferable.

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EXPERIMENTAL I

1. Acetophenone

To a solution of 2.40 g. (0.02 mol.) of distilled acetophenone in 25 g. of trichloracetic acid at 55° was added 2.0 g. (0.031 mol.) of powdered sodium azide all at one time.

After seven hours at 55-60°, with occasional stirring, the pasty mass was poured into 150 ml. of cold water and neutralized with sodium carbonate. The resulting tan solid was filtered off and the filtrate was extracted with three 25 ml. portions of benzene. The extracts were dried over anhydrous sodium sulfate and the solvent blown off on a steam bath. The combined solids amounted to 1.78 g. when dry.

The filtrate after extraction was acidified with concentrated hydrochloric acid and treated with bromine water. The white, fluffy 2,4,6-tribromoaniline was filtered off and, when dry, amounted to 1.00 g., melting at 115-117° (lit. 119°).

acetanilide + N-methyl-benzamide ...	1.78 g. ...	0.0132 mol.
2,4,6-tribromoaniline	1.00 g. ...	0.0030 mol.
Total moles of product isolated		0.0162 moles.
Extent of Schmidt reaction		81%

Hydrolysis.- The 1.78 g. of mixed amides was refluxed for seven hours with 100 ml. of 25% methanolic potassium hydroxide. The strongly alkaline solution was extracted with three 20 ml. portions of benzene, and the extracts were dried over anhydrous sodium sulfate and then acetylated with 5 ml. (0.054 mol.) of acetic anhydride by warming the benzene solution of amines and acetylating agent on a steam bath for fifteen minutes. The

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mixture was then blown down to dryness and yielded 1.45 g. of acetanilide, melting at 110-112°.

The acetanilide obtained by an alternate procedure involving the distillation of the alkaline hydrolysis mixture did not vary appreciably from the value given above.

The alkaline solution remaining after the extraction of aniline was chilled and acidified with concentrated hydrochloric acid. The acid mixture was then extracted with three 25 ml. portions of benzene, dried over anhydrous sodium sulfate and carefully evaporated to dryness. This yielded 0.13 g. of benzoic acid, melting at 118-120° (lit. 122°).

A typical set of data follows:

acetophenone	2.40 g.	0.02 mol.
acetanilide	1.45 g.	0.0107 mol.
2,4,6-tribromoaniline	1.00 g.	0.0030 mol.
		0.0137 mol.
benzoic acid	0.13 g.	0.0011 mol.
Total moles isolated	0.0148 or $\frac{0.0148}{0.0162}$ x 100 = 91.3%	
acetanilide	93%	
N-methyl-benzamide	7%	

Average of three determinations -

acetanilide	95%
N-methyl-benzamide	5%

2. Propiophenone

In a three-necked 500 ml. flask provided with mechanical stirring, a reflux condenser, and a dropping funnel, was added 75 g. (0.56 mol.) of anhydrous aluminum chloride to a mixture of 100 ml. (1.13 moles) benzene and 100 ml. of carbon disulfide. Then, with the reaction mixture gently refluxing

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on a steam bath, 26 g. of propionic anhydride was added over a period of an hour.

After an additional hour's reflux, the carbon disulfide was carefully distilled. The mixture was then poured on cracked ice and the benzene layer drawn off in a separatory funnel. The aqueous layer was extracted twice with benzene and the extracts were combined with the initial separations and washed successively with dilute sodium hydroxide and water. The benzene solution was then dried over anhydrous sodium sulfate and distilled. This method yielded 15 g. (60%) of propiophenone, distilling at 90-91°/13 mm. (Shriner and Turner,[66] 115-120°/21 mm.).

To a solution of 2.68 g. (0.02 mol. of propiophenone in 25 g. of trichloroacetic acid at 55° was added 2 g. (0.031 mole) of powdered sodium azide all at once. After seven hours at 55-60°, with occasional stirring, the mixture was poured into 150 ml. of cold water and alkalyzed with ammonium hydroxide. The tan product was filtered from the cooled solution and washed with water and warm petroleum ether (60-75°); yield, 2.31 g. of mixed amides. The alkaline solution was acidified with hydrochloric acid and treated with bromine water. The 2,4,6-tribromoaniline was filtered off and, when dry, weighed 0.13 g., melting at 114-117° (lit. 119°).

A typical set of data follows:

N-ethyl-benzanilide + propionanilide	2.31 g. ...	0.0155 mol.
2,4,6-tribromoaniline	0.13 g. ...	0.0004 mol.
		0.0159 mol.

This would correspond to an 80% yield based on 0.02 mol. of propiophenone.

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Hydrolysis.- The 2.31 g. of mixed amides were hydrolyzed for eighteen hours with 100 ml. of 20% methanolic potassium hydroxide. The alkaline solution was extracted with three 20 ml. portions of benzene and the latter dried over anhydrous sodium sulfate. To this dried benzene solution was added 5 ml. (0.054 mol.) of reagent acetic anhydride and the mixture was warmed on a steam bath for fifteen minutes. The mixture was then blown down to dryness, leaving 1.64 g. of acetanilide, melting at 108-111° (lit. 114°) and free from the characteristic sharp odor of acetic anhydride.

The cool alkaline solution was acidified with concentrated hydrochloric acid and extracted with three 20 ml. portions of benzene. This solution was likewise dried over anhydrous sodium sulfate, then carefully evaporated to dryness, yielding 0.27 g. of benzoic acid melting at 117-119° (lit. 122°).

A typical set of data is presented below.

Propiophenone	2.68 g.	0.02 mol.
Acetanilide	1.64 g.	0.0122 mol.
2,4,6-tribromoaniline	0.13 g.	0.0004 mol.
		0.0126 mol.
Benzoic acid	0.27 g.	0.0022 mol.
		0.0148 mol. (93%)

Average of two determinations-

Propionanilide	85%
N-ethyl-benzamide	15%

3. Isobutyrophenone

Preparation.- a) Grignard Reagent: Isopropylmagnesium bromide was prepared in the usual manner from 166.3 g. (1.36 mol.) of isopropylbromide, 34 g. (1.4 mol.) of magnesium and 200 ml. of ether.

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b) The Grignard reagent was diluted with 200 ml. of dry benzene and from a dropping funnel 70 g. (0.68 mol.) of benzonitrile, diluted with an equal volume of benzene, was added during the course of an hour while the reaction mixture was refluxing. Refluxing was continued for four hours after all the benzonitrile had been added. The mixture was then cooled to 0° by means of an ice-salt bath, and an aqueous solution of ammonium chloride was added dropwise with constant stirring.

The aqueous layer was separated from the benzene-ether phase and the former heated for an hour on a steam bath. The resulting oil was extracted three times with benzene, dried over anhydrous sodium sulfate and distilled. This procedure yielded 63 g. (68%) of isobutyrophenone collected at 99-105°/15mm. (Faworsky[23], 95-98°/10 mm.).

Isobutyrophenone was also prepared in good yield (66%) by treating benzoyl chloride with diisopropylcadmium. However, this method is somewhat longer, involving the extra step of preparing the dialkylcadmium and the yield is not comensurate with the additional time required.

An attempt to prepare this ketone by treating isobutyryl chloride with phenylmagnesium bromide at 0° resulted in a high yield of tertiary alcohol and only a 15% yield of isobutyrophenone.

Schmidt Reaction.- To a solution of 2.96 g. (0.02 mole) of isobutyrophenone in 25 g. of trichloroacetic acid at 60° was added 2 g. (0.031 mol.) of powdered sodium azide all at once. After an hour, addition of small quantities of sodium

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azide was begun again so that in three hours another 2 g. had been introduced.

After standing for eighteen hours at 60-65°, the pasty mass was poured into 150 ml. of water and the solution alkalized with ammonium hydroxide. The oil that persisted was separated and the aqueous solution extracted with three 25 ml. portions of benzene. After combining the benzene extractions with the original separation, the mixture was steam distilled and the distillate collected in a receiver containing 15 ml. of 1:3 hydrochloric acid.

The benzene phase of the distillate was separated and dried over anhydrous sodium sulfate, then blown off on a steam bath. The residue was dissolved in alcohol and converted to a 2,4-dinitrophenylhydrazone, weighing 1.85 g. and melting at 155-158°. A single recrystallization from methanol raised the melting point to 160-162° (lit[65], m.p. of 2,4 dinitrophenylhydrazone of isobutyrophenone, 163°).

The hydrochloric acid solution was evaporated to dryness but yielded no amine salts. The residue in the still pot was extracted three times with benzene and in the usual fashion 1.35 g. of mixed amides were obtained. The ammoniacal solution remaining from the initial benzene extraction was refluxed for an hour to destroy the trichloroacetic acid and then extracted with benzene. However, there was no trace of any benzoic acid on working up this benzene extraction.

The results of the Schmidt reaction on isobutyrophenone were as follows:

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Isobutyrophenone	2.68 g.	0.02 mol.
Mixed amides	1.85 g.	.0113 mol.
D.N.P. isobutyrophenone ...	1.85 g.	0.0054 mol.
Total recovery		0.0167 mol. or 84%

The mixed amides were hydrolyzed with 100 ml. of 25% methanolic potassium hydroxide for eighteen hours, and in the manner described in the previous cases 0.69 g. of acetanilide and 0.62 g. of benzoic acid were isolated.

Acetanilide	0.69 g.	0.0051 mol.
Benzoic acid	0.62 g.	0.0052 mol.
Total recovery		0.0103 mol. or 92%

Thus, on the basis of the total moles recovered, the values for the isomeric amides are:

Isobutyranilide	49%
N-isopropylbenzamide	51%

4. Phenylacetone

Preparation.-(41) The ketone was prepared by refluxing a mixture of 100 g. (0.735 mol.) of phenylacetic acid, 167 ml. (182 g., 1.78 mol.) of acetic anhydride and 50 g. (0.61 mol.) of anhydrous sodium acetate for eighteen hours.

The reaction mixture was poured into 500 ml. of water and extracted three times with benzene. The benzene solution was neutralized with a sodium bicarbonate solution, then washed with water and dried over anhydrous sodium sulfate.

The solvent was removed by distillation and the phenylacetone was collected at 96-98°/13 mm. (Danilov(20), 100-101°/14 mm.). The yield was 35 g. or 35% of the theoretical value.

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This same ketone was prepared in 60% yield by condensing phenylacetonitrile with ethyl acetate in the presence of sodium ethoxide and hydrolyzing the resulting phenylacetoacetonitrile. However, this method was very time-consuming and required a great deal of attention compared to the relatively simple method described in the preceding paragraph.

Schmidt Reaction.- To a two-phase mixture of 2.68 g. (0.02 mol.) of phenylacetone and 10 ml. of concentrated hydrochloric acid at room temperature was added 2 g. (0.031 mol.) of powdered sodium azide over a period of an hour. A more rapid addition causes a large increase in temperature.

After standing for eight hours, the mixture was diluted with 100 ml. of water and extracted with three 25 ml. portions of benzene. The benzene solution was dried over anhydrous sodium sulfate and then blown down to dryness on a steam bath, yielding 1.50 g. of a tan solid. The aqueous solution remaining from the benzene extraction was alkalyzed with ammonium hydroxide, extracted with three 25 ml. portions of benzene, and dried over anhydrous sodium sulfate. The solvent was blown off on a steam bath and yielded, when dry, 0.59 g. of a white solid.

Thus, 2.09 g. (0.0141 mol.) amount to a 70% yield of mixed amides for this ketone. The average of several determinations was 63%.

Hydrolysis.- The combined solids (2.09 g.) were hydrolyzed by refluxing for twelve hours with 100 ml. of 25% methanolic potassium hydroxide. The alcoholic solution was steam distilled and the distillate was caught in a receiver containing 15 ml. of 1:3 hydrochloric acid. The acid solution

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of amine hydrochlorides was evaporated to dryness, and then taken up in 50 ml. of water which was then treated with potassium hydroxide to liberate the free amines. The amines were extracted with benzene, dried over anhydrous sodium sulfate and then converted to the corresponding benzamides by treatment with 3 ml. (0.026 mol.) of benzoyl chloride. This yielded 1.25 g. of N-benzylbenzamide which after a single recrystallization from aqueous methanol melted at 103-105° (Beckmann[5], 105°).

The alkaline residue in the still pot was acidified, extracted with benzene and dried in the usual fashion, and yielded 1.06 g. of phenylacetic acid, melting at 73-76° (lit. 78°).

Phenylacetone	2.68 g.	0.02 mol.
Phenylacetic acid	1.06 g.	0.0080 mol.
N-benzyl-benzamide	1.25 g.	0.0059 mol.
Total recovery		0.0139 mol. or 98%

N-methyl-phenylacetamide 58%
N-benzylacetamide 42%

Average of several determinations -

N-methyl-phenylacetamide 50%
N-benzylacetamide 50%

5. Benzylacetone

Preparation.- This ketone was prepared by the action of β-phenylethylmagnesium bromide on acetic anhydride at -70°, as described for similar methyl ketones by Newman[50].

β-phenylethyl bromide was prepared by refluxing a mixture of 67 g. (0.55 mol.) of β-phenylethyl alcohol, 0.5 g. (0.005 mol.)

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95% sulfuric acid, and 240 g. (0.3 mol. or 330 ml.) of constant boiling (48%) hydrobromic acid (sp. gr. 1.49) for twelve hours.

The oily layer was drawn off in a separatory funnel and the acid layer extracted twice with benzene. The extractions were combined with the original separation and shaken with a sodium carbonate solution, followed by a washing with water. The benzene solution was dried over anhydrous sodium sulfate and the solvent removed by distillation. This yielded 91 g. (89%) of β-phenylethyl bromide, collected at 111-115°/20 mm. (Rupe[56], 92°/11 mm.).

The Grignard reagent was prepared in the usual fashion from 91 g. (0.49 mol.) of β-phenylethyl bromide, 12 g. (0.5 g. atom) of magnesium of 400 ml. of anhydrous ether.

After the reaction was over, a 2 ml. aliquot was titrated with standard acid and found to contain 9.5×10^{-4} mol. of β-phenylethylmagnesium bromide/ml.

During the course of an hour 210 ml. (0.2 mol.) of the titrated Grignard reagent was conducted through a glass coil, cooled externally by a dry ice, chloroform and carbon tetrachloride mixture, into a three-necked, 500 ml. flask provided with mechanical stirring, an efficient reflux condenser and containing 40 g. (0.39 mol.) of reagent acetic anhydride. The flask itself was set in a beaker of the same cooling mixture and the beaker in turn placed in a wooden box insulated with excelsior. In this way there was no difficulty in reducing the temperature of the reaction mixture to -70° and

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preventing it from rising above -58° throughout the entire addition of Grignard reagent.

Following the introduction of β-phenylethylmagnesium bromide, the mixture was stirred for three hours, whereupon the cooling bath was removed and the reaction mixture was treated with 100 ml. of a 0.3 molar ammonium chloride solution.

The ether solution was separated and the aqueous solution was twice extracted with 50 ml. portions of ether and dried over anhydrous sodium sulfate. The ether was removed by distillation and 22 g. (75%) of benzylacetone was collected at 125-130°/23 mm. (lit.[42], 118-122°/15-16 mm.).

Schmidt Reaction.- To a stirred solution of 1.48 g. (0.01 mol.) of benzylacetone in 25 ml. of a 0.675 molar (0.017 mol.) hydrogen azide-benzene solution, prepared as described in "Organic Reactions",[76] was added, by means of an "eye dropper", 1 ml. (0.018 mol.) of 95% sulfuric acid.

After an hour, nitrogen evolution appeared to cease and additional 10 ml. of the benzene-hydrogen azide solution was added and the stirring continued for another hour. The benzene was blown off on a steam bath and the residue diluted with 50 ml. of water. An oil resulted which was extracted with three 25 ml. portions of benzene and dried over anhydrous sodium sulfate. Evaporation of the benzene yielded an oil which failed to crystallize on cooling in the refrigerator for several days.

Therefore, the oil was dissolved in methanol and hydrolyzed with 100 ml. of 25% alcoholic potassium hydroxide for

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eighteen hours.

The alcoholic solution was extracted with three 25 ml. portions of benzene and the latter dried over anhydrous sodium sulfate. To the dry benzene solution was added 5 ml. of 4.18 N (0.021 mol.) of hydrogen chloride in dioxane, causing the precipitation of the amine salts. These were filtered off and dried. The product weighed 0.98 g. and melted at 195-200°. Dissolving the impure salt in absolute ethanol and crystallizing the pure product by addition of ether gave 0.94 g. of β-phenylethylamine hydrochloride, melting at 215-216°. (Filete[24], 216°)

The alkaline solution was acidified with concentrated hydrochloric acid and extracted with three 20 ml. portions of benzene. The solution was dried over anhydrous sodium s[illegible] amount of oil which crystallized from petroleum ether (60-75°). ar[illegible] This gave 15 mg. of β-phenylpropropionic acid, m.p. 40-45°. Th[illegible] (lit. 48°.)
(lit. 48°.)

Since the amount of mixed amides was unknown due to the fact that the oil failed to crystallize, the percent of each isomer is based on 0.01 mol. of benzylacetone.

β-phenylethylamine hydrochloride	0.94 g.	0.00595 mol.
β-phenylpropionic acid	0.015 g.	0.0001 mol.

N-β-phenylethylacetamide	60%
N-methyl-β-phenylpropionamide	1%

The yields are far superior using trichloroacetic as both solvent and catalyst, as shown by Smith[68], and correspondingly the amount of isomeric amides is higher.

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6. Pivalophenone (t-butylphenyl ketone)

a) Pivalyl chloride (trimethylacetyl chloride)

To a 250 ml. round-bottomed flask fitted with a calcium chloride tube were added 60 g. (0.59 mol.) of pivalic acid[57] and 51 ml. of thionyl chloride (0.69 mol.). The mixture was allowed to stand at room temperature for eighteen hours and then the excess thionyl chloride was removed by distillation. The pivalyl chloride was fractionated through a Snyder column and 54 g. (76%) of product was collected at 100-101°/750 mm. (Haller and Bauer[30], 105-106°/760 mm.).

b) Phenylmagnesium bromide

This Grignard reagent was prepared in the usual fashion from 47 g. (0.3 mol.) of bromobenzene, 7.7 g. (0.32 mol.) of magnesium and 250 ml. of ether. A sample was withdrawn, titrated with standard acid and found to contain 0.0011 mol./ml. (95%).

c) Coupling Reaction

In a three-necked, 500 ml. round-bottomed flask equipped with a reflux condenser, a mechanical stirrer and dropping funnel were added 22 g. (0.18 mol.) of pivalyl chloride and 100 ml. of anhydrous ether. The solution was cooled to 0° and 200 ml. (0.22 mol.) of the titrated phenylmagnesium bromide was added in the course of three hours.

The reaction mixture was treated with water and the ether layer drawn off, while the aqueous layer was extracted with two 50 ml. portions of ether. The combined extracts were washed with sodium carbonate and water, then dried over calcium chloride.

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The ether was removed and the product collected at 96-100°/10 mm. (Nef.[48], 102°/12 mm.). The yield was 17.5 g. or 60% of the theoretical value. An attempted synthesis of this ketone through a Friedel and Crafts reaction resulted in the formation of a ketone whose boiling point and 2,4-dinitrophenylhydrazone did not agree with literature values. Shortly thereafter, Pearson[54] showed that pivalyl chloride gave, under controlled conditions, p-tertiary-butylpivalophenone in 80% yield. This would then account for the observed anomaly in our attempt to prepare pivalophenone.

7. Acetomesitone (mesitylmethyl ketone)

This ketone was prepared from acetic anhydride and mesitylene according to the directions of Noller and Adams.[52] The procedure gave an 85% yield of acetomesitone collected at 106-109°/10 mm. (Noller and Adams[52], 122-123°/19 mm.).

8. Tertiary butylmesityl ketone

a) Preparation of mesitylmagnesium bromide

The Grignard reagent was prepared in the usual fashion from 60 g. (0.3 mol.) of bromomesitylene, 8 g. (0.33 mol.) of magnesium and 250 ml. of ether. A sample was withdrawn, titrated with standard acid and found to contain 0.00225 mol./ml. of mesitylmagnesium bromide.

b) Coupling Reaction

In a 500 ml. three-necked, round-bottomed flask, fitted with a reflux condenser, a mechanical stirrer and dropping funnel, was added 17 g. (0.14 mol.) of pivalyl chloride

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in 100 ml. of anhydrous ether. 250 ml. (0.225 mol.) of the titrated mesitylmagnesium bromide was added to the stirred ether solution of acid chloride, which was warmed on a steam bath at a rate commensurate with gentle reflux. After all the Grignard reagent had been added, the reaction mixture was refluxed for an additional hour. The ether solution was cooled to 0° and treated with dilute hydrochloric acid.

The ether layer was drawn off in a separatory funnel and the acid layer extracted with two 100 ml. portions of ether. The combined separations were washed with a dilute sodium carbonate solution, then with water and finally dried over calcium chloride.

The ether was removed and the product distilled at 126-130°/11 mm. and amounted to only 10 g. (0.05 mol.) or 35% of the theoretical value.

Carbon calculated 82.31%	Carbon found
Hydrogen calculated 9.80%	Hydrogen found

Attempts to oximate this ketone, even in a sealed tube at 160° in pyridine solution, proved futile.

9. β,β-dimethyl-α-tetralone

a) α,α-dimethylsuccinic anhydride

In a 500 ml, round-bottomed flask, fitted with a reflux condenser closed with a calcium chloride tube, 175 ml. of acetic anhydride and 75 g. (0.51 mol.) of α,β dimethylsuccinic acid, the preparation of which is given in the section on alkylsuccinic acids, were heated gently on a steam bath with occasional shaking until a clear solution was obtained and then one-half hour longer.

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The acetic acid and unreacted acetic anhydride were removed by distillation and the α,α-dimethylsuccinic anhydride collected at 96-97°/10 mm. (Vorlander and Gartner[73], 117°/22 mm.). The yield was 54 g. (0.43 mol.) or 83% of the theoretical amount.

b) α,α-dimethyl-β-benzoylpropionic acid

In a one l., three-necked, round-bottomed flask, fitted with a mechanical stirrer and two reflux condensers, were placed 54 g. (0.43 mol.) of α,α-dimethylsuccinic anhydride and 222 g. (2.8 mols.) of dry, thiophene-free benzene. The stirrer was started and while the mixture was at room temperature, 130 g. (0.96 mol.) of powdered, anhydrous aluminum chloride was added all at once. Hydrogen chloride was evolved and the reaction became hot. It was then heated in an oil bath and refluxed with continuous stirring for half an hour. The flask was surrounded by cold water and 200 ml. of water introduced by means of a dropping funnel inserted in one of the condensers. The excess benzene was removed by steam distillation and the residue acidified with concentrated hydrochloric acid. The crude solid acid was filtered off and the large lumps broken up and suspended in a liter of water containing 250 g. of sodium carbonate. This mixture was boiled for two hours and the resulting solution filtered with suction. The filter cake was washed with hot water and the filtrate acidified carefully with concentrated hydrochloric acid. The precipitated α,α-dimethyl-β-benzoylpropionic acid was filtered, washed with hot water and dried in an oven at

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100° for two hours. This procedure yielded 74 g. of acid, melting at 170-171° (Sengupta[59], 170-171°).

c) α,α-dimethyl-γ-phenylbutyric acid

Amalgamated zinc was prepared by shaking for five minutes a mixture of 370 g. of mossy zinc, 37 g. of mercuric chloride, 600 ml. of water and 18 ml. of concentrated hydrochloric acid contained in a two l. round-bottomed flask. The solution was decanted and the following reagents were added to the zinc in the order named: 225 ml. of water, 370 ml. of concentrated hydrochloric acid, and 74 g. (0.35 mol.) of α,α-dimethyl-β-benzoylpropionic acid. The flask was fitted with a vertical condenser connected to a gas absorption trap and the reaction mixture was boiled vigorously for eighteen hours. Three 50 ml. portions of concentrated hydrochloric acid were added at approximately five hour intervals during the refluxing period.

After cooling to room temperature, the mixture was extracted with three 100 ml. portions of ether; the extracts were dried over calcium chloride, and the ether was removed. The acid was distilled under reduced pressure, yielding 42 g. (61%) of α,α-dimethyl-γ-phenylbutyric acid distilling at 175-177°/10 mm. and melting at 96-97° (lit.[60], 98°).

d) β,β-dimethyl-α-tetralone

To a solution of 42 ml. of water in 126 ml. of concentrated sulfuric acid was added 42 g. (0.22 mol.) of α,α-dimethyl-γ-phenylbutyric acid. The mixture was heated on a steam bath for one hour with continual stirring. The acid solution was poured on ice and extracted with three

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50 ml. portions of ether. After the extract was dried over anhydrous sodium sulfate, the ether was removed and the β,β-dimethyl-α-tetralone collected at 119-121°/9 mm. (lit.[61], 150°/27 mm.).

10. Fluorenone

Schmidt Reaction.- To a solution of 1.80 g. (0.01 mol.) of fluorenone in 20 ml. of concentrated sulfuric acid at room temperature was added, with stirring, 1.0 g. (0.015 mol.) of sodium azide over a period of half an hour. The mixture was then poured on 50 g. of ice and the precipitated phenanthridone was filtered, washed with water, and finally with warm petroleum ether (60-75°).

This yielded 1.93 g. (99%) of product melting at 290-293° with sublimation (Graebe and Wander[29], 293°).

11. 4,4'-dichlorobenzophenone

The ketone was prepared in 74% yield from 1,1,1-trichloro-2,2-bis (p-chlorophenyl) ethane (D.D.T.), following the direction of Forrest, Stephenson and Waters.[27]

Schmidt Reaction.- To a solution 2.52 g. (0.01 mol.) of 4,4'-dichlorobenzophenone in 15 g. of trichloroacetic acid was added first 2 ml. of concentrated sulfuric acid and then 2 g. (0.031 mol.) of powdered sodium azide. The mixture was allowed to stand at a temperature of 55-60° with occasional stirring for twelve hours, and then poured into 100 ml. of water. The precipitated 4,4'-dichlorobenzanilide was filtered off, and when dry, washed with warm petroleum ether. This gave 2.52 g. (94%) of product, melting at 206-207°. (Dittrich[22], 207-208°)

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12. p-Chlorobenzophenone

Preparation.- This ketone was prepared in 70% yield from benzoyl chloride, benzene and aluminum chloride according to the directions of Gomberg and Cone[28]. Recrystallization from alcohol gave a product melting at 77-78°. (Gomberg and Cone[28], 77-78°.)

Schmidt Reaction.- To a solution of 2.17 g. (0.01 mol.) of p-chlorobenzophenone in 15 g. of trichloroacetic acid and 2 ml. (0.036 mol.) of concentrated sulfuric acid at 55° was added 2 g. (0.031 mol.) of powdered sodium azide all at once. With occasional stirring the mixture was held at a temperature of 55-60° for eight hours and then poured into 150 ml. of water, which precipitated the crude amides. The mixture was alkalyzed with ammonium hydroxide and the white solid filtered off. After drying for twenty-four hours, the solid material amounted to 2.27 g. The lumps were broken up and once more treated with 10 ml. of ammonium hydroxide in 50 ml. of water, then dried again in vacuum desiccator. The solid weighed 2.24 g. and was then washed with warm petroleum ether (60-75°). This gave 2.17 g. (0.094 mol.) or 94% of mixed amides.

Hydrolysis.- The amides were dissolved by refluxing them with 35 ml. of glacial acetic acid, and then 10 ml. (0.18 mol.) of concentrated hydrochloric acid was introduced through the top of the reflux condenser. The solution was refluxed for forty-eight hours during which time an additional 10 ml. of hydrochloric acid was added and the solution heated for another forty-eight hours.

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The acid mixture was poured into 200 ml. of water and the solution extracted with three 25 ml. portions of benzene. The benzene solution was shaken with 20 ml. of a 25% potassium hydroxide solution and then the latter acidified with concentrated hydrochloric acid. The precipitated acids were filtered off, washed with 10 ml. of cold water; weight, 0.98 g. when dry. The mixed acids were heated with 100 ml. of water and filtered when cool. This gave 0.48 g. of p-chlorobenzoic acid, melting at 225-230° (Beilstein and Schlun[7], 235°). The benzoic acid, by difference, was 0.50 g.

p-Chlorobenzoic acid	0.48 g.	0.0031 mol.
Benzoic acid	0.50 g.	0.0041 mol.
Total acid recovered	0.98 g.	0.0072 mol.

Thus, the moles recovered account for 77% of the mixed amides and the values for the isomeric amides based on this recovery are as follows:

Benz(p-chloro)anilide	57%
p-Chlorobenzanilide	43%

The aqueous acid solution was evaporated to dryness and the amine salts taken up in 50 ml. of water. The solution was alkalyzed with potassium hydroxide and extracted with three 25 ml. portions of benzene. The extract was dried over potassium hydroxide pellets and then treated with 5 ml. of acetic anhydride. After heating the mixture for fifteen minutes on a steam bath, the excess benzene and acetic anhydride were blown off, leaving, when dry, 1.35 g. of mixed anilides. These were heated to boiling with 100 ml. of water and filtered when cool. This gave 0.90 g. of p-chloroacetanilide, melting at 166-170° (Beilstein and Kurbatow[6],

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172.5°) and 0.45 g. of acetanilide by difference.

Acetanilide	0.45 g.	0.0033 mol.
p-Chloroacetanilide ..	0.90 g.	0.0053 mol.
Total anilides recovered:		
	1.35 g.	0.0086 mol.

Thus the moles of anilides recovered account for 92% of the mixed amides and the values for the mixed amides based on this recovery are as follows:

Benz(p-chloro)anilide	62%
p-Chlorobenzamide	38%

The average value based on the amount of p-chloroacetanilide recovered are:

N-p-chlorophenylbenzamide	60%
p-Chlorobenzamide	40%

13. p-Nitrobenzophenone

In a three-necked, 500 ml. round-bottomed flask, fitted with a mechanical stirrer, a reflux condenser provided with a hydrogen chloride trap and a thermometer-well, were added 23 g. (0.12 mol.) of para-nitrobenzoyl chloride 200 ml. (2.6 mol.) of dry, thiophene-free, benzene and 33 g. (0.24 mol.) of anhydrous aluminum chloride powder. The stirrer was started and the reaction mixture heated to a gentle reflux by means of a "glas-col" heating mantle, and the heating continued until hydrogen chloride ceased to be evolved (one hour).

The mixture was then poured on ice and hydrochloric acid, and the benzene layer was separated and washed first with a solution of sodium carbonate and then with water. The

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benzene solution was returned to the original flask and the solvent removed by steam distillation. The residue in the flask, consisting of crude p-nitrobenzophenone, was filtered off and the ketone recrystallized from 200 ml. of hot glacial acetic acid.

This procedure gave 20 g. (0.08 mol.) or 75% of the theoretical amount of p-nitrobenzophenone, melting at 135-136° (Schroeter[64], 138°).

Schmidt Reaction.- To a solution of 2.27 g. (0.01 mol.) of p-nitrobenzophenone in 2 ml. (0.036 mol.) of concentrated sulfuric acid and 15 g. of trichloroacetic acid at 55° was added 2 g. (0.031 mol.) of powdered sodium azide all at once. The mixture was held at a temperature of 55-60° for ten hours with occasional stirring and then poured into 100 ml. of water. The yellow solid was filtered off, the lumps broken up and then digested with 60 ml. of 1:5 ammonium hydroxide. The solid was refiltered, washed with water and finally with warm petroleum ether (60-75°). This gave 2.26 g. (93%) of mixed amides.

There appeared to be no noticeable difference in the rate of nitrogen evolution between para-nitrobenzophenone and the other benzophenones.

Hydrolysis.- The amides were dissolved by refluxing them with 50 ml. of glacial acetic acid and then 20 ml. of concentrated hydrochloric acid was introduced through the top of the condenser. The refluxing was continued for twenty-four hours at the end of which time the mixture was poured into 200 ml. of water. In a short time a fair amount of needle-like material deposited, and was filtered off.

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The filtrate was extracted with three 25 ml. portions of ether and the extracts were dried over anhydrous sodium sulfate. The ether was then blown off on a steam bath and the resulting solid combined with the solid obtained by filtration. The mixture of solids was dissolved in 100 ml. of ether and then shaken with 25 ml. of a 25% aqueous potassium hydroxide solution. The ether layer was drawn off, washed once with water and once again dried over anhydrous sodium sulfate. After the ether was removed on the steam bath, there remained 0.57 g. of p-nitroaniline, melting at 140-143° (Merz and Ris[46], 145°).

The alkaline solution containing the mixed acids was acidified with concentrated hydrochloric acid and the resulting solid extracted with three 25 ml. portions of ether and this solid dried over anhydrous sodium sulfate. Removal of the ether in the usual fashion gave 1.07 g. of mixed acids.

The acids were dissolved in 50 ml. of ethanol and reduced by shaking the mixture for an hour with hydrogen in the presence of platinous oxide-norite (Adam's) catalyst, giving a colorless solution.

The alcoholic solution was alkalyzed with potassium hydroxide and evaporated to dryness. The salt residue was taken up in 100 ml. of water and made distinctly acid with sulfuric acid. The solution was extracted with three 20 ml. portions of ether and the extract dried over anhydrous sodium sulfate. After evaporating the ether, there remained 0.45 g. of benzoic acid, melting at 117-119°. The nitrobenzoic acid, by difference, then was 0.62 g.

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Benzoic acid	0.45 g.	0.0037 mol.
p-Nitrobenzoic acid ...	0.62 g.	0.0037 mol.
Total acid isolated ...	1.07 g.	0.0074 mol.

Thus 0.0074 mol. of acids were isolated from 0.0093 mol. of mixed amides or 80% of the theoretical amount. The relative amount of mixed amides are:

p-Nitrobenzanilide	50%
Benz(p-nitro)anilide	50%

The acid solution still containing the aniline was evaporated to dryness and taken up in 50 ml. of water, and then alkalyzed with potassium hydroxide. The alkaline solution was then extracted with three 25 ml. portions of benzene, dried over potassium hydroxide and then acetylated with 3 ml. of acetic anhydride. After evaporating the benzene and excess acetic anhydride, there remained 0.55 g. of acetanilide, melting at 110-112°.

A typical set of data based on the recovery of both p-nitroaniline and acetanilide follows:

p-Nitroaniline	0.57 g.	0.0041 mol.
Acetanilide	0.55 g.	0.0040 mol.
Total	1.02 g.	0.0081 mol. or 87% of 0.0093 mol.

The mixed amides based on the recovery of basic material is then:

p-Nitrobenzanilide	49%
Benz(p-nitro)anilide	51%

14. p-Methylbenzophenone

Preparation.- This ketone was prepared in 60% yield from p-tolymagnesium bromide and benzonitrile.

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a) p-Tolylmagnesium bromide

The Grignard reagent was prepared in the usual manner from 85.5 g. (0.5 mol.) of p-bromotoluene, 13.2 g. (0.55 mol.) of magnesium and 200 ml. of anhydrous ether.

b) Nitrile addition

After the completion of the above reaction, 200 ml. of dry benzene was added and the mixture heated to a gentle reflux. From a dropping funnel 52 g. (0.5 mol.) of benzonitrile, diluted with an equal volume of dry benzene, was added with constant stirring at such a rate that the reaction did not reflux too vigorously. After the last of the benzonitrile had been added, the mixture was refluxed an additional hour.

From a dropping funnel, 100 ml. of a 5 molar ammonium chloride solution was introduced to the reaction mixture, previously cooled to 5° by means of an ice-salt bath. The aqueous layer was drawn off and heated on a steam bath for an hour to hydrolyze the ketimine hydrochloride. The resulting oil was then separated and the aqueous layer was extracted with two 50 ml. portions of benzene. The combined extracts were dried over anhydrous sodium sulfate and distilled. This yielded 59 g. (60%) of p-methylbenzophenone, boiling at 180°/15 mm. (311-312°/720 mm.). The white solid was recrystallized from aqueous ethyl alcohol and melted at 53-55°. (Marshall[43], 60° - metastable modification 55°.)

Schmidt Reaction.- To a solution of 1.96 g. (0.01 mol.) of p-methylbenzophenone, 15 g. of trichloroacetic acid and 2 ml. (0.036 mol.) of concentrated sulfuric acid at 55° was added 2 g. (0.031 mol.) of powdered sodium azide all at once.

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With occasional stirring the mixture was held at 55-60° for eight hours and then poured into a 100 ml. of water. The tan solid was filtered off, the lumps broken up and warmed with 60 ml. of 1:5 ammonium hydroxide. The solid material was once again filtered off, dried and washed with warm petroleum ether (60-75°). This gave 1.87 g. of mixed amides or 89% of the theoretical value.

In other determinations, yields as high as 96.5% of mixed amides were obtained.

Hydrolysis.- The mixed amides were dissolved by refluxing them with 25 ml. of glacial acetic acid and then 10 ml. of concentrated hydrochloric acid were introduced through the top of the reflux condenser, and the mixture refluxed for forty-eight hours. At the end of this time an additional 10 ml. of concentrated hydrochloric acid was added and the refluxing continued for another forty-eight hours, a total of ninety-six hours of refluxing.

The mixture was poured into 200 ml. of water and the incompletely precipitated acids were extracted with three 25 ml. portions of benzene. The latter was shaken with 20 ml. of a 25% potassium hydroxide solution and the alkaline solution was separated from the benzene layer. The former was acidified and extracted with three 20 ml. portions of ether and this solution was dried over anhydrous sodium sulfate. The ether was carefully blown off, leaving 0.96 g. of mixed acids.

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The mixed acids were heated with 25 ml. of water containing 0.55 ml. of 40% potassium hydroxide until solution was complete. Then an additional 2 ml. of potassium hydroxide was added, followed by 1 g. of potassium permanganate, and the mixture heated for one hour on a steam bath. The manganese dioxide was filtered, washed with water and the filtrate was acidified. This gave 0.50 g. of terephthalic acid which sublimed in the melting point capillary at 300°. (Bonz[9], sublimes at 300° without melting.). The amount of terephthalic acid was converted to the corresponding value for p-toluic acid and the benzoic acid ascertained by subtracting the latter value from the weight of mixed acids.

Terephthalic acid	0.50 g.	0.0030 mol.
p-Toluic acid	0.41 g.	0.0030 mol.
Benzoic acid	0.52 g.	0.0043 mol.
Total acid recovered	0.93 g.	0.0073 mol.

Thus, the recovery of acids amounted to 82% of the mixed amides and corresponded to the following figures for the mixed amides.

Benz(p-methyl)anilide	59%
p-Methylbenzanilide	41%

The average for three determinations was:

Benz(p-methyl)anilide	54%
p-Methylbenzanilide	46%

The amines were isolated in the form of their N-acetyl derivatives, but no satisfactory quantitative separation of the anilides could be attained.

15. p-Phenylbenzophenone

Preparation.- To a mixture of 65 ml. (0.44 mol.) of dry benzene, 38.5 g. (0.28 mol.) of anhydrous aluminum chloride

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powder, and 27.5 g. (0.18 mol.) of biphenyl, contained in a three-necked 500 ml. round-bottomed flask, fitted with mechanical stirring, a reflux condenser and a dropping funnel, was slowly added 50 g. (0.35 mol.) of benzoyl chloride. The mixture became quite warm with each addition of acid chloride and it was necessary to extend the addition over a period of ninety minutes in order to keep the reaction under control. The flask was then warmed on a steam bath with continued stirring for thirty minutes, following the addition of benzoyl chloride.

The contents of the flask were cooled externally with an ice-salt bath and then 100 ml. of water were introduced to decompose the complex. The mixture was acidified with concentrated hydrochloric acid and then steam distilled. The crude solid was recrystallized from a benzene-ligroin solution, yielding 30 g. (65%) of p-phenylbenzophenone, melting at 45-99°. An additional recrystallization from ethanol yielded 24 g. of white, needle-like solid, melting at 101-102°.

Schmidt Reaction.- To a solution of 2.58 g. (0.01 mol.) of p-phenylbenzophenone 15 g. of trichloroacetic acid and 2 ml. (0.036 mol.) of concentrated sulfuric acid at 55° was added 2 g. (0.031 mol.) of sodium azide all at once. With occasional stirring, the mixture was held at a temperature of 55-60° for twelve hours, and then poured into 100 ml. of water. The crude mixed amides were filtered off and weighed, when dry, 2.75 g. However, a distinct Beilstein test was obtained from the crude amides so the solid was warmed with 50 ml. of 1:5 ammonium hydroxide, filtered and finally washed

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with warm petroleum ether. This gave 2.67 g. of mixed amides or 97% of the theoretical value.

Hydrolysis.- The amides were dissolved by refluxing them with 50 ml. of glacial acetic acid for thirty minutes. Then 10 ml. of concentrated hydrochloric acid was introduced through the top of the reflux condenser, which invariably caused the precipitation of the amides. Hence, it was found necessary to add another 10 ml. of glacial acetic acid, and after a few hours refluxing, the solid gradually went into solution. After refluxing for twenty-four hours, an additional 10 ml. of concentrated hydrochloric acid was added. This addition did not cause any reprecipitation and the refluxing was then continued for a total of ninety hours. The mixture was then poured into 200 ml. of water and the solid acids were filtered off, and the filtrate extracted with three 25 ml. portions of benzene. The acids were not separated since it was found in previous determinations that the recovery was far from quantitative due to mechanical losses on repeated separations.

In one case, however, where the acids were separated on the basis of the large differential in water solubility, the following set of data was obtained:

Mixed amides	2.71 g.	0.0099 mol.
4-Biphenylcarboxylic acid	0.59 g.	0.00293 mol.
Benzoic acid (isolated)	0.42 g.	0.00344 mol.
Total		0.00637 mol.

From the moles of acid actually recovered, the percent of mixed amides were calculated and found to be the following:

p-Phenylbenzanilide	56%
Benz(p-phenyl)anilide	44%

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The acid solution was evaporated to dryness and the amine salts were suspended in 50 ml. of water and alkalyzed with potassium hydroxide. This mixture was then extracted with three 25 ml. portions of benzene and dried over potassium hydroxide pellets. The dry benzene solution was warmed with 5 ml. of acetic anhydride and the benzene and excess acetic anhydride blown off on a steam bath. This yielded 1.58 g. of acetanilides. The mixture of anilides was heated with 100 ml. of water, allowed to cool to room temperature and then filtered. This yielded 0.88 g. of 4-acetamidobiphenyl, melting at 166-168°. (Heusler[32], 171°.) The acetanilide by difference was then 0.70 g.

4-Acetamidobiphenyl	0.88 g.	0.0042 mol.
Acetanilide	0.70 g.	0.0052 mol.
Total anilides recovered	1.58 g.	0.0094 mol. or 96% of 0.01 mol.

The values of the isomeric amides based on the amount of 4-acetamidobiphenyl and acetanilide isolated are:

p-Phenylbenzanilide	55%
Benz(p-phenyl)anilide	45%

These values represent the average of five determinations.

16. p-Methoxybenzophenone

Preparation.- In a three-necked 500 ml. round-bottomed flask fitted with mechanical stirring, reflux condenser and a dropping funnel was placed a solution of 34 g. (0.25 mol.) of anhydrous zinc chloride in 100 ml. of dry, thiophene-free benzene. Then 28 g. (0.2 mol.) of benzoyl chloride were added and the mixture warmed to a gentle reflux. With constant

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stirring, 22 g. (0.2 mol.) of anisole was slowly added from the dropping funnel. After all the anisole had been added, the mixture was refluxed an additional hour and then poured on a mixture of ice and hydrochloric acid. The upper oil layer was drawn off and washed first with a 5% sodium hydroxide solution and then with water.

The excess benzene was removed by steam distillation, leaving an oil which crystallized to a white solid on cooling. The crude solid was filtered off and recrystallized from methanol, giving 25 g. (60%) of p-methoxybenzophenone, melting at 60-62° (Rennie[55], 61-62°).

An attempt was made to prepare this ketone by the usual Friedel-Crafts technique, employing aluminum chloride and carbon disulfide. However, a number of side reactions apparently occurred which resulted in a large diminution of yield. Thus, from 0.5 mol. of anisole, only 10 g. of p-methoxybenzophenone and an equivalent quantity of p-hydroxybenzophenone were obtained. In addition, a small amount (2 g.) of 2-hydroxybenzophenone was isolated.

Schmidt Reaction.- To a solution of 2.12 g. (0.01 mol.) of p-methoxybenzophenone 15 g. of trichloroacetic acid and 2 ml. (0.036 mol.) of concentrated sulfuric acid at 55° was added 2 g. (0.031 mol.) of powdered sodium azide all at once. With occasional stirring the mixture was allowed to stand at this temperature for six hours, and then poured into 100 ml. of water. At first only a dark oil appeared, but after standing for a half hour, this oil crystallized to a brown solid.

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The crude amides were filtered dry but still contained trichloroacetic acid which was evident from a Beilstein test. The dry solid was powdered and then suspended in 60 ml. of a 1:5 ammonium hydroxide solution. After digesting this mixture on a steam bath for thirty minutes and allowing it to cool to room temperature, the crude amides were filtered once again. The solid material was washed first with water and then with warm petroleum ether. This gave, when dry, 2.06 g. of mixed amides.

Hydrolysis.- As mentioned in the previous section, it appeared that the conditions necessary to bring about the Schmidt reaction on p-methoxybenzophenone had also caused a certain amount of demethylation. Consequently, the 2.06 g. of mixed amides probably consisted of a mixture of p-hydroxy and p-methoxy anilides. It was then necessary to discard the contemplated methoxyl determination in favor of a method of separating p-hydroxybenzoic acid from benzoic acid.

It was found that 0.76 g. (0.005 mol.) of p-anisic acid gave 0.66 g. (0.00485 mol.) of p-hydroxybenzoic acid, melting at 200-208° (Fisher[25], 210°, also 213-214°) when heated to 100° in a sealed tube with a 30% solution of hydrogen bromide in glacial acetic acid. Thus, it was possible to obtain a 97% demethylation by simply placing the sealed tube in a steambone for twenty-four hours.

Further, from a mixture of 0.5 g. (0.0041 mol.) of p-anisic acid and 0.5 g. (0.0036 mol.) of benzoic acid, 0.41 g. (0.0030 mol.) of p-hydroxybenzoic acid (91%) and 0.48 g.

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(0.0039 mol.) of benzoic acid (96%) were obtained, using a carbon disulfide separation of the resulting acid mixture. These same conditions, necessary to bring about demethylation, were found to be equally applicable to the hydrolysis of benz-p-anisidide. With the experience gained from working with known mixtures, we proceeded to the task of analyzing the unknown mixture of amides.

The 2.06 g. of mixed amides were placed in an eight-inch pyrex tube with 25 ml. of a 30% solution of hydrogen bromide in glacial acetic acid. The tube was sealed, wrapped in a towel and placed in a steam cone for twenty-four hours. The tube was cooled by pouring cold water into the steam cone and then opened by carefully directing a thin oxygen flame at the tip of the tube. Apparently, the reaction mixture does not generate appreciable amounts of gaseous products under these conditions, since the tube opened repeatedly with only a mild expansion of gases.

The contents of the tube were poured into 200 ml. of water and the walls of the tube carefully washed with a stream of cold water. This solution was extracted with three 25 ml. portions of ether and the extract shaken with 25 ml. of a saturated sodium carbonate solution. The latter was acidified with concentrated hydrochloric acid and the mixture of acids was once more extracted with three 25 ml. portions of ether. Evaporation of the ether under an air jet gave, when dry, 1.10 g. of mixed acids.

The mixed acids were allowed to stand for an hour in the cold with 100 ml. of carbon disulfide. The insoluble material

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was filtered off. This amounted to 0.46 g. of product, melting at 160-175°. The filtrate was evaporated, yielding 0.54 g. of crude benzoic acid, melting at 111-115°. The material, melting at 160-170°, was heated to boiling with 10 ml. of benzene and allowed to stand for twelve hours, and then the insoluble material was filtered off, giving 0.38 g. of p-hydroxybenzoic acid, melting at 204-207° (lit. 210°). The benzene filtrate was evaporated to dryness by directing an air jet over the liquid at room temperature and there remained 0.70 mg. of solid, melting at 95-105°.

This impure mixture was once more treated with 10 ml. of carbon disulfide and the insoluble acid was filtered off. An additional 20 mg. of p-hydroxybenzoic acid was recovered which also melted at 204-207°. Evaporation of the carbon disulfide filtrate yielded 45 mg. of benzoic acid, melting at 111-115°.

Totaling the benzoic and p-hydroxybenzoic acids isolated in each separation, the following data was obtained:

Benzoic acid	0.585 g.	0.0048 mol.
p-Hydroxybenzoic acid	0.40 g.	0.0029 mol.
Total acid isolated	0.985 g.	0.0077 mol.

Then, the amount of isomeric amides based on this recovery is as follows:

p-Methoxybenzanilide	32%
Benz(p-methoxy) anilide	68%

The acetic acid solution remaining from the ether extraction of the aromatic acids was evaporated to dryness and then taken up in 100 ml. of water. This solution was alkalyzed with potassium hydroxide and the aniline was extracted with

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three 25 ml. portions of benzene. After the benzene solution was dried over potassium hydroxide pellets, it was acetylated in the usual fashion and 0.42 g. of acetanilide, melting at 105-110° were obtained in the manner previously described. Thus, 0.42 g. of acetanilide or 0.0031 mol. agrees fairly well with the moles of p-hydroxybenzanilide obtained (0.0029 mol.).

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EXPERIMENTAL II
Substituted Succinic Acids

1. Unsymmetrical Dimethylsuccinic Acid

A. Condensation.- In a two l. round-bottomed flask were placed 58 g. (1 mol.) of dry acetone, 113 g. (1 mol.) of ethyl α-cyanoacetate, 79 g. (1 mol.) of pyridine and 63 g. (1 mol.) of glacial acetic acid. The mixture was refluxed for an hour, and then 100 ml. of ethyl alcohol was introduced through the top of the reflux condenser. When the reaction mixture had cooled below the reflux temperature (70-75°), 65 g. (1 mol.) of potassium cyanide was added by momentarily removing the reflux condenser. A spontaneous reaction occurred which spent itself in about an hour. It was then necessary to reflux the mixture for an additional half hour.

The flask was allowed to come to room temperature, during which time the potassio salt crystallized. 400 ml. of 1:3 hydrochloric acid was added, and the mixture gently warmed until all the solid disappeared.

The oily layer was drawn off in a separatory funnel and the aqueous layer extracted with two 100 ml. portions of ether. The ether extract was neutralized with a saturated sodium bicarbonate solution, and then washed with 50 ml. of water. The washings were then extracted with 50 ml. of ether and the combined ether extracts were dried over anhydrous sodium sulfate. The ether was removed and the product was distilled at 130-141°/9 mm. The yield was 120 g. (70%).

B. Hydrolysis.- 126 g. (0.7 m.) of the dinitrile and 600 ml. of concentrated hydrochloric acid were refluxed for

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five hours in a one l. flask. 150 ml. more acid was added and the refluxing continued for another three hours. The acid solution was distilled to dryness under reduced pressure and the residue treated with 300 ml. of boiling ether. The ether-salt mixture was filtered and further treated with two 100 ml. portions of boiling ether. The ether solution was evaporated to about 125 ml., whereupon the acid began to crystallize. Then 1 liter of benzene was added and the mixture heated until all the acid dissolved. It was then cooled in an ice-salt bath which caused the acid to crystallize completely in large glassy prisms. The yield was 77 g. (76%) of α,α-dimethylsuccinic acid, melting at 138-139°.

The yields are somewhat smaller using a 0.1 mol. of reactants and condensing agent; specifically, a 61% yield of dinitrile was obtained, based on a 0.1 mol. of acetone.

2. 1-Carboxycyclohexylacetic Acid

A. Condensation.- 9.8 g. (0.10 mol.) of freshly distilled cyclohexanone and a 0.10 mole of each of the other reactants were refluxed for two hours with no other deviation in the procedure already described for acetone. This yielded 16.5 g. (75%) of ethyl (α-cyanocyclohexyl)α-cyanoacetate; boiling point, 177-179°/10 mm. (Dickens, Horton and Thorpe[21], 210-212°/22 mm.).

B. Hydrolysis.- It was necessary to modify the hydrolysis procedure for this dicyanoester as the cyclohexyl residue increased the benzene solubility to a point where crystallization from this solvent was no longer feasible.

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The 16.5 g. of dicyanoester was refluxed for five hours with 70 ml. of concentrated hydrochloric acid. Then another 30 ml. of acid was added and refluxing was continued overnight (10 hours). On cooling to room temperature, the solid acid crystallized and was filtered and sucked dry. The filtrate was distilled to dryness under reduced pressure and the solids combined.

This mixture of acid and ammonium chloride was extracted with three 30 ml. portions of boiling ether and then the solvent was evaporated to dryness. The residue was dissolved in a minimum of hot benzene, cooled to room temperature and the organic acid forced out by adding an excess of petroleum ether (60-75°). This procedure gave 10.5 g. (75%) of 1-carboxycyclohexylacetic acid, melting at 127-129°. A single recrystallization from hot water raised the melting point to 131-132°. (Dickens, Horton and Thorpe[21], 132°.)

3. α-Ethyl-α-methylsuccinic Acid

A. Condensation.- 7.2 g. (0.10 mole) of butanone, previously dried over calcium chloride and distilled (76.5°), and a 0.10 mole each of pyridine, acetic acid and ethyl α-cyanoacetate were refluxed for two hours. The procedure previously described for the preparation of ethyl α,β-dicyano-β-methylbutyrate was followed exactly. A 49% yield (9.5 g.) of ethyl α,β-dicyano-β-methylvalerate was obtained which distilled at 145-146°/10 mm. (Higson and Thorpe[33], 162°/20 mm.).

B. Hydrolysis.- When 5 g. of this dicyanoester were refluxed for six hours with 20 ml. of concentrated hydrochloric

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acid, 3.0 g. (73%) of α-ethyl-α-methylsuccinic acid was obtained, melting at 90-95°. A single recrystallization from a dilute hydrochloric acid solution raised the melting point to 101-102°. (Higson and Thorpe[33], 102-103°.)

4. Ethylsuccinic Acid

A. Condensation.- 5.8 g. (0.1 mol.) of freshly distilled propionaldehyde and 0.1 mole of each of the other reactants were refluxed for fifteen minutes. Longer refluxing caused a marked decrease in yield with a large tar-like residue in the still pot.

With no other variation in the procedure, 9.5 g. (53%) of ethyl α,β-dicyanovalerate, collected at 158-160°/12 mm., was obtained.

Analysis: Calculated- Nitrogen, 15.56% for $C_9H_{12}O_2N_2$
Found- Nitrogen, 15.62%

B. Hydrolysis.- 8.5 g. (0.0473 mole) of the ester and 35 ml. of concentrated hydrochloric acid were refluxed for five hours. By the usual method of isolation 4.5 g. (60%) of ethylsuccinic acid was obtained, melting at 98-100°. (Fittig and Frankel[26], 98-99°.)

5. Isopropylsuccinic Acid

A. Condensation.- 7.2 g. (0.10 mol.) of isobutyraldehyde which was distilled a few minutes before using and a 0.1 mole of each of the other reagents were refluxed for one hour. Following the addition of potassium cyanide, 13.0 g. (67%) of ethyl α,β-dicyano-γ-methylvalerate was obtained, distilling at 151-155°/10 mm.

Analysis: Calculated- Nitrogen, 14.43% for $C_{10}H_{14}O_2N_2$
Found- Nitrogen, 14.41%

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B. Hydrolysis.- 11 g. (0.565 mol.) of the ester and 50 ml. of concentrated hydrochloric acid were refluxed for thirty-six hours. At the end of this time there still appeared to be some unreacted material. 25 ml. more of acid were introduced and the refluxing continued for an additional three hours.

In the usual manner, 7 g. (78%) of isopropylsuccinic acid was obtained, melting at 115-116°. (von Braun and Reinhardt[10], 116°.)

6. α-Phenyl-α-methylsuccinic Acid

A. Condensation.- 10.8 gm. (0.10 mol.) of acetophenone and 0.1 mole each of the other reagents were refluxed twelve hours. The alcohol and potassium cyanide were then added as before, and the mixture was refluxed for thirty minutes. This yielded in the usual fashion 4 gm. (16 1/2%) of ethyl α,β-dicyano-β-phenylbutyrate, boiling at 140-145°/0.1 mm.

B. Hydrolysis.- 4 gm. of the ester was hydrolyzed by refluxing with concentrated hydrochloric acid until complete solution was achieved; 2 gm. (60%) of α-phenyl-α-methylsuccinic acid separated on cooling. This acid crystallized from hot water in glassy prisms which melted at 157-8°.

Analysis: Calculated for $C_{11}H_{12}O_4$; C, 63.45°; H, 5.77%
Found; C, 63.32%; H, 5.82%

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SUMMARY

Two aralkyl ketones, three aryl alkyl ketones, and five diaryl ketones have been subjected to the Schmidt reaction according to improved procedures, and the proportions of isomeric amides produced were determined by a combination of previously known methods with several methods newly developed for this purpose.

1) The results of this investigation indicate that the steric environment of the carbonyl group is the dominant factor in the relative amounts of isomeric amides obtained.

2) It appears that the electrophilic or nucleophilic character of the migrating group has only a very minor influence on the proportion of isomeric amides.

3) The ratio of isomeric amides is governed by the orientation of the nitrogen chain in the transient intermediate $R - \underset{\underset{N - N_2^+}{\|}}{C} - R'$ and is a statistical phenomenon in the absence of bulk effects in the neighborhood of the carbonyl group.

In addition to the study of the Schmidt reaction, a number of aldehydes and ketones have been condensed with ethyl α-cyanoacetate and potassium cyanide, and the resulting α,β-dicyano-esters were hydrolyzed to the corresponding alkylsuccinic acids. The characteristics of this new synthesis for unsymmetrical di-substituted succinic acids are:

1) The yields compare quite favorably with the more laborious and sensitive reaction of Higson and Thorpe, whose method first requires the preparation and isolation of the cyanohydrin.

2) The use of the readily available aldehyde or ketone reduces the described method to the simplest of operations with the minimum of mechanical losses through the absence of excessive handling.

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3) The reaction is apparently limited to aliphatic aldehydes and sterically unhindered ketones as shown by the poor yields obtained with acetophenone, benzaldehyde and diisopropylketone.

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