

THE REACTION OF AMINE N-OXIDES WITH
 α -HYDROXYKETONES

by

LILIAN CHIA-SHEOU KAO

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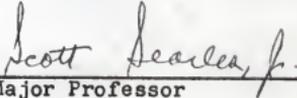
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Approved by:


Major Professor

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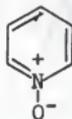
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INTRODUCTION

Amine N-oxides are compounds which have the structure of an amine with an oxygen attached to the amino nitrogen atom by a dative bond. They are of two types, aliphatic (I) and aromatic (II), and are formed by treating the corresponding amines with aqueous hydrogen peroxide or peracids.



I

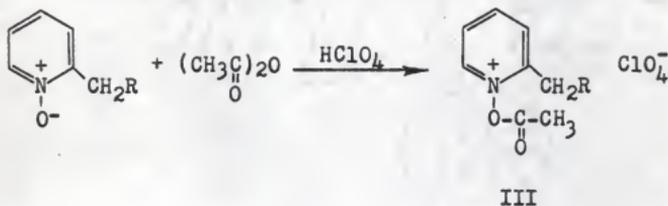


II

Peracids are required particularly for N-oxide formation from aromatic heterocyclic amines, since aqueous hydrogen peroxide alone is not sufficiently reactive for these weaker bases. Ochiai (29) reported that the amine N-oxides of the pyridine and quinoline series could be obtained in good yield by using hydrogen peroxide as an oxidant and a carboxylic acid, such as glacial acetic acid, as a catalyst. Other methods of preparing amine N-oxides include reaction of ozone with tertiary amines (15), cyclization of nitro compounds (19), and oxidation of tertiary amines with hydrogen peroxide in the presence of acid forming elements of group VA, VIA, VIB and VIII as catalyst (44).

The dative nature of the bond between oxygen and nitrogen in amine N-oxides has been clearly shown by the reactions of amine N-oxides. The oxygen atom can be easily removed, regenerating the corresponding amine, by deoxygenation with phosphorous

trichloride, phosphorous tribromide and catalytic hydrogenation. Another reaction which provides evidence for the structure is O-acylation. Recently, Traynelis (40) reported the isolation of the O-acetyl pyridinium cation (III) as its perchlorate.



Other properties which reveal the semipolar N-O bond of the amine N-oxides are: First, amine N-oxides have large dipole moments, as would be expected from the semipolar bond; the dipole moment of trimethylamine N-oxide has been determined as 5.02 D. (33), and that of pyridine 1-oxide 4.18 D. (36). Second, the basic strength of the amine N-oxides is weaker than that of the corresponding amines, the pK_a of trimethylamine N-oxide being 4.65 (33) and that of pyridine 1-oxide 0.79 (17). The decreasing in basicity is due to the negative inductive effect of the N-O bond. Third, amine N-oxides are very soluble in water and, except for aromatic heterocyclic N-oxides, usually not soluble in non-polar solvents. Fourth, complexes are formed from iodine and trimethylamine N-oxide or pyridine 1-oxides, and these complexes are much stronger than that of the usual carbonyl compounds (21). It was concluded that the oxygen atom in amine N-oxides is much more negative than that of the usual carbonyl compounds.

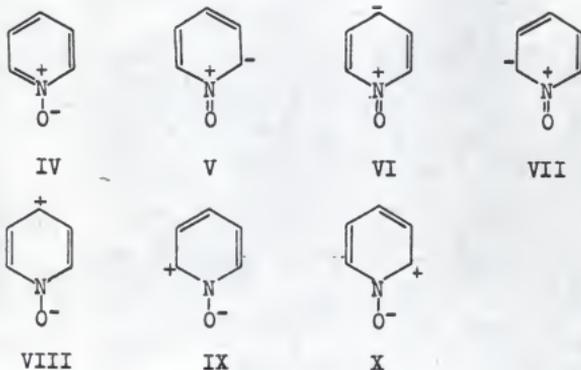
Although both types of amine N-oxides I and II undergo deoxygenation as mentioned above, the susceptibility to reduction is very different. Ochiai (29) reported that the reduction potential for trimethylamine N-oxide was -0.4562 volt, and that of pyridine 1-oxide was -1.2786 volts. The aliphatic tertiary amine N-oxides can be reduced to the parent tertiary amines with reducing agents such as stannous chloride, sodium hyposulfite and sodium arsenite. On the other hand, aromatic heterocyclic amine N-oxides are less easily reduced to the corresponding amines. According to Ochiai (29) this probably was due to increased resonance involving the oxygen atom. However, Hayashi (14) reported that the 4-substituted pyridine and quinoline N-oxides could be reduced catalytically to the corresponding aromatic amines by means of Rany nickel. Reducing agents such as PCl_3 (29) and PBr_3 (29) also can be used.

The melting points of the two types of amine oxides are also different. The melting points of the aliphatic and the saturated heterocyclic N-oxides are very high; for example, the melting point of trimethylamine N-oxide is 208° (33), and those of the aromatic heterocyclic amine N-oxides are lower. The amine N-oxides in the pyridine and quinoline series can be distilled under reduced pressure (29).

Spectroscopic studies showed that the N-O stretching frequency of pyridine 1-oxide (38) was 1278 cm^{-1} , while that for trimethylamine N-oxide (13) was 937 cm^{-1} . From the spectral data, the N-O bond stretching force constant and N-O bond length in trimethylamine N-oxide were $3.8 - 4.8 \times 10^{-5}$ dyne/cm. and

1.51 \pm 0.001 A, respectively (13). This bond length is approximately the same as that of the N-O single bond predicted by Pauling (31). On the other hand, Tsaucaries (41) reported the N-O bond length in pyridine 1-oxide to be 1.37 A which indicates a 30 per cent double bond character.

The reason for the differences between these two categories of amine oxides can be discerned by examination of the possibility for resonance. In the aliphatic and the saturated heterocyclic tertiary amine N-oxides, there is no possibility for delocalization of electrons. The properties, such as high polarity, ease of reduction, and high melting point, are representative of a pure coordinate covalent nitrogen-oxygen linkage. In the aromatic heterocyclic amine N-oxides, the delocalization of electrons is possible. The following resonance hybrid structures have been cited by many chemists for pyridine 1-oxide (22, 29):



Linton (22) said that the structures V, VI and VII were responsible for the much lower dipole moment observed for

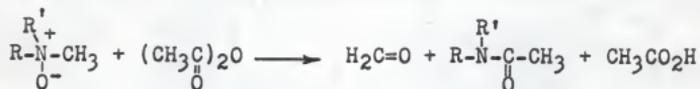
pyridine 1-oxide than that calculated from the group moment of N-oxide function (4.38D) and the dipole moment of pyridine (2.2D).

Due to the contribution of structure V, VI and VII, pyridine and the related aromatic N-oxides undergo electrophilic substitutions in the α - and γ - carbons much easier than their corresponding amines. The predominance of γ - reactivity over α - reactivity is a consequence of the strong inductive effect of the N-oxide group. Besides, an electrophile can also attack the oxygen atom of the amine N-oxides; this is revealed by the salt formation. The nucleophilic substitutions at α - and γ - positions by the powerful nucleophiles such as Grignard reagents (6), can be understood on the basis of contribution of structures VIII, IX and X.

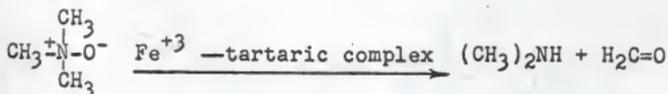
One of the reactions which has been intensively studied recently is the rearrangement reaction of amine N-oxides. About eighteen years ago Katada and Ochiai (30 a, b) discovered the rearrangement of pyridine 1-oxide with acetic anhydride, and since then numerous workers have studied this rearrangement. Briefly stated, the rearrangement of aromatic heterocyclic N-oxides with acyl anhydrides and acyl halides can be divided into two classes: The first class involves those amine N-oxides which do not have an α -substituent, such as pyridine and 4-picoline 1-oxides. Oae (27) studied these rearrangements by using O^{18} tracer; he concluded that in the absence of solvents, the rearrangement of 4-picoline 1-oxide with acyl anhydrides proceeds by an intermolecular ionic pathway, while in the presence of

solvents, the intermolecular ionic process was substantially suppressed and the intramolecular radical pair process became dominant. The second class belongs to the aromatic heterocyclic amine N-oxides with α -alkyl substituents. Boekelheide (3) has proposed a free radical mechanism for this type of reaction. Traynelis (40) considered the mechanism of this kind of rearrangement as an intramolecular ionic process, but Oae has recently reported evidence that this rearrangement proceeded through a radical ion pair (27).

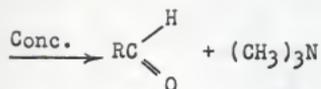
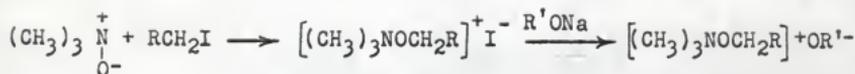
The reaction of acyl anhydrides with aliphatic tertiary amine N-oxides gives mainly formaldehyde and the corresponding amide (32). This reaction also appears to involve a hemolytic cleavage of the N-O bond to form a radical pair (8).



In aqueous solution containing ferric tartaric complex, such amine oxides give formaldehyde and a secondary amine as products; a similar mechanism has been postulated by Craig (8).



In 1913 Meisenheimer (24) reported that when the quarternary salts, which were made by treating trimethylamine N-oxide with alkyl iodide followed by sodium hydroxide or sodium alkoxide, were concentrated, trimethylamine and the aldehyde from the corresponding alkyl iodide were formed:



R = H, CH₃, CH₃CH₂

R' = H, CH₃, CH₃CH₂, CH₃CH₂CH₂

Later, Ochiai (30 c) applied the reaction to the addition compounds of pyridine 1-oxide and observed the formation of formaldehyde and acetaldehyde. Katritzky (20) studied this reaction as a method of deoxygenating the pyridine 1-oxides under non-reducing conditions and reported the formation of the corresponding bases in fair yield. In 1957, Boekelheide, Feely, and Lehn reported (4) that N-benzyloxy pyridinium salts, which were obtained by heating the appropriate pyridine 1-oxides with benzyl bromide or a similar halide in acetonitrile, underwent the alkali decomposition in the same manner as their aliphatic analogues to form aromatic aldehydes in excellent yield, and the corresponding pyridines. The benzaldehyde (XIV) was isolated in 90-92 per cent yield, while pure *o*-nitrobenzaldehyde (XV) was isolated in 60 per cent yield after being chromatographed over alumina. The yields of pyridine (XVI) and α -picoline (XVII) were 78 and 84 per cent, respectively.



(XI) R₁ = R₂ = H

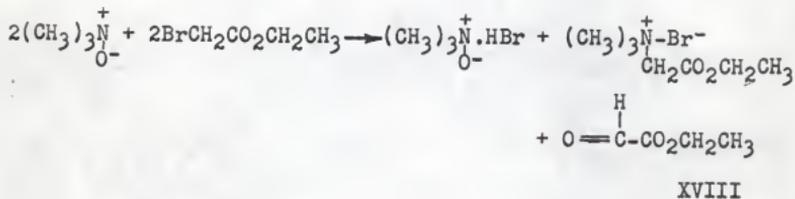
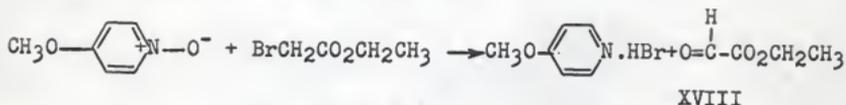
(XIV) R₁ = H (XVI) R₂ = H

(XII) R₁ = H, R₂ = CH₃

(XIII) R₁ = NO₂, R₂ = H

(XV) R₁ = NO₂ (XVII) R₂ = CH₃

The oxidation of halogen compounds to the corresponding carbonyl compound by amine N-oxides has been known. Javellana (18) reported when ethyl bromoacetate was treated either with 4-methoxypyridine 1-oxide or trimethylamine N-oxide gave ethyl glyoxate (XVIII) in excellent yield.



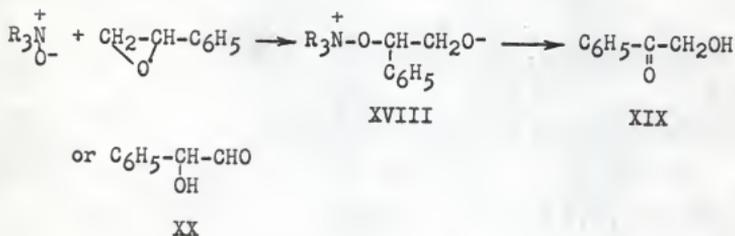
STATEMENT OF THE PROBLEM

The problem of interest in this thesis is to establish the nature of a new reaction of amine N-oxides with α -hydroxyketones, resulting in oxidative cleavage of the latter to the corresponding carboxylic acids and carbonyl compounds, which was discovered in the early phase of this work.

RESULTS AND DISCUSSION

The reaction of amine N-oxides with commercial epoxides has been observed (34), but the chemistry involved has not been elucidated. Because of the similarity of reactions of epoxides and alkyl halides with many nucleophilic reagents, such as hydroxide and cyanide ions, it seemed reasonable that an epoxide,

such as styrene oxide, may react with an amine N-oxide in the following manner. The initial product expected was the zwitterion, $R_3\overset{+}{N}-O-\underset{\text{C}_6\text{H}_5}{\text{CH}}-\text{CH}_2\overset{-}{\text{O}}$, (XVIII), but this might decompose to give 2-hydroxyacetophenone (XIX) or its tautomer, mandelaldehyde (XX). The amine N-oxides were 1-methylpyrrolidine 1-oxide and trimethylamine N-oxide.



These products, however, were not observed. The infrared spectrum of the crude products indicated the presence of benzoic acid. It seems possible that the 2-hydroxyacetophenone may have been reacted further. The problem then developed to investigate the reactions of α -hydroxyketones such as 2-hydroxyacetophenone with amine N-oxides.

The reaction of equimolar amounts of 2-hydroxyacetophenone with 1-methylpyrrolidine 1-oxide in acetonitrile under reflux gave benzoic acid, 1-methylpyrrolidine, and formaldehyde as products. Benzoic acid, which was isolated in yields up to 64 per cent, was identified by its melting point and the comparison of its infrared spectrum with an authentic sample.

The method of isolation of benzoic acid greatly affected the isolated yield, indicating that losses occurred. Higher yields

were obtained by distillation of acetonitrile and 1-methylpyrrolidine followed by bicarbonate extraction of the ether solution of the residue, than by directly passing anhydrous hydrogen chloride into the reaction mixture to precipitate the 1-methylpyrrolidine as its hydrochloride, followed by bicarbonate extraction.

1-Methylpyrrolidine, isolated as its hydrochloride as well as its picrate, was identified by the melting point of its picrate and by the infrared spectrum of its hydrochloride, which was identical to that of authentic 1-methylpyrrolidine hydrochloride. The isolated yield of 1-methylpyrrolidine varied from 73.5 to 14 per cent, owing to volatility losses on isolation.

The formaldehyde was obtained as paraformaldehyde which precipitated with 1-methylpyrrolidine hydrochloride. No method was found to be successful for separating these two compounds, but the infrared spectrum of this mixture showed the 9.3μ (C-O-C stretching) band characteristic of paraformaldehyde. The weight of this mixture was considerably in excess for the theoretical amounts of 1-methylpyrrolidine hydrochloride. The crude 1-methylpyrrolidine hydrochloride gave a positive Tollen's test on heating. Attempts were made to isolate formaldehyde from the mixture as its dimedone and 2,4-dinitrophenylhydrazone derivatives, but no pure derivative was obtained. It is probable that there is considerable loss of formaldehyde in the prior distillation and other manipulations, as shown by the 55 per cent recovery of paraformaldehyde after treatment with 1-methylpyrrolidine 1-oxide in acetonitrile, with about 30 per cent of

the recovered paraformaldehyde condensing in bottom of the reflux condenser.

Reaction of 2-hydroxyacetophenone with two molecular equivalents of 1-methylpyrrolidine 1-oxide gave results similar to those from the equimolar reaction, while omission of the amine N-oxide showed that no reaction occurred; 2-hydroxyacetophenone alone was stable in refluxing acetonitrile.

When 2-hydroxyacetophenone was reacted with two molecular equivalents of trimethylamine N-oxide in a similar manner as in the case of 1-methylpyrrolidine 1-oxide, benzoic acid was obtained in a 43 per cent yield. Owing to the high volatility of trimethylamine, quantitative determination of trimethylamine formed is very difficult. Attempt was made to trap trimethylamine in dilute hydrochloric acid, but the trimethylamine hydrochloride, obtained in low yield, was too hygroscopic for further purification. Its presence, however, was indicated by a quinhydrone test (23).

When the above reaction was carried out in water, the reaction was much slower. After the same reaction time, 2-hydroxyacetophenone was recovered to the extent of 15 per cent, and the yield of benzoic acid based on unrecovered starting material was 21 per cent. Also, more black tar was formed. The low yield of benzoic acid in aqueous solution is probably due to the hydration of amine N-oxide, which would decrease its nucleophilicity; for it seems likely that the reaction commences by nucleophilic attack on the carbonyl carbon as has been postulated in the case of the reaction of amine N-oxides with carboxylic

anhydrides (40).

The results obtained from the reaction of 2-hydroxyacetophenone with 1-methylpyrrolidine 1-oxide and with trimethylamine N-oxide can be used to explain the results obtained from either of these two amine N-oxides reacted with styrene oxide. In both cases, the expected product, 2-hydroxyacetophenone or its tautomer, mandelaldehyde, reacted further with the amine N-oxide present in the reaction mixture to form the oxidative cleavage product - benzoic acid accompanied with other unidentified products. This oxidative cleavage reaction, which is similar to the results obtained from the oxidative cleavage of α -ketols with lead tetracetate (2), has never been reported before.

The reaction of trimethylamine N-oxide with phenylglyoxal hydrate served as another example of the oxidative cleavage reaction. The infrared spectrum showed that phenylglyoxal existed mainly as the aldehyde hydrate, $C_6H_5-\underset{O}{\underset{|}{C}}-CH(OH)_2$, since the characteristic aldehyde C-H band (3.67μ) showed only as a slight shoulder at 3.7μ . An equimolar mixture of the phenylglyoxal hydrate and trimethylamine N-oxide in acetonitrile under reflux gave benzoic acid, formic acid and trimethylamine as products. The yield of benzoic acid isolated was 61 per cent, and it was identified as previously described. Formic acid, identified by its Duclaux constant, was obtained in only 9.5 per cent yield according to titration data, but volatility losses were quite likely. It was shown that it could not have been lost by oxidation with trimethylamine N-oxide, since no reaction occurred when formic acid was heated under reflux in acetonitrile with tri-

methylamine N-oxide. As before, the trimethylamine obtained was identified qualitatively, owing to its volatility.

No reaction was found between pyridine 1-oxide and 2-hydroxyacetophenone even with prolonged refluxing in acetonitrile, for the ketol was recovered practically quantitatively. The low reactivity of the pyridine 1-oxide may parallel its greater resistance to other deoxygenation reactions and may be due to greater resonance, as pointed out in the introduction. A related case, reported by Umezawa (42), is the lack of reaction of 3,4-dihydroisoquinoline 2-oxide toward sulfur dioxide and triphenylphosphite, which has been ascribed to the partial double bond character of the N-O bond in this aromatic amine N-oxide.

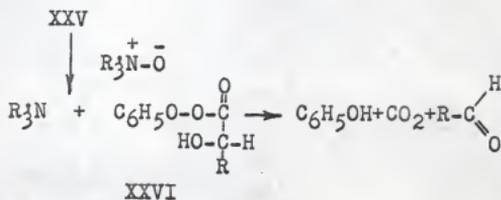
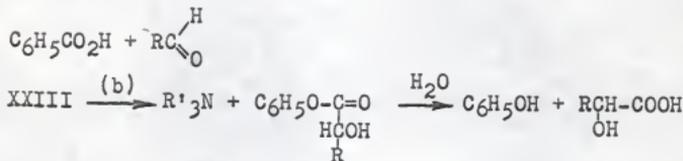
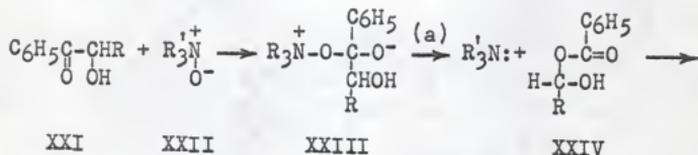
The amine N-oxides used for this oxidative reaction should fulfill the following two requirements: First, the amine N-oxide oxygen must be sufficiently nucleophilic to add to the carbonyl carbon atom of the α -ketol. Therefore, amine N-oxides derivative from stronger bases are better. Second, there must be no beta hydrogen or the beta hydrogen must be sterically confined to a cyclic structure, so that it cannot undergo pyrolysis to form olefins. Based on these two reasons, 1-methylpyrrolidine 1-oxide and trimethylamine N-oxide were chosen for the reaction. The former had the advantage of being more reactive as has been found in the reaction of amine oxides with epoxy resins (34). Trimethylamine N-oxide had the advantage of easy purification over 1-methylpyrrolidine 1-oxide, but the high volatility of trimethylamine makes difficult a quantitative determination of the amine formed.

Because of the low yield of formaldehyde in the reaction of 2-hydroxyacetophenone with either trimethylamine N-oxide or 1-methylpyrrolidine 1-oxide, the possibility of any reaction between simple aldehydes or ketones with amine N-oxides was checked. Benzaldehyde or acetophenone under reflux with trimethylamine N-oxide in acetonitrile led to the recovery of the starting material and no oxidation-reduction products found. Craig reported that there was no reaction between formaldehyde and N-benzyl dimethylamine N-oxide (9).

Several mechanisms can be postulated for the reaction of amine N-oxides (XXII) with α -hydroxyketones of the general formula $C_6H_5-C(=O)-CHR$ (XXI).

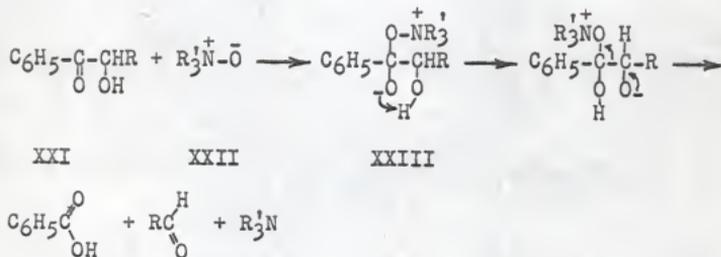
(1) Ionic type:

(A) Benzylic acid type rearrangement (43)



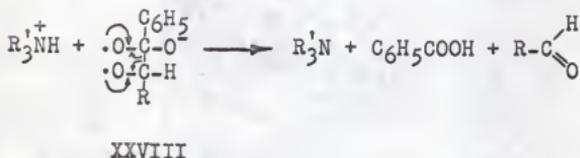
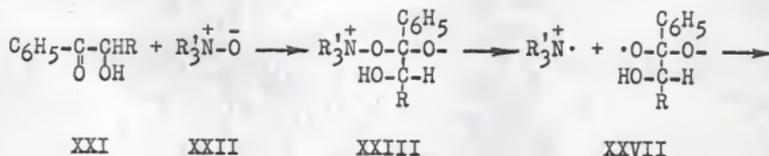
The first step can be considered as the nucleophilic attack by the N-oxide oxygen on the carbonyl carbon generating the zwitterion (XXIII). This zwitterion can undergo a heterolytic cleavage, followed by an intramolecular rearrangement to the temporarily electron-deficient oxygen atom, similar to the benzoic acid (43) rearrangement either by pathway (a) or (b) to form the hydroxyester (XXIV) or (XXV), respectively. The driving forces for this step can be reasoned as being due to the positive charge on the nitrogen atom, which attracts the electrons to itself, and also the formation of the carbonyl group. Route (a) would give the observed products, since the hydroxy ester (XXIV) would decompose easily to a carboxylic acid and a carbonyl compound, but reaction course (b) here seems more probable from the standpoint of migratory aptitude. The hydroxyl ester (XXV) from (b) might react with another mole of amine N-oxide to form the α -hydroxyperacid ester (XXVI) which then might decompose to form phenol, carbon dioxide, carbonyl compound. But, there apparently has been no evidence observed for such products.

(B) β -Elimination Process



As in the first postulated mechanism, the initial step is the formation of the zwitterion (XXIII). This zwitterion (XXIII) then may undergo a β -elimination process with elimination of a tertiary amine to form benzoic acid and the carbonyl compound.

(2) Free radical type:



As in the ionic type, the first step is the formation of the zwitterion (XXIII), which may cleave homolytically to form the ion radical pair (XXVII). A similar kind of cleavage was reported by Oae in the reactions of 2-picoline 1-oxide with carboxylic anhydrides (27), and in the reaction of quinaldine 1-oxide with benzoyl chloride (28). The ion radical $\text{R}_3\text{N}^+\cdot$ can abstract a hydrogen atom from the hydroxyl group to form the ion diradical (XXVIII) which can cleave to form carboxylic acid(s) ($\text{R}=\text{OH}$) and/or aldehyde ($\text{R}=\text{H}$). Or, one may visualize that all those steps occurred simultaneously through a six-membered ring transition state as indicated below:

Here we assume that the zwitterion (XXX) cleaves homolytically to form the ion radical pair (XXXII). The ion radical $R_3\overset{+}{N}\cdot$ can abstract a hydrogen from either of the hydroxyl groups to form the ion diradical (XXXIII a) or (XXXIII b). These ion diradicals (XXXIII a) and (XXXIII b) then might react further to form benzaldehyde, a carboxylic acid, i.e., formic acid (R=H) or carbonic acid (R=OH) in the case of 2-hydroxyacetophenone or phenylglyoxal hydrate, respectively.

However, none of the products expected from the enediol form was observed in either the reaction of the 2-hydroxyacetophenone or the phenylglyoxal hydrate with the amine N-oxides.

In order to confirm that the enediol form is not necessary for the oxidative cleavage reaction, the reaction of amine N-oxides with an α -hydroxyketone which does not have an enolizable hydrogen was investigated. n-Butylbenzoin (XXXIV) at first seemed most convenient to use, since its synthesis had been reported by Crawford, Saeger, and Warneke (10) from benzil and n-butylmagnesium bromide by Grignard reaction. The present experience, however, was that the product obtained was mainly the reduction product benzoin, accompanied with small amount of n-butylbenzoin (14.5 per cent), which was accordingly difficult to obtain pure in a useful amount.

The synthesis of α -methylbenzoin (XXXV) was then undertaken, since the methylmagnesium iodide has no beta hydrogen and thus cannot give reduction. This was carried out by the reaction of benzil with a slight excess of methylmagnesium iodide (10 per cent excess based on methyl iodide). An inverse Grignard

reaction was used in order to avoid the formation of the diaddition product, diphenylpinacol. α -Methylbenzoin was obtained in 80 per cent yield. The structure of this new α -hydroxyketone was confirmed by its elemental analysis, infrared spectrum, and nuclear magnetic resonance spectrum which are discussed in the experimental section.

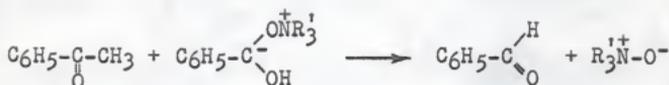
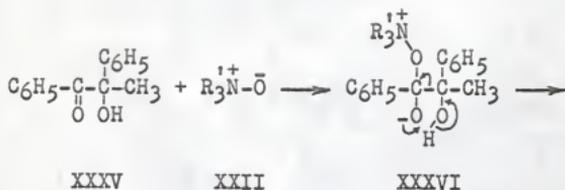
The reaction of equimolar amounts of α -methylbenzoin and trimethylamine N-oxide was much slower than the reaction of trimethylamine N-oxide with 2-hydroxyacetophenone. After 125 hours of reflux in acetonitrile, the products obtained were benzoic acid, acetophenone, benzaldehyde and trimethylamine. Benzoic acid was isolated in 42 per cent yield based on the reacted starting material, and was identified as previously described. Only a qualitative identification of trimethylamine was obtained. Vacuum distillation of the neutral fraction gave besides benzaldehyde, acetophenone as the major fraction (79 per cent conversion yield). Benzaldehyde was identified by its infrared spectrum and by the fact that it was oxidized by air to benzoic acid. Acetophenone was identified by its boiling point and phenylhydrazone derivative. Its infrared spectrum was identical with that of the authentic sample except two additional absorption bands at 8.3μ and 12μ , which presumably were caused by some impurity which has not as yet been identified. The starting ketol was recovered to the extent of 69 per cent. The reaction of α -methylbenzoin with a slight excess of 1-methylpyrrolidine 1-oxide was carried out in the same manner as that with the trimethylamine N-oxide but refluxed only for 23 hours. The products

obtained based on the reacted starting material were 87 per cent of acetophenone, 15 per cent of benzaldehyde, and a trace of benzoic acid, with a 30 per cent recovery of the starting ketol. Another run of the reaction with equal amount of the methylbenzoin and 1-methylpyrrolidine 1-oxide was refluxed for 48 hours. The products obtained based on the reacted starting material were: 7 per cent of benzoic acid, 11.5 per cent of acetophenone, and 13 per cent of benzaldehyde. The recovery of the starting material was 49 per cent.

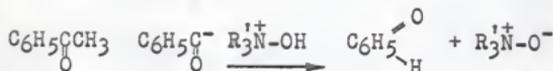
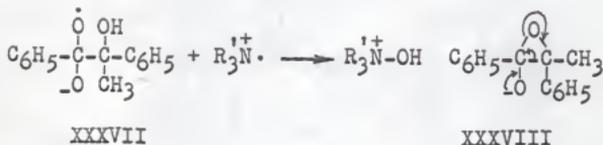
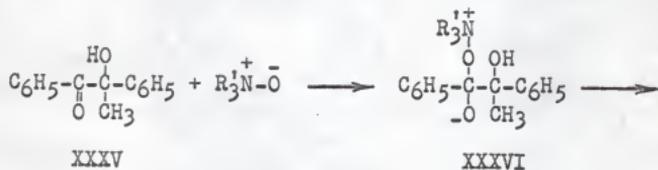
Because of the low yield of benzoic acid in these reactions, the possibility of benzoic acid reacting with 1-methylpyrrolidine 1-oxide was investigated. No reaction was found, for benzoic acid was recovered to the extent of 92 per cent after 24 hours of reflux in acetonitrile for 24 hours.

The formation of benzoic acid and acetophenone from the α -methylbenzoin offers another example of the oxidative cleavage induced by amine N-oxides. These results can well be explained by the proposed free radical mechanism (2), as well as by the postulated ionic mechanism (1)-(A)-(a), (1)-(B), and the concerted cyclic mechanism involving the six membered ring transition state.

The formation of benzaldehyde, which was unexpected might be explained by a modification of mechanism (1)-(B). Here, the zwitterion (XXXVI), which is formed as described before, undergoes a reverse-benzoin condensation with elimination of the amine N-oxide to form benzaldehyde and acetophenone. The reverse-benzoin condensation reaction has been reported by Ide and Buck (16).

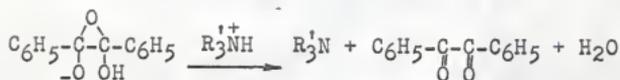
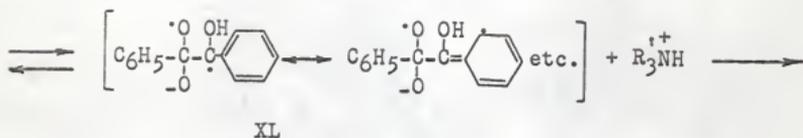
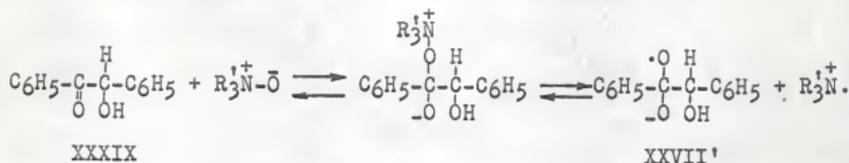


A modified free radical mechanism of (2) can also be used to explain the formation of benzaldehyde. The ion radical (XXXVII), which is formed by nucleophilic attack of the amine N-oxide oxygen on the carbonyl carbon followed by homolytic cleavage of the N-O bond can cleave through an epoxide transition state (XXXVIII) to form benzaldehyde and acetophenone.

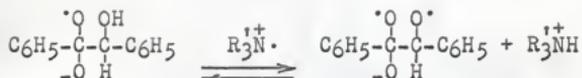


The reaction of benzoin (XXXIX) with trimethylamine N-oxide gave the simple oxidation product, benzil, instead of oxidative

cleavage products. Pure benzil was isolated in 86 per cent yield, and was identified by mixed melting point and comparison of the infrared spectra with the authentic sample. When 1-methylpyrrolidine 1-oxide was used, the isolated yield of pure benzil was 77 per cent. In addition, 1-methylpyrrolidine was isolated in 80 per cent yield as its hydrochloride and was identified as its picrate. The formation of the simple oxidation product, benzil, can be explained by the postulated free radical mechanism (2). The ion radical $R_3N^{\cdot+}$, which is formed as described previously, may abstract a hydrogen atom from the alpha carbon to form the ion diradical (XL) instead of abstraction of a hydrogen atom from the hydroxyl group to form the ion diradical (XLI). The former can attain extra stabilization through delocalization of the unpaired electron on the phenyl ring while the latter cannot.



or

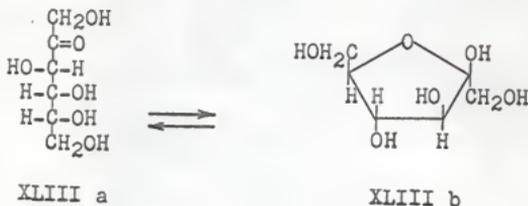


XLI

However, the ion diradical (XLI) cannot be excluded completely, since in the presence of water the reaction of benzoin with either trimethylamine N-oxide or 1-methylpyrrolidine 1-oxide gave a trace of benzoic acid (17 per cent conversion yield in both cases) with 87 and 86.5 per cent recovery of the benzoin, respectively. These results can be explained if we assume that the formation of the ion diradicals (XL) and (XLI) from the ion radical pair (XXVII') are reversible with the rate of formation of (XLI) faster than that of (XL). In the absence of water, the more stable ion diradical (XL) is the reacting species. But, in the presence of water, owing to the hydration of the amine N-oxide, its nucleophilicity is greatly decreased. The ion radical pair, (XXVII') which is formed by nucleophilic attack of the amine N-oxide on the carbonyl carbon followed by a homolytic cleavage, exists only in a small concentration. Under this circumstance, the less stable but quickly formed ion diradical (XLI) becomes the reacting species giving the oxidative product--benzoic acid.

Another mechanism which might be used to explain the benzil formation is the cyclic concerted mechanism in which the amine N-oxides function as an acid and a base. A similar mechanism had been postulated by Tawney, Williams, and Relyea for the oxidation of hydrazobenzene by pyridine 1-oxide (39).

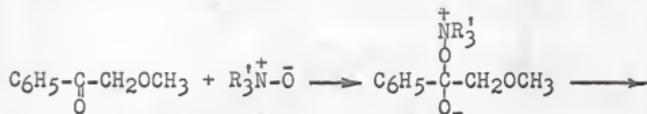
solution, two additional spots, one with higher R_f value, the other with lower R_f value than D-fructose, were obtained. D-arabinose, a possible oxidative cleavage product, had a R_f value so close to that of D-fructose, that its presence would have been obscured by unreacted D-fructose present. No further identification was carried out.

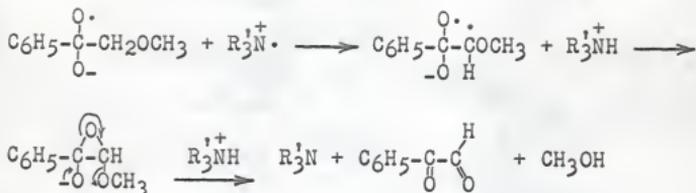


Some of the mechanisms under consideration differ in respect to the function of the alpha hydrogen atom and the hydroxyl hydrogen atom. Investigation of compounds not having one or the other of these hydrogen atoms should enable elimination of some of the possible mechanisms. The study of α -methylbenzoin, which has no alpha hydrogen, permitted us to discard mechanisms (3) and (4) which involve the enediol form of the α -hydroxyketones. As an example of a derivative not having a hydroxyl hydrogen atom, the reaction of ω -methoxyacetophenone with 1-methylpyrrolidine 1-oxide and trimethylamine N-oxide was investigated. The preparation of ω -methoxyacetophenone (XLV) was carried out according to the procedure of Moffett and Shriner (25) using phenylmagnesium bromide and methoxyacetonitrile. The latter was prepared according to the procedure of Scarrow (35) from sodium cyanide and paraformaldehyde followed by dimethyl sulfate.

When ω -methoxyacetophenone was treated with 1-methylpyrrolidine 1-oxide by the same procedure used for oxidative cleavage of 2-hydroxyacetophenone, the keto-ether was recovered pure to the extent of 73.5 per cent. From the residue a trace of benzoic acid (6.7 per cent based on reacted starting material) was identified. The reaction of ω -methoxyacetophenone and trimethylamine N-oxide was carried out under reflux in acetonitrile for 18 hours. No trimethylamine was observed, and pure ω -methoxyacetophenone was recovered to the extent of 84 per cent. The residue gave traces of benzoic acid. In both cases color change was observed during reflux; no phenylglyoxal was found.

The lack of reaction between ω -methoxyacetophenone and amine N-oxides can be understood by the postulated free radical mechanism (2). Here, the abstraction of a hydrogen atom from the hydroxyl group by the ion radical R_3N^+ is blocked. Another possibility might be to abstract a hydrogen from the alpha carbon, to give phenylglyoxal. This was not observed, but the traces of benzoic acid might have been due to its further reaction, for undoubtedly traces of water were present which could have hydrated any phenylglyoxal formed as an intermediate. The small amount of benzoic acid formed would indicate preferential loss of hydrogen from oxygen as compared to carbon in this case, if the free radical mechanism is operating.



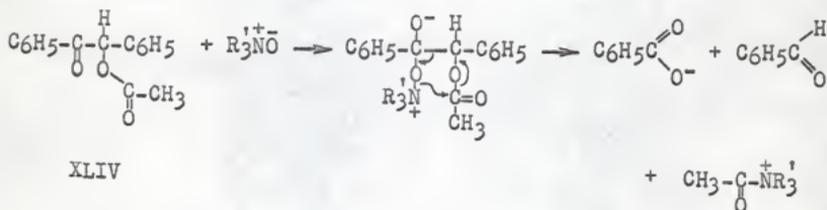


The postulated β -elimination type mechanism (1)-(B) can be used to explain the lack of reaction between ω -methoxyacetophenone and amine N-oxides, since this postulated mechanism involved a hydrogen transfer from the alpha hydroxyl group to the oxygen anion, and in the case of ω -methoxyacetophenone this transfer is not possible. It cannot explain the formation of traces of benzoic acid, unless some hydrolysis to 2-hydroxyacetophenone occurred, owing to traces of water present.

The lack of reaction of ω -methoxyacetophenone with amine N-oxides excluded the proposed ionic mechanism (1)-(A), because the rearrangement would occur in the case of ω -methoxyacetophenone as in the case of 2-hydroxyacetophenone. The postulated concerted cyclic mechanism, which either goes through an ionic or a free radical pathway, also can be used to explain the result. This is because it also requires a hydrogen transfer from the hydroxyl group to the amine residue of the amine N-oxide. This leaves the free radical mechanism (2), the β -elimination type mechanism (1)-(B) and the postulated concerted cyclic mechanism, as possible mechanisms for the oxidative cleavage reaction.

The absence of reaction in the cases of simple aldehydes

and ketones implies that an adjacent hydroxyl group is necessary for this oxidative cleavage reaction. An experiment was carried out to test the importance of hydroxyl hydrogen in the simple oxidation reaction of benzoin with amine N-oxides. Benzoin acetate (XLIV), prepared according to the procedure of Corson (7), was heated under reflux with trimethylamine N-oxide in acetonitrile solution for 12 hours, but practically no reaction was observed, in contrast to the 86 per cent yield of benzil under these conditions. Apparently the hydroxyl hydrogen is essential in the oxidation process also. A trace of benzoic acid isolated might have been formed by a slow reaction of the following type which can be considered as a modified mechanism of (I)-(B).



XLIV

As in the beginning stage of the investigation of any new reaction, these experiments, which were covered in this thesis, are only preliminary attempts to understand the nature of this reaction. More work needs to be done in order to understand the details of this new oxidative cleavage reaction which is interesting and challenging.

EXPERIMENTAL

Preparation of 1-Methylpyrrolidine. According to the modified procedure of Clarke (5), 130 ml. (80-90%, 2.3 moles) of formic acid was added in small portions to 71 g. (1 mole) of ice-cold pyrrolidine. The reaction was strongly exothermic. After addition was complete, 95 ml. (36-38%, approx. 1.1 moles) of formaldehyde was added to the mixture through the top of the reflux condenser. Carbon dioxide started to bubble off slowly right after the addition of formaldehyde. After the addition was complete, the mixture was heated under reflux for 10 hours. Large amounts of carbon dioxide evolved after reflux for 20 minutes. After cooling, the mixture was made basic with 40% sodium hydroxide solution and then steam distilled. The distillate was dried over potassium hydroxide pellets. On distillation of the liquid, 78.4 g. (92% yield) of the product was obtained, boiling at 74.5-78° (lit. (5) 77-78). Another run of the reaction with the same amount of reactants except using 150 ml. of formic acid, gave 63.5 g. (75%) of product, b.p. 76°.

Preparation of 1-Methylpyrrolidine 1-Oxide. According to the procedure of Searles (34), 57 g. (approx. 0.5 mole) of 30 per cent hydrogen peroxide was added slowly to 42.5 g. (0.5 mole) of 1-methylpyrrolidine. The reaction was exothermic; and the temperature was kept at 50-55° during the reaction period (5 hours). The reaction mixture was let stand overnight for complete reaction. Anhydrous ether and alcohol were added to the mixture, and set up on a rotatory evaporator to remove most

of the water. A viscous liquid was obtained. The viscous liquid was dried over phosphorous pentoxide in vacuo; brown crystals of the crude product were obtained. The crude product was washed with anhydrous ether, followed by anhydrous benzene to remove the soluble impurities; then, it was dried over phosphorous pentoxide. Light brown needles, 48 g. (95%), of the product were obtained.

The original procedure used more than the theoretical amount of hydrogen peroxide which was decomposed by means of platinum wire at the end of the reaction.

Attempted Reaction of Styrene Oxide with Trimethylamine N-oxide. To 12 g. (0.1 mole) of styrene oxide was added 7.5 g. (0.1 mole) of trimethylamine N-oxide, and 25 ml. of nitromethane was added as the solvent. There was no visible reaction in the cold. Heating caused the amine N-oxide to dissolve, with concurrent red coloration. The solution became clear and red; further heating caused darkening until practically black. After heating for 30-60 minutes, trimethylamine evolution was definitely noted. It was trapped with concentrated hydrochloric acid in a beaker with an inverted funnel. After reflux for 6 hours, approximately one-half (20 g.) of the reaction mixture was placed in a distillation apparatus; under water pump vacuum, the nitromethane was removed. Then, the residue was vacuum distilled. The oil pump could pull down only to 15-20 mm., owing to the decomposition occurring simultaneously, forming gaseous material which had the odor of trimethylamine. About 2 g. of yellow oil was collected (b.p. 120-130°). Infrared spectrum: 2.8-3.1 μ

(OH, hydrogen-bonded), 3.6 μ (aldehyde C-H, shoulder), 5.6 μ and 5.8 μ (C=O), 6.3 μ (phenyl), 6.1 μ (C=C, shoulder), 9.0 μ (-CH-OH), 9.5 μ (CH₂OH). The residue from vacuum distillation showed only polymeric character and was soluble in acetone. The other half of the reaction mixture was extracted first with hot water, then the aqueous layer was extracted with ether. The ether extract was dried, and the ether was removed by evaporation under a current of air. The infrared spectrum of this oily residue was about the same as that of the distilled product showing still a mixture. From the aqueous layer, a white solid (m.p. 63^o, from Skelly solvent C) was obtained in small amount. Its infrared spectrum showed that it was probably phenylethylene glycol, but no further identification of this solid was carried out. Attempts to isolate 2-hydroxyacetophenone were not successful.

Attempted Reaction of Styrene Oxide with 1-Methylpyrrolidine 1-Oxide. Styrene oxide (12 g., 0.1 mole) was added to a solution of 11.3 g. (approx. 0.11 mole) of 1-methylpyrrolidine in 50 ml. of acetonitrile under magnetic stirring. The mixture was heated under reflux for 12 hours, and a red color was observed after addition of the amine N-oxide. After the reflux was complete, the reaction mixture was steam distilled. The distillate, a milky solution, was extracted with ether. From the ether extract, a brown oil was obtained. Attempts to crystallize this oil were not successful. Its infrared spectrum showed a broad hydrogen-bonded OH band and a carbonyl band. Attempts to isolate 2-hydroxyacetophenone from either the distillate or the tar-like residue were not successful.

Reaction of 2-Hydroxyacetophenone with 1-Methylpyrrolidine 1-Oxide. A solution of 7 g. (0.051 mole) of 2-hydroxyacetophenone, 6.05 g. (0.06 mole) of 1-methylpyrrolidine 1-oxide and 150 ml. of acetonitrile was heated under reflux for 11 hours under mechanical stirring. The solution turned to a red color after being heated under reflux for 15 minutes. After the reflux was complete, the mixture was distilled. Paraformaldehyde, 1-methylpyrrolidine and acetonitrile were distilled out at 76-81°; a total of 160 ml. of the distillate was obtained. The residue from distillation was diluted with ether and extracted several times with equal volume of 5 per cent sodium bicarbonate solution. The aqueous layers were combined, acidified with hydrochloric acid to Congo red, and extracted with ether. The ether layer was washed with water, dried over anhydrous magnesium sulfate, then evaporated to dryness under vacuum. From this ether solution, 4 g. (64%) of benzoic acid was obtained (m.p. 121°, from distilled water). The infrared spectrum of this sample was identical with that of benzoic acid; and a mixed melting point with equal amount of benzoic acid showed no depression. To 10 ml. of the distillate alcoholic picric acid was added giving 0.4 g. (73.5%) of 1-methylpyrrolidine picrate, m.p. 217-218° (lit. (11) 218°). Hydrogen chloride was bubbled into the rest of the distillate to prepare the hydrochloride; a beige solid was obtained after the acetonitrile was removed in vacuo. The infrared spectrum of this beige solid showed that it was a mixture of paraformaldehyde (9.43 μ , C-O-C) and 1-methylpyrrolidine hydrochloride. When this solid was treated with Tollen's

reagent, a black precipitate was formed on warming, indicating the presence of formaldehyde. After recrystallization from absolute ethanol, pure 1-methylpyrrolidine hydrochloride was obtained which sublimed at 180° . Its infrared spectrum was identical with that of the 1-methylpyrrolidine hydrochloride.

Another run with twice the amount of the amine N-oxide gave approximately the same result (60% benzoic acid) indicating that the reaction of amine N-oxide and 2-hydroxyacetophenone is a 1 to 1 reaction.

Stability Study of 2-Hydroxyacetophenone. A solution of 1.36 g. (0.01 mole) of 2-hydroxyacetophenone in 15 ml. of acetonitrile was heated under reflux for 12 hours. The solvent was then removed in vacuo. 1.35 g. (99.5%) of 2-hydroxyacetophenone was recovered (m.p. $84-86^{\circ}$, from Skelly solvent C). Mixture melting point with an equal amount of authentic 2-hydroxyacetophenone (m.p. $84-86^{\circ}$) showed no depression.

Attempted Reaction of 2-Hydroxyacetophenone with Pyridine 1-Oxide. A solution of 2.72 g. (0.02 mole) of 2-hydroxyacetophenone, 2.8 g. (0.04 mole) of pyridine 1-oxide and 35 ml. of acetonitrile was heated under reflux for 22 hours. The reaction mixture was processed in the same manner as described for the reaction of this ketol with 1-methylpyrrolidine 1-oxide. From the ether extract was obtained 2.06 g. of light yellow solid, identified as 2-hydroxyacetophenone by its infrared spectrum, its melting point ($85-86^{\circ}$) and the lack of melting point depression when mixed with authentic 2-hydroxyacetophenone. From the organic layer an additional 0.6 g. of 2-hydroxyacetophenone was

recovered, making a total recovery of 97.5 per cent of the starting material. No benzoic acid was obtained. It was concluded that no reaction had occurred between 2-hydroxyacetophenone and pyridine 1-oxide.

Reaction of 2-Hydroxyacetophenone with Trimethylamine N-oxide in Acetonitrile. A solution of 2.04 g. (0.015 mole) of 2-hydroxyacetophenone, 2.25 g. (0.027 mole) of trimethylamine N-oxide and 30 ml. of acetonitrile were heated under reflux for 12 hours. Trimethylamine could be detected by a wet Hydrion paper (pH 9) during the reaction. After the reflux was complete, the reaction mixture was treated in the same manner as previously described for this ketol with 1-methylpyrrolidine 1-oxide. Benzoic acid (m.p. 121-122°, from water) was obtained in the amount of 0.76 g. (43%). Its infrared spectrum was identical with that of the authentic sample.

Reaction of 2-Hydroxyacetophenone with Trimethylamine N-oxide in Water. 2-Hydroxyacetophenone, 2.72 g. (0.02 mole), trimethylamine N-oxide, 3 g. (0.04 mole) and 40 ml. of water were heated under reflux for 12 hours and processed in the usual manner. The evolution of trimethylamine during the reaction was noticed by its strong odor from the top of the condenser. Benzoic acid was obtained in the amount of 0.45 g. (21%, based on the reacted starting material), and it was identified by its infrared spectrum which was identical with that of the authentic sample. 2-Hydroxyacetophenone was recovered in 15 per cent yield (0.4 g., m.p. 74-78°) from the ether solution after benzoic acid was removed. The identification of 2-hydroxyacetophenone

was by its infrared spectrum.

Reaction of Phenylglyoxal hydrate with Trimethylamine 1-oxide. A solution of 2.7 g. (0.016 mole) of phenylglyoxal hydrate, 1.5 g. (0.02 mole) of trimethylamine 1-oxide and 38 ml. of acetonitrile were heated under reflux for 12 hours. After reflux for about 20 minutes, the reaction mixture changed from yellow to rose red; the color kept on getting darker as the reaction proceeded. No carbon dioxide was detected during the reaction when a trap filled with clear barium hydroxide solution was used. When the reflux was complete, the reaction mixture was distilled. Trimethylamine was collected in water before the distillation began and identified by the quinhydrone test (23). Acetonitrile distilled out at 79-80°. The residue from the distillation was diluted with ether and was extracted twice with 5 per cent sodium bicarbonate. The bicarbonate layer was acidified with 6N sulfuric acid, and extracted twice with ether. The ether solution was washed with saturated sodium chloride solution followed by distilled water. Then, it was dried over anhydrous magnesium sulfate, and treated with decolorizing charcoal. On removal of the ether in vacuo, 1.4 g. of benzoic acid (m.p. 121-124°) was obtained. After recrystallization from water, 1.2 g. (61% theoretical) of benzoic acid (m.p. 121-122°) was obtained. Its infrared spectrum was identical with that of the authentic sample, and a mixed melting with the authentic sample did not show depression. After the benzoic acid had been removed, the aqueous solution was distilled at 97-98°, 210 ml. of distillate was obtained. The Duclaux constants ($A = 3.6$, $B = 4.6$, $C = 4.9$)

of the distillate determined by the procedure given by Shriner, Fuson and Curtin (37a) indicated that the acid was formic acid (literature values of Duclaux constants (37a) for formic acid are: $A = 3.95$, $B = 4.4$, $C = 4.55$, where for acetic acid, the Duclaux constants (37a) are: $A = 6.8$, $B = 7.1$, $C = 7.4$). The per cent yield of formic acid was determined by titration with sodium hydroxide ($3.8 \times 10^{-3} N$) as 9.5 per cent.

Attempted Reaction of Formic Acid with Trimethylamine N-oxide. Formic acid, 3 ml. (88%, 0.04 mole), and 3 g. (0.04 mole) of trimethylamine N-oxide were dissolved in 30 ml. of acetonitrile. The mixture was heated under reflux under nitrogen gas for 10 hours. Attempts were made to trap carbon dioxide with a gas trap filled with clear saturated solution of barium hydroxide. No carbon dioxide was detected. After the solvent was removed by means of a rotatory evaporator, absolute ethanol was added to the mixture and heated under reflux for 5 hours in order to change the formic acid into ethyl formate. The volatiles were then removed in vacuo. 2.5 g. (84% recovery) of trimethylamine N-oxide was obtained; its infrared spectrum was identical with that of the authentic sample.

Attempted Reaction of Acetophenone with Trimethylamine N-oxide. A solution of 1.8 g. (0.015 mole) of acetophenone, 1.13 g. (0.015 mole) of trimethylamine N-oxide, and 30 ml. of acetonitrile were heated under reflux for 15 hours. No trimethylamine was given off during the reaction. On standing, 0.94 g. (83% recovery) of white solid separated out, and it was identified as trimethylamine N-oxide by its infrared spectrum.

The acetophenone was recovered as its 2,4-dinitrophenylhydrazone (4 g., 91% recovery, m.p. 249-250°, lit. (37b) 250°) which was prepared as the procedure given by Shriner, Fuson and Curtin (37c). The recovery of the starting materials indicated that no reaction between trimethylamine N-oxide and acetophenone had occurred.

Attempted Reaction of Benzaldehyde with Trimethylamine N-oxide. A mixture of 2.4 ml. (2.54 g., 0.024 mole) of benzaldehyde and 1.8 g. (0.024 mole) of trimethylamine N-oxide were dissolved in 30 ml. of acetonitrile and heated under reflux for 12 hours under nitrogen gas. After letting it stand overnight at room temperature, a white solid was obtained, m.p. 8.6-9.6° (lit. (33) trimethylamine N-oxide dihydrate, m.p. 96°). When the solvent was removed by means of a rotatory evaporator, more trimethylamine N-oxide dihydrate was obtained. A total of 1.75 g. (97% recovery) of trimethylamine N-oxide dihydrate (m.p. 86-96°) was recovered. The recovered trimethylamine N-oxide dihydrate gave an infrared spectrum which was identical with that of the starting trimethylamine N-oxide, indicating that there was no reaction between trimethylamine N-oxide and benzaldehyde.

Attempted Reaction of Benzaldehyde with 1-Methylpyrrolidine 1-oxide. A mixture of 3.8 ml. (3.95 g., 0.038 mole) of benzaldehyde, 3.91 g. (0.038 mole) of 1-methylpyrrolidine 1-oxide and 120 ml. of acetonitrile was heated under reflux and nitrogen for 21.5 hours. After the reflux was completed, most of the acetonitrile was removed by distillation. The residue was distilled

under water pump vacuum; three fractions were collected: fraction 1, b.p. 69° (25 mm.), 1.07 g.; fraction 2, b.p. 67° (24 mm.), 1.22 g.; fraction 3, b.p. 61° (24 mm.), 0.57 g. All these three fractions gave identical infrared spectra with the authentic benzaldehyde. The gas chromatographical analysis of these three fractions gave three peaks respectively. The first peak had a retention time of 1.20 minutes, was separated only in traces, and was not identified. The second peak had a retention time of 1.6 minutes and was identified as water by its infrared spectrum. The third peak had a retention time of 3.1 minutes and was identified as benzaldehyde by comparison of the retention time with that of the authentic benzaldehyde. No benzyl alcohol was found by gas chromatographical analysis. The residue from vacuum distillation gave an N-O characteristic absorption band (10.7 μ) on the infrared spectrum. No free amine was detected by gas chromatography. The total recovery of benzaldehyde was 72.5 per cent. This experiment together with the preceding one which led to 97 per cent recovery of trimethylamine N-oxide, confirmed that no reaction was occurred between benzaldehyde and amine N-oxides.

Attempted Reaction of Paraformaldehyde with 1-Methylpyrrolidine 1-oxide. A mixture of 1.1 g. (0.037 mole) of paraformaldehyde, 3.88 g. (0.037 mole) of 1-methylpyrrolidine 1-oxide and 100 ml. of acetonitrile was heated under reflux for 23 hours. No 1-methylpyrrolidine was noticed during reaction or in the recovered solvent when it was analyzed by gas chromatography. Traces of formaldehyde and methanol were shown on the gas chromatograph of the recovered solvent, and they were identified

respectively by comparison of their retention times with that of the authentic samples. Paraformaldehyde, which solidified on the neck of the condenser during the reflux period, weighed 0.19 g. An additional amount of paraformaldehyde (0.44 g.) was obtained from the first 20 ml. of the distillate and from the condenser. The total recovery of paraformaldehyde was 55 per cent. The crude residue from the distillation weighed 4.5 g. and had a characteristic N-O absorption band of 1-methylpyrrolidine 1-oxide at 10.8μ (lit. (34) 10.7μ). No formic acid was found by gas chromatography.

Preparation of n-Butylbenzoin (1,3-Diphenyl-2-hydroxyhexanone-1) XXXIV. n-Butylmagnesium bromide, prepared from 2.6 g. (0.107 mole) of magnesium, 13.7 g. (11 ml.) of n-butyl bromide and a total of 75 ml. of anhydrous ether with mechanical stirring, was added slowly to a solution of 21 g. (0.1 mole) of benzil, 50 ml. anhydrous benzene, and 100 ml. anhydrous ether stirred by a magnetic stirrer. Benzene was added because of the low solubility of benzil in ether. After the addition was complete, the reaction mixture was refluxed for 3 hours and then it was hydrolyzed with aqueous ammonium chloride. A white solid, which separated out with magnesium hydroxide, was recrystallized from 1:1 ethanol-water. The white solid weighed 8.2 g. (32.5% yield) consisted mainly of benzoin, as showed by its melting point of $123-127^\circ$ (lit. (10) 124°), mixed melting point with authentic benzoin: $121-126^\circ$ (benzoin m.p. $130.5-133^\circ$, from storeroom), and the n.m.r. spectrum which showed a carbinol C-H doublet centering at 4.678 (in CCl_4 solution) to have an area about one-

fifteenth of the aromatic C-H area. Further repeated recrystallization from 95 per cent ethanol or 1:1 benzene—*n*-hexane (by volume) followed by 95 per cent ethanol gave 3.8 g. (14.5%) of *n*-butylbenzoin, m.p. 125-126° (lit. (10) 124°). Crawford, Saeger and Warneke (10) reported *n*-butylbenzoin in yields up to 5.6 per cent using direct addition of the Grignard reagent to benzil.

Preparation of α -Methylbenzoin XXXVI. A solution of 30 g. (13.4 ml., 0.21 mole) of methyl iodide in 100 ml. of anhydrous ether was added slowly in 30 minutes to 5 g. (0.22 mole) of magnesium which was soaked in 65 ml. of anhydrous ether. The whole mixture was stirred vigorously by a magnetic stirrer. After the addition was complete, the mixture was heated under reflux for 15 minutes, cooled, and transferred to an adding funnel. The Grignard reagent prepared above was added slowly through the adding funnel to a solution of 42 g. (0.2 mole) of benzil in 100 ml. of anhydrous thiophene free benzene and 160 ml. of anhydrous ether. The whole mixture was stirred vigorously and mechanically. The reaction was exothermic and the addition took 90 minutes. After the addition was complete, the mixture was heated under reflux for four and half hours, cooled, and hydrolyzed by 37 g. (0.69 mole) of ammonium chloride in 150 ml. distilled water. Stirring was continued for 40 minutes. The magnesium hydroxide formed was filtered off; the aqueous layer was extracted two times with benzene-ether (1:1 by volume). The ether-benzene extracts combined with the organic layer was concentrated to one-fifth of its original volume using a rotatory

evaporator. An equal volume of n-hexane was added to the solution. α -Methylbenzoin separated out as white needles upon cooling in an ice bath. A total of 36 g. (80% theoretical) of α -methylbenzoin was obtained. The crystals were washed several times with n-hexane, dried and melted at 64-65°. N. m. r. spectrum: 1.68 δ (CH₃, singlet), 4.45 δ (OH, singlet). Infrared spectrum: 2.98 μ (OH), 5.95 μ (C=O), 6.8 μ , 7.3 μ (CH₃).

Anal. Calcd. for C₁₅H₁₄O₂: C, 79.64; H, 6.19. Found: C, 79.43; H, 6.14.

Reaction of α -Methylbenzoin XXXV with Trimethylamine N-Oxide. A solution of 10 g. (0.044 mole) of α -methylbenzoin, 3.4 g. (0.045 mole) of trimethylamine N-oxide and 160 ml. of acetonitrile was heated under reflux for 125 hours. No reaction seemed to occur during the first 3 hours. After heating under reflux for 6 hours, the trimethylamine given off could be detected by a wet litmus paper from the top of the reflux condenser. An attempt was made to trap the trimethylamine formed in a dry ice trap, but it was not successful. After the reflux was complete, the mixture was distilled at 79-80° to remove most of the acetonitrile. Trimethylamine was noticed by its odor, and was collected into water before acetonitrile started to distill over. A positive quinhydrone test (23) for tertiary amine was obtained. The residue from distillation was diluted with ether, and extracted four times with a 20% sodium carbonate solution. From the carbonate extract 0.7 g. (42% conversion) of benzoic acid was obtained; it was identified by its infrared spectrum and by mixed melting point. The organic layer left

behind from the carbonate extraction was washed with water until the washes were neutral to litmus; it was then dried over anhydrous magnesium sulfate. After the ether was removed in vacuo, the residue was vacuum distilled. Three fractions were collected: The first fraction (b.p. below 40° at 1.5 mm.) gave 0.3 g. (20% conversion) of benzaldehyde which was identified by its infrared spectrum and by the fact that when it was standing in air, it was air oxidized to benzoic acid. The second fraction (b.p. $43-44^{\circ}$, 1.25 mm.) gave 1.3 g. (79% conversion) of acetophenone; its infrared spectrum was essentially identical with that of the authentic sample. Further confirmation was obtained from the phenylhydrazone, which melted at $103-104^{\circ}$ (lit. (37b) 105°). The third fraction (b.p. $123-133^{\circ}$, 0.5 mm.) gave 3 g. of α -methylbenzoin (m.p. $60-64^{\circ}$) which was identified by its infrared spectrum. From the residue of the vacuum distillation, another 3.9 g. of the α -methylbenzoin was recovered (69% total recovery).

Reaction of α -Methylbenzoin XXXV and 1-Methylpyrrolidine 1-Oxide. A solution of 10 g. (0.04 mole) of α -methylbenzoin, 4.8 g. (0.047 mole) of 1-methylpyrrolidine 1-oxide and 150 ml. of acetonitrile was heated under reflux for 23 hours. After the reflux was complete, the reaction mixture was distilled. 1-Methylpyrrolidine and acetonitrile distilled at $79-81^{\circ}$; a total of 120 ml. of distillate was obtained. The residue was diluted with twice its volume of ether and then extracted with 5 per cent aqueous sodium bicarbonate solution; only a trace of benzoic acid was obtained. The organic layer was treated as previously described for this ketol with trimethylamine N-oxide, and it was

then vacuum distilled. Three fractions were collected: Fraction 1 (b.p. 51° at 4 mm., 55° at 3.8 mm.) gave 0.5 g. (15% conversion) of benzaldehyde, which was identified by its infrared spectrum. Fraction 2 (b.p. 61° at 3.5 mm.) and fraction 3 (b.p. 56° at 0.5-1.3 mm.) gave a total of 2.8 g. (87% conversion) of acetophenone; its infrared spectrum was essentially identical with that of the authentic sample. A further confirmation was obtained from the 2,4-dinitrophenylhydrazone which had a melting point of $249-250^{\circ}$ after recrystallization from a mixture of ethanol and ethyl acetate (lit. (37b) 250°). From the residue of vacuum distillation, 3 g. (30%) of α -methylbenzoin was recovered (m.p. $63-65^{\circ}$).

Another run of the reaction with 8 g. (0.035 mole) of α -methylbenzoin, 3.6 g. (0.035 mole) of 1-methylpyrrolidine 1-oxide and 105 ml. acetonitrile heated under reflux for 48 hours gave the following results: 7 per cent of benzoic acid, 11.5 per cent of acetophenone (b.p. 43° at 1.3 mm.), 13 per cent of benzaldehyde (b.p. $83-88^{\circ}$ at 40° mm., using a water pump), and 49 per cent of recovered α -methylbenzoin (b.p. 134° at 0.8 mm.). The benzoic acid, benzaldehyde, and acetophenone were identified by their infrared spectra. The α -methylbenzoin was identified by infrared spectrum together with the mixed melting point with the authentic sample.

Attempted Reaction of Benzoic Acid and 1-methylpyrrolidine 1-Oxide. A solution of 2.5 g. (0.021 mole) of benzoic acid, 2.2 g. (0.022 mole) of 1-methylpyrrolidine 1-oxide and 80 ml. of acetonitrile was heated under reflux for 24 hours, followed by

distillation at $79-80^{\circ}$ to remove most of the acetonitrile. No free amine had been noticed. The residue was treated in the usual manner as in the cases of 2-hydroxyacetophenone with amine N-oxides. On removal of the ether in vacuo, 2.3 g. (92%) of the benzoic acid was recovered, and identified by infrared spectrum and by the mixed melting point. No benzaldehyde had been isolated.

Reaction of Benzoin XXXIX with Trimethylamine N-Oxide.

A solution of 2.12 g. (0.01 mole) of benzoin, 0.75 g. (0.01 mole) of trimethylamine N-oxide and 30 ml. of acetonitrile was heated under reflux for 12 hours. Trimethylamine was given off during the reaction and was bubbled into water from the top of the condenser. It was identified by the quinhydrone test (23) as a tertiary amine. After the reflux was complete, the volatiles were removed in vacuo and 2.34 g. of yellow solid was obtained (m.p. $85-90^{\circ}$). After recrystallized from n-hexane, 1.81 g. (86% theoretical) of yellow needle crystals was obtained (m.p. $95-96^{\circ}$). The infrared spectrum of these crystals was identical with that of benzil; and a mixed melting point showed no depression.

Reaction of Benzoin XXXIX with 1-Methylpyrrolidine 1-Oxide.

A solution of 6 g. (0.028 mole) of benzoin, 3 g. (0.03 mole) of 1-methylpyrrolidine 1-oxide, and 80 ml. of acetonitrile was heated under reflux for 12 hours. The reaction mixture turned to a red color after reflux for 20 minutes. After the reflux was complete, the reaction mixture was distilled. 1-Methylpyrrolidine and acetonitrile were distilled over at $79-80^{\circ}$. A total of 88 ml. of the distillate was obtained. The distillate (20 ml.) was used to prepare the picrate, using the procedure given by Shriner, Fuson,

and Curtin (37d). The picrate obtained had a m.p. of 217-218° (lit. (11) 218°). The rest of the distillate was used to prepare the hydrochloride by passing anhydrous hydrogen chloride into the distillate for half an hour. On removal of the solvent in vacuo, 2.1 g. (80% theoretical) of flesh color solid was obtained. It was washed with anhydrous ether followed by n-hexane. After recrystallization from absolute ethanol, a white solid was obtained. Its infrared spectrum was identical with that of the 1-methylpyrrolidine hydrochloride. The residue from the distillation was a yellow oil which solidified on stirring. After being recrystallized from n-hexane, 4.5 g. (77% theoretical) of benzil (m.p. 94-95°) was obtained. A mixed melting point did not show depression.

Reaction of Benzoin XXXIX with 1-Methylpyrrolidine 1-Oxide in the Presence of Water. A solution of 2.2 g. (1.03×10^{-2} mole), of benzoin, 1.2 g. (1.05×10^{-2} mole) of 1-methylpyrrolidine 1-oxide, 15 ml. of acetonitrile, and 10 ml. of water were heated under reflux for 12 hours. After the reflux was complete, the mixture was processed in the usual manner. Benzoic acid which was identified by its infrared spectrum was obtained in the amount of 0.2 g. (17% conversion). After benzoic acid was removed, the organic layer was washed with water until the washes were neutral to litmus paper, then dried over anhydrous magnesium sulfate. On removal of the volatiles in vacuo 1.9 g. (86.5% recovery) of benzoin was recovered. No benzil was found among the reaction products.

Reaction of Benzoin XXXIX with Trimethylamine N-Oxide in the Presence of Water. A solution of 2.3 g. (0.0108 mole) of benzoin,

0.9 g. (0.012 mole) of trimethylamine N-oxide, 15 ml. acetonitrile, and 10 ml. of distilled water was refluxed and processed as previously described. A trace of trimethylamine was detected during the reaction by the quinhydrone test (23). Benzoic acid (0.2 g., 17% conversion yield) was obtained as the isolated product, and it was identified by its infrared spectrum. The recovery of benzoin was 87 per cent (2 g., m.p. 133-134° from *n*-hexane). No benzil had been found.

Reaction of Acetoin XLII with Trimethylamine N-Oxide. A mixture of 3.9 g. (0.044 mole) of acetoin and 3.1 g. (0.042 mole) of trimethylamine N-oxide was heated under reflux for 5 hours. The mixture changed from light yellow to golden brown after reflux for half an hour. Trimethylamine could be detected by a piece of wet red litmus paper on the top of the condenser. The mixture was distilled, and water was distilled out. The residue was a thick syrup material. When acetone was added to the residue, a white solid was obtained. No further identification of this white solid was done, since it was thought that it was a polymer of acetoin.

Reaction of Acetoin with 1-Methylpyrrolidine 1-Oxide. A solution of 6.4 g. (0.075 mole) of acetoin, 5.5 g. (0.055 mole) of 1-methylpyrrolidine 1-oxide, and 50 ml. of nitromethane was heated under reflux for 12 hours. The mixture was then distilled; water and nitromethane were collected. No 2,3-butadione was obtained.

Attempted Reaction of D-Fructose XLIII with Trimethylamine N-Oxide. D-fructose 1.8 g. (0.01 mole) and trimethylamine N-oxide

0.75 g. (0.01 mole) and 10 ml. of water were heated under reflux for 30 hours. The reaction mixture changed from colorless, yellow to brown. Samples were taken at six-hour intervals, and were analyzed by paper chromatography (26). When developed with a water, acetic acid, and n-butanol mixture, and sprayed with silver nitrate solution, two other spots, one with a higher R_f value, the other with a lower R_f value than D-fructose, were obtained. No further identification was carried out.

Preparation of Benzoin Acetate XLIV. Benzoin acetate was prepared according to the procedure of Corson and Saliani (7), using 106 g. (0.5 mole) of benzoin, 100 ml. of glacial acetic acid, 100 ml. (1.25 moles) of acetic anhydride and 10 ml. of concentrated sulfuric acid. Benzoin acetate melted at $81-82^{\circ}$ (lit. (7) $81.5-82.5^{\circ}$) was obtained in 86.5 per cent yield (110 g.).

Attempted Reaction of Benzoin Acetate XLIV with Trimethylamine N-Oxide. Benzoin acetate, 5.2 g. (0.02 mole) and trimethylamine N-oxide, 1.6 g. (0.022 mole) were dissolved in 60 ml. of acetonitrile. The mixture was heated under reflux for 12 hours and was treated in the usual manner after the reflux was complete. The crude recovery of benzoin acetate was 100 per cent (m.p. $75-78^{\circ}$), while the recovery of the pure benzoin acetate was 79 per cent (m.p. $81-82^{\circ}$ from 95% ethanol). No trimethylamine was found when the distillate was analyzed mass spectroscopically. A trace of benzoic acid (0.1 g., m.p. $118-120^{\circ}$, 11% conversion yield) was obtained and identified.

Preparation of ω -Methoxyacetophenone XLV. ω -Methoxy-

acetophenone(XLV) was prepared according to the procedure of Moffett and Shriner (25) using phenylmagnesium bromide and methoxyacetonitrile. The latter was prepared according to the procedure of Allen and Scarrow (35) from sodium cyanide, para-formaldehyde and dimethyl sulfate. The prepared methoxyacetonitrile boiled at 118° (lit. (35) $118-122^{\circ}$), while the ω -methoxyacetophenone had a boiling point of 97° at 5 mm. (lit. (25, 1) $118-120^{\circ}/15$ mm. and $110-112^{\circ}/9$ mm.). N.M.R. spectrum: 2.85 δ (CH_3 , singlet), 4.1 δ (CH_2 , singlet).

Reaction of ω -Methoxyacetophenone XLV with 1-Methylpyrrolidine 1-Oxide. A solution of 7.5 g. (0.05 mole) of ω -methoxyacetophenone, 5.2 g. (0.05 mole) of 1-methylpyrrolidine 1-oxide, and 130 ml. of acetonitrile was heated under reflux for 12 hours. After reflux was complete, most of the acetonitrile was removed by distillation and the residue was extracted two times with anhydrous ether. After drying over anhydrous magnesium sulfate, the ether was removed in vacuo; then, the residue was vacuum distilled. Pure ω -methoxyacetophenone was recovered in 73.5 per cent yield (5.5 g.), b.p. 107° (12 mm.); its nuclear magnetic resonance spectrum was identical with that of the authentic sample. No phenylglyoxal or benzaldehyde was found. From the residue of vacuum distillation a trace of benzoic acid (0.1 g., 6.3% conversion yield) was identified by its infrared spectrum.

Reaction of ω -Methoxyacetophenone XLV with Trimethylamine N-Oxide. A solution of 7.5 g. (0.05 mole) of ω -methoxyacetophenone, 3.75 g. (0.05 mole) of trimethylamine N-oxide and 130

ml. of acetonitrile was heated under reflux and processed as described for this ether with 1-methylpyrrolidine 1-oxide, except that the period of reflux was 18 hours, and trimethylamine N-oxide precipitated out when ether was added. Pure ω -methoxyacetophenone was recovered in 84 per cent yield (6.3 g.), b.p. 85-87° (4 mm.). The recovery of crude trimethylamine N-oxide was 2.9 g. (77%). A few milligrams of benzoic acid, isolated from the residue of vacuum distillation, was identified by its infrared spectrum. No phenylglyoxal or benzaldehyde was found.

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THE REACTION OF AMINE N-OXIDES WITH
 α -HYDROXYKETONES

by

LILIAN CHIA-SHEOU KAO

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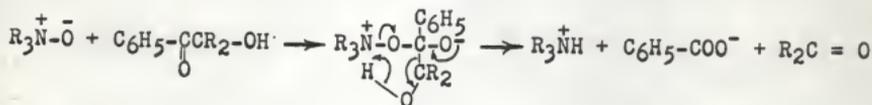
Department of Chemistry

KANSAS STATE UNIVERSITY
Manhattan, Kansas

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Although amine N-oxides are moderately strong nucleophilic reagents towards alkyl halides, phosphorous halides and iodine, no reaction has been reported between amine N-oxides and carbonyl compounds, except acyl anhydrides and acyl halides which have been extensively investigated. In this work, the lack of reaction of simple aldehydes and ketones with amine N-oxides has been confirmed and is considered to be due to the lack of stability of the adduct and to its being unable to decompose in another way, as in the case of the acyl anhydride-amine N-oxide adduct.

It appears possible, however, that appropriately substituted ketones might form amine N-oxide adducts which could decompose by a conjugate elimination process. One type would be:



An example of this type of process has been found with several α -hydroxyketones when caused to react with aliphatic amine N-oxides in acetonitrile solution. Oxidative cleavage was observed with 2-hydroxyacetophenone, α -methylbenzoin, and phenylglyoxal hydrate ($C_6H_5-CO-CH(OH)_2$), giving benzoic acid and formaldehyde, acetophenone or formic acid, respectively. The amine N-oxides studied, trimethylamine N-oxide and 1-methylpyrrolidine 1-oxide, were deoxygenated to the corresponding amines. Pyridine 1-oxide did not react.

Benzoin was oxidized to benzil in high yield by these amine N-oxides under the same conditions, with no oxidative cleavage

being observed. There appeared to be some reverse-benzoin condensation occurring with α -methylbenzoin, for a significant amount of benzaldehyde was isolated in that case.

Preliminary studies of the mechanisms of these reactions included attempted reaction of derivatives of α -hydroxyketones in which the hydroxyl hydrogen atom was replaced by methyl and acetyl groups. The failure of ω -methoxyacetophenone to react with these amine N-oxides indicates the importance of this hydrogen atom in the oxidative cleavage reaction, and it eliminates a benzylic acid-type rearrangement mechanism as a possibility. A similar lack of reaction of benzoin acetate suggests that a concerted, cyclic mechanism involving the hydroxyl hydrogen atom and similar to that proposed for the oxidation of hydrazobenzene by pyridine 1-oxide may apply to the oxidation process here.