THE REACTIONS OF UNSATURATED KETONES AND DERIVATIVES WITH AMINO COMPOUNDS

AMINO KETONES

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CONTENTS

I. INTRODUCTION

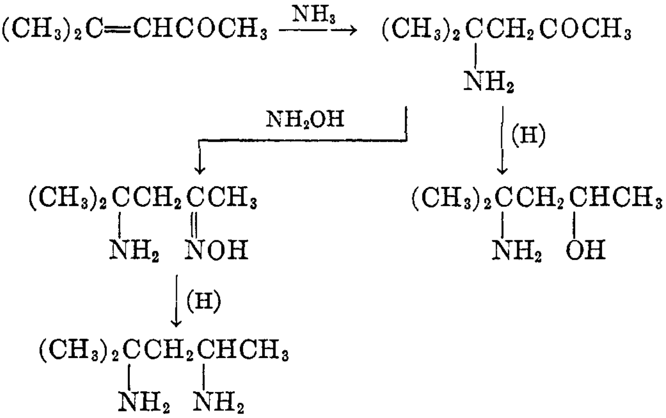
The reactions of vinyl ketones, acetylenic ketones, 1,3-diketones, and related derivatives with amino compounds yield as primary products various types of saturated and unsaturated amino ketones and heterocyclic compounds. The present review must be concerned mainly with these reactions, since the chemistry of some of the resulting types of amino ketones is not yet extensive. The study and development of such reactions has evolved several interesting theoretical considerations with regard to reaction mechanisms and molecular rearrangements. Moreover, preliminary studies of the resulting products have revealed interesting physical, chemical, and pharmacological properties in relation to their various structures. The amino ketones serve as starting materials or intermediates for the synthesis of various amino alcohols, diamines, heterocyclic nitrogen compounds, etc.

II. REACTION OF AMINES WITH UNSATURATED KETONES

A. β-AMINO KETONES FROM VINYL KETONES

The first reported reaction of an amino compound with a vinyl ketone (C═C—CO) was the reaction of ammonia with mesityl oxide, reported by Sokoloff and Latschinoff (109) in 1874. These early investigators had discovered, apparently simultaneously with Heintz (61), that acetone reacted with aqueous ammonia to form several condensation products, among which was the compound diacetone amine, to which the structure $(CH_3)_2C(NH_2)CH_2COCH_3$ was assigned. Sokoloff and Latschinoff showed that diacetone amine decomposed on heating to give ammonia and mesityl oxide. Furthermore, they demonstrated that mesityl oxide would add ammonia in aqueous solution to re-form the diacetone amine. Indeed, the modern method for preparing this important base involves similar conditions, although the product is now isolated as the more stable hydrated acid oxalate salt (96). Recently, Smith and Adkins (108) have shown that anhydrous ammonia adds readily to mesityl oxide at ordinary temperatures to give good yields of diacetone amine.

Evidence was eventually accumulated to show that diacetone amine contained a primary amino group and a carbonyl group, but no hydroxyl group. Heintz (62) reduced this β-amino ketone to the β-amino alcohol, using sodium amalgam in dilute hydrochloric acid solution. Harries (57) prepared the oxime and reduced it to 2-methyl-2,4-diaminopentane with sodium and alcohol.



$$(CH_3)_2C{=}CHCOCH_3 \xrightarrow{NH_3} (CH_3)_2\underset{\displaystyle NH_2}{\underset{|}{C}}CH_2COCH_3$$

$$\xrightarrow{NH_2OH} (CH_3)_2\underset{\displaystyle NH_2}{\underset{|}{C}}CH_2\underset{\displaystyle NOH}{\underset{\|}{C}}CH_3 \xrightarrow{(H)} (CH_3)_2\underset{\displaystyle NH_2}{\underset{|}{C}}CH_2\underset{\displaystyle NH_2}{\underset{|}{C}}HCH_3$$

$$\xrightarrow{(H)} (CH_3)_2\underset{\displaystyle NH_2}{\underset{|}{C}}CH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_3$$

Thus the general nature of the addition of amino compounds to α,β-unsaturated ketones has been known since the rather early beginnings of structural organic chemistry.

Following these early studies, mesityl oxide was shown to add in the same manner aliphatic amines in aqueous solution, such as methylamine (65), dimethylamine (65), and ethylamine (78). In recent years Jones and Kerner (71) added benzylamine, aniline, *m*-toluidine, and *p*-toluidine to mesityl oxide by heating the mixtures for several days to give about 25 per cent yields of the corresponding β-amino ketones.

In 1886 Beyer (13) developed a quinoline synthesis for which he postulated the intermediate formation of β-amino ketones from the addition of arylamines to α,β-unsaturated ketones. This method of quinoline synthesis is discussed in Section V,C,1. Tambor and Wildi (116) studied the reaction of ammonia and of many aromatic amines with benzalacetophenone. They found that this α,β-unsaturated ketone would add ammonia and primary aromatic amines, but not secondary aromatic nor mixed secondary aromatic–aliphatic bases. One molecule of the base was found to react with either one or two molecules of the unsaturated ketone (see table 1). In some cases it was necessary to add sodium hydroxide to the reaction mixtures to secure addition. Later, Georgi and Schwyzer (56) added piperidine, Stewart and Pollard (114) piperazine and morpholine, and Cromwell and Burch (34) tetrahydroisoquinoline to benzalacetophenone by heating the reagents together in hydrocarbon solvents or in alcohol. One mole each of morpholine, piperidine, and tetrahydroisoquinoline, respectively, reacted with 1 mole of benzalacetophenone, while 1 mole of piperazine reacted with 2 moles of the unsaturated ketone.

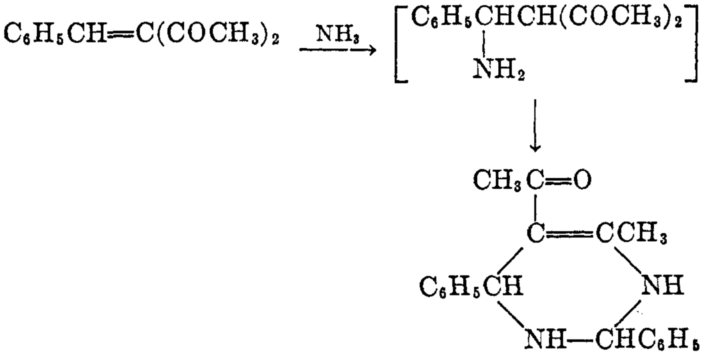
TABLE 1

β-Amino ketones from benzalacetophenone (116)

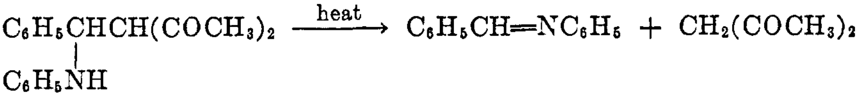
AMINE	ADDITION PRODUCT*	MELTING POINT
		°C.
Ammonia	$(C_6H_5COCH_2CHC_6H_5)_2NR$	163
Methylamine		167 (35)
o-Nitroaniline		243
p-Nitroaniline		252
m-Nitroaniline		240
p-Nitro-*o*-toluidine		203
α-Naphthylamine		180
Aniline	$(C_6H_5COCH_2CHC_6H_5)NHR$	175
p-Toluidine		172
β-Naphthylamine		200

* Only the products indicated could be isolated.

Benzalacetone has been shown to add methylamine in aqueous solution (79), aniline (90) and tetrahydroisoquinoline (34) in alcohol solution, and morpholine and piperidine in petroleum ether solutions (44) to give the expected β-amino ketones. Ruhemann and Watson (105), in an extensive investigation of the addition of organic bases to unsaturated ketones, found ammonia to form a heterocyclic product with α-acetylbenzalacetone and explained the reaction as follows:



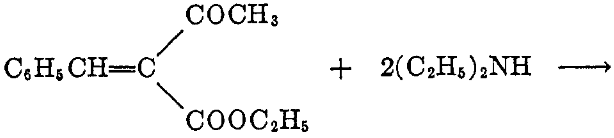
These investigators also were able to add aniline to this unsaturated system to obtain a β-aminoketone which on heating decomposed as indicated:



$$C_6H_5\underset{\displaystyle C_6H_5NH}{CH}CH(COCH_3)_2 \xrightarrow{\text{heat}} C_6H_5CH{=}NC_6H_5 + CH_2(COCH_3)_2$$

In a later investigation (106) these workers were able to add *m*-toluidine, *m*-chloroaniline, *p*-chloroaniline, β-naphthylamine, and piperidine to obtain β-amino ketones, but were unable to add *o*-toluidine, α-naphthylamine, or tetrahydroquinoline to α-acetylbenzalacetone. Certain *o*-substituted benzenoid bases had previously been shown by Tambor and Wildi (116) to be relatively unreactive towards α,β-unsaturated carbonyl systems.

In 1898, Knoevenagel and Faber (72) had reported that ethyl benzalacetoacetate (I) in the presence of diethylamine gave ethyl benzylidinebisacetoacetate (III). They explained the reaction as follows:

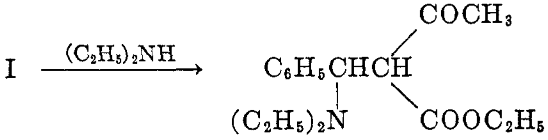


I

$$C_6H_5CH(N(C_2H_5)_2)_2 + \underset{\text{II}}{CH_3COCH_2COOC_2H_5}$$

$$\text{I} + \text{II} \longrightarrow \underset{\text{III}}{C_6H_5CH[CH(COCH_3)COOC_2H_5]_2}$$

Ruhemann and Watson (106), however, believed this reaction might best be explained by postulating the intermediate formation of a β-amino ketone (IV).



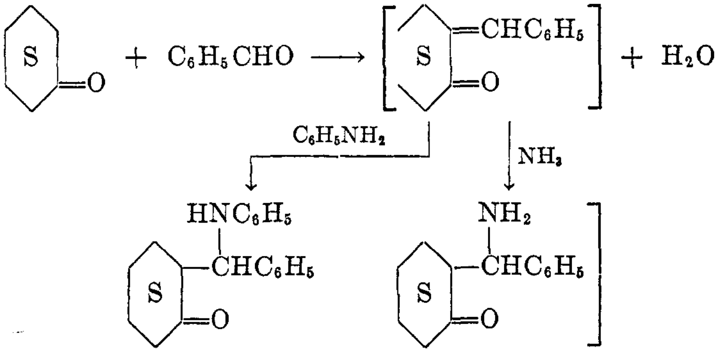
IV

$$IV \xrightarrow{H_2O} (C_2H_5)_2NH + C_6H_5CHO + II$$

$$IV + II \longrightarrow III + (C_2H_5)_2NH$$

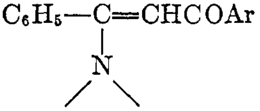
They offered as evidence for this mechanism the fact that piperidine, which adds to such systems, brings about the same reaction, while tetrahydroquinoline, which does not add readily, failed to give the reaction. Furthermore, it was pointed out that the presence of moisture was necessary for the formation of the final product.

An interesting series of reactions reported by Pirrone (97) seems to involve the intermediate formation of an α,β-unsaturated ketone, which then adds the amino compound in the usual way.



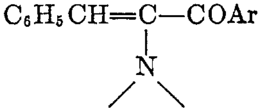
B. β-AMINO-α,β-UNSATURATED KETONES FROM ACETYLENIC KETONES

As a part of an investigation dealing with the preparation of acetylenic ketones, Watson (118) found that amines added readily to such compounds in a manner analogous to the addition of amines to olefinic ketones. Aniline was added to benzoylphenylacetylene to give a yellow crystalline product melting at 104°C., and *p*-methoxybenzoylphenylacetylene added piperidine to give a yellow product melting at 127°C. Watson was not able to decide between the structures A and B for these products.



A

and

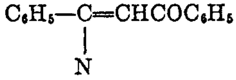
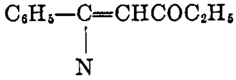
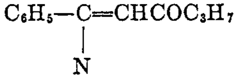
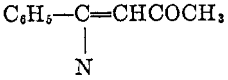


B

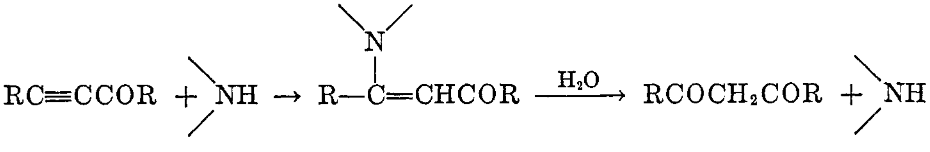
A few years later, in a more extensive investigation, André (3) added several primary and secondary aliphatic, heterocyclic, and aromatic amines to various acetylenic ketones, and proved these products to be β-amino-α,β-unsaturated ketones (see table 2).

TABLE 2

β-Amino-α,β-unsaturated ketones from acetylenic ketones (3)

AMINE	MELTING POINT
	 $C_6H_5-\underset{\substack{\vert \\ N}}{C}=CHCOC_6H_5$
	°C.
Benzylamine	100
Diethylamine	63
Piperidine	81, 99 (50)
N-Methylaniline	87
	 $C_6H_5-\underset{\substack{\vert \\ N}}{C}=CHCOC_2H_5$
Diethylamine	45
Cyclohexylamine	100
	 $C_6H_5-\underset{\substack{\vert \\ N}}{C}=CHCOC_3H_7$
Diethylamine	40
Cyclohexylamine	75
	 $C_6H_5-\underset{\substack{\vert \\ N}}{C}=CHCOCH_3$
Di-*n*-propylamine	47

These addition reactions were carried out in ether solutions either at room temperature or slightly above. Of all of the acetylenic ketones used, benzoylphenylacetylene seemed to be the most reactive. Since acid hydrolysis of these products gave β-diketones, this constituted a new synthesis of these compounds.



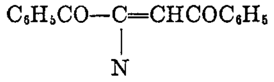
$$RC\equiv CCOR + \rangle NH \rightarrow R-\overset{\substack{\diagdown\,\diagup \\ N \\ \vert}}{C}=CHCOR \xrightarrow{H_2O} RCOCH_2COR + \rangle NH$$

In more recent years Dupont (52) has added various amino compounds to diaroylacetylenes in toluene solution to give α-amino-α,β-diaroylethylenes (see table 3).

It is interesting to see that the acetylenic carbon atom in these compounds is sufficiently electrophilic to attract even the non-base pyrrole, a reaction which the author of this review has found to fail with various olefinic ketones.

TABLE 3

α-Amino-α,β-diaroylethylenes from diaroylacetylenes (52)

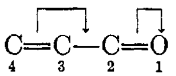
AMINE	MELTING POINT
	 $C_6H_5CO-\underset{\substack{\mid \\ N}}{C}=CHCOC_6H_5$
	°C.
Ammonia	142
Dimethylamine	144
Piperidine	181
Aniline	121
β-Naphthylamine	143
Pyrrole	175

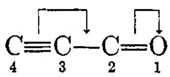
C. MECHANISM OF ADDITION

α,β-Unsaturated ketones

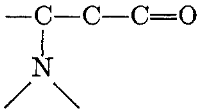
$$\overset{4}{C}=\overset{3}{C}-\overset{2}{C}=\overset{1}{O} \quad \text{and} \quad \overset{4}{C}\equiv\overset{3}{C}-\overset{2}{C}=\overset{1}{O}$$

in general undergo 1,2-, 3,4-, and 1,4-additions. The position favored depends on (*a*) the groups attached to the conjugated system, (*b*) the experimental conditions, and (*c*) the nature of the addenda. Factor (*b*) is of importance mainly in the consideration of the addition of such carbonyl reagents as hydroxylamine (see Section IV). It has been recognized for some time that the highly polar carbonyl group would be expected to confer electrophilic character on the olefinic carbon atom 4 by electromeric relay (99) in such conjugated systems.

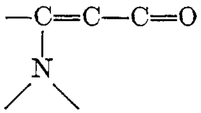




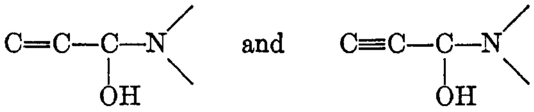
Since bases are also known to add to the carbonyl double bond, carbon atoms 2 and 4 must be expected to be in competition as electrophilic centers. The product of addition to such systems is not always determined by the relative rates of the two competing reactions. In fact, it seems probable in the case under consideration that the relative stability of the products resulting from the competing reactions is of major importance. That is,



and



are more stable and less susceptible to reversal than



especially when no hydrogen is available on the nitrogens for subsequent loss of water, as it is in oxime formation. Furthermore, other things being equal, resonance would be expected to favor the attack by the base at carbon atom 4 (see pages 468–70 of reference 20). Although the carbonyl group would be expected to activate the olefinic double bond and acetylenic triple bond, when conjugated with them, one does not expect the reverse to be true. The carbonyl group in such systems would be expected to be less reactive toward bases than when it occurs isolated.

The transition state for the addition of a base to a conjugated system has been described by Branch and Calvin (20). It seems logical that the driving force for such reactions is the attraction of the electrophilic carbon atom 4 for the unshared electrons of the amino nitrogen. It must be remembered, however, that the ability of amines to form C—N bonds, although related to, may not be directly proportional to the basic strengths of the amines. Although strong bases are strongly nucleophilic toward carbon, weaker bases retain a more than proportional activity toward carbon. The factor of stability of the product and the steric factor of ease of approach of the nitrogen atom to carbon atom 4 are of major importance (106).

One phase in the mechanism of the addition of bases to such conjugated systems that has not been extensively discussed as yet has to do with the mode of migration of the hydrogen that ultimately ends on carbon atom 3. One of the possible ways in which this may come about has been suggested by Cromwell and Cram (37), who postulate a six-membered chelate-ring structure as an intermediate.

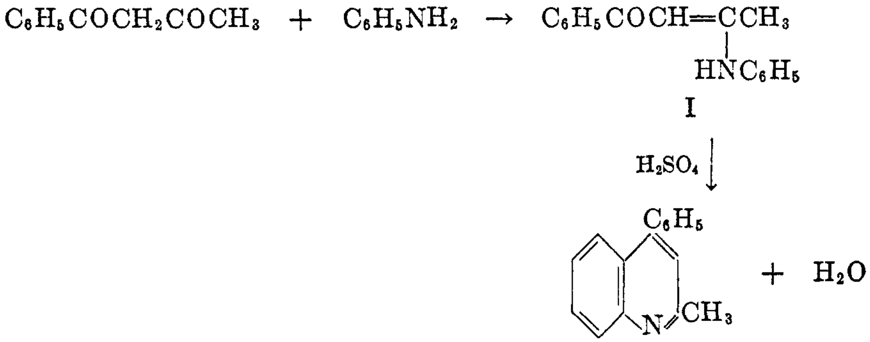
III. Reaction of Amines with Derivatives of Unsaturated Ketones

A. PREPARATION OF β-AMINO-α,β-UNSATURATED KETONES

1. Reaction of amines with 1,3-diketones

The first reaction of a β-diketone with an amino compound seems to have been carried out in 1885 by Fisher and Bülow (55). These workers showed that the newly discovered benzoylacetone reacted on being heated with concentrated ammonium hydroxide to give a base, $C_{10}H_{11}NO$, melting at 143°C., to which they did not assign a structure.

In his early studies with β-diketones, Beyer (14) developed an excellent method for preparing substituted quinolines, which he showed involved the intermediate formation of a β-amino-α,β-unsaturated ketone. When benzoylacetone was heated with aniline at 150°C., without solvent, or refluxed with it in glacial acetic acid, a basic product melting at 110°C. resulted. Since this substance was cyclized to the known γ-phenylquinaldine (II) in excellent yields in concentrated sulfuric acid, the structure was assigned as 1-phenyl-3-anilino-2-buten-1-one (I).



$$C_6H_5COCH_2COCH_3 + C_6H_5NH_2 \rightarrow C_6H_5COCH{=}\underset{\underset{HNC_6H_5}{|}}{C}CH_3$$

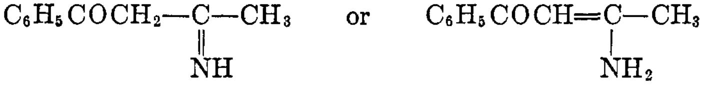
I

II

γ-Phenylquinaldine

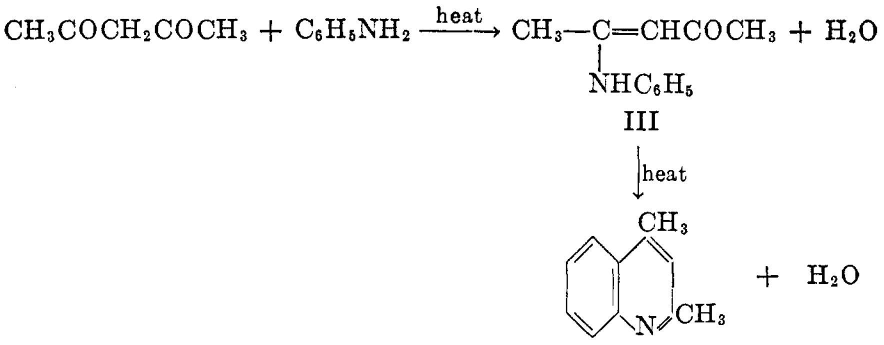
A detailed discussion of this and similar quinoline syntheses is given elsewhere in this review (section V,C,2).

Beyer and Claisen (16) reported in the same year that ammonia reacted with benzoylacetone to give a base melting at 143°C., the structure for which was written as



$$C_6H_5COCH_2{-}\underset{\underset{NH}{\|}}{C}{-}CH_3 \quad \text{or} \quad C_6H_5COCH{=}\underset{\underset{NH_2}{|}}{C}{-}CH_3$$

by analogy with the proven aniline derivative. This was the base previously prepared by Fisher and Bülow (55). In the same year Combes (24) reported in the publication of his doctoral thesis on acetylacetone, that this β-diketone reacted with aniline to give a base boiling at 285–288°C. In the following year Combes (25) reported that this base could be cyclized by distillation or treatment with concentrated sulfuric acid to give 2,4-dimethylquinoline (IV) in excellent yields. Thus the structure of the base boiling at 285–288°C. and melting at 48°C. was written as indicated below (formula III):



$$CH_3COCH_2COCH_3 + C_6H_5NH_2 \xrightarrow{heat} CH_3{-}\underset{\underset{NHC_6H_5}{|}}{C}{=}CHCOCH_3 + H_2O$$

III

IV

TABLE 4

β-Amino-α,β-unsaturated ketones from β-diketones

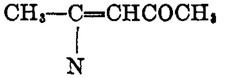
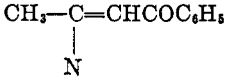
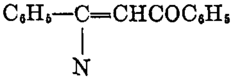
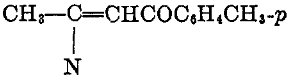
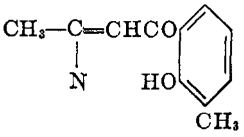
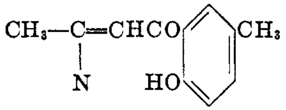
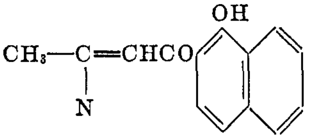
AMINE	MELTING POINT* OR BOILING POINT	REFERENCES
 $\mathrm{CH_3{-}\underset{\overset{\vert}{N}}{C}{=}CHCOCH_3}$		
	°C.	
Ethylamine	215/760 mm.	(26, 103)
Diethylamine	156/24 mm.	(26)
Ethanolamine	73	(73)
Benzylamine	183/17 mm.	(104)
Aniline	48	(25)
 $\mathrm{CH_3{-}\underset{\overset{\vert}{N}}{C}{=}CHCOC_6H_5}$		
Ammonia	143	(55, 16)
Methylamine	75	(15)
Diethylamine	71	(28)
Benzylamine	62	(33)
Cyclohexylamine	54	(33)
Aniline	110	(14)
Piperidine	98	(45)
Morpholine	146	(30)
 $\mathrm{C_6H_5{-}\underset{\overset{\vert}{N}}{C}{=}CHCOC_6H_5}$		
Diethylamine	62	(28)
Benzylamine	101	(33)
Cyclohexylamine	78	(33)
Piperidine	No product	(45)
Morpholine	97	(29)
Aniline	103	(100)
 $\mathrm{CH_3{-}\underset{\overset{\vert}{N}}{C}{=}CHCOC_6H_4CH_3\text{-}\mathit{p}}$		
Ammonia	93	(9)
Aniline	137	(9)
		
Ammonia	101	(123, 124)
Dimethylamine	110	(124)
Aniline	91	(124)

TABLE 4—*Concluded*

AMINE	MELTING POINT* OR BOILING POINT	REFERENCES
		
	°C.	
Ammonia	102	(124)
Aniline	106	(124)
		
Ammonia	154	(124)
Aniline	157	(124)

* Throughout these tables the boiling points are those numbers followed by a value for pressure, i.e., 156/24 mm.; all other values are melting points.

Since these early studies, various primary and secondary amines have been condensed with several β-diketones to give β-amino-α,β-unsaturated ketones, some of which are listed in table 4, while others are included in table 15.

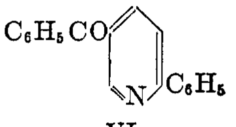
Wittig (123) reported in 1925 that 2-hydroxy-3-methylbenzoylacetone reacted with alcoholic ammonia to give two products to which he assigned the structures 3-amino-2,8-dimethylchromanone and 2-amino-2,8-dimethylchromanone, respectively. In a later more extensive investigation it was shown that such β-diketones react in the usual way with ammonia and amines to give the expected β-amino-α,β-unsaturated ketones (124) (see table 4).

2. Reaction of amines with β-substituted α,β-unsaturated ketones

Benary (11) has reported the preparation of a series of β-amino-α,β-unsaturated ketones by reacting several amine hydrochlorides in alcohol solution with the sodium salts of various β-hydroxy-α,β-unsaturated ketones of the type $RCOCH{=}CHONa$. Some of the products he prepared are given in table 5.

With hydroxymethyleneacetophenone and ammonium chloride the possible initial formation of the β-amino ketone (V) was apparently followed by a complex intermolecular condensation to give 2-phenyl-5-benzoylpyridine (VI), the only product isolated from this reaction.

$$C_6H_5COCH{=}CHONa + NH_4Cl \longrightarrow \underset{V}{[C_6H_5COCH{=}CHNH_2]} \longrightarrow$$



VI

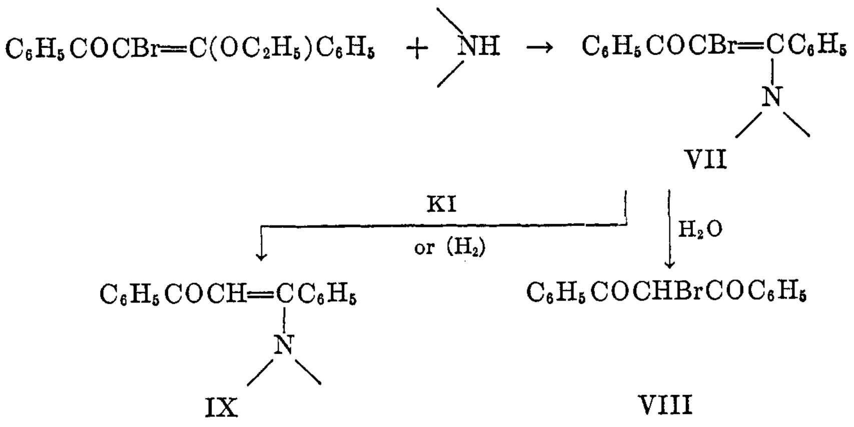
Several patents (53) have been granted for the preparation of β-amino-α,β-unsaturated ketones from β-halogenated α,β-unsaturated ketones ($RCOCH{=}CHCl$) and ammonia or amines in alcohol solution.

β-Alkoxy-α,β-unsaturated ketones ($RCOCH{=}C(OR)R$) react smoothly with amino compounds to form β-amino-α,β-unsaturated ketones. Dufraisse and Netter (51) reacted α-bromo-β-ethoxybenzalacetophenone with diethylamine, piperidine, and benzylamine to obtain the corresponding α-bromo-β-aminobenzalacetophenones (VII). The structures of these products were shown by their hydrolysis to bromodibenzoylmethane (VIII), and reduction to β-amino-α,β-unsaturated ketones (IX). The halogen in these products is stable to hydrolysis but labile to either catalytic reduction (37) or reduction with potassium iodide (51).

TABLE 5

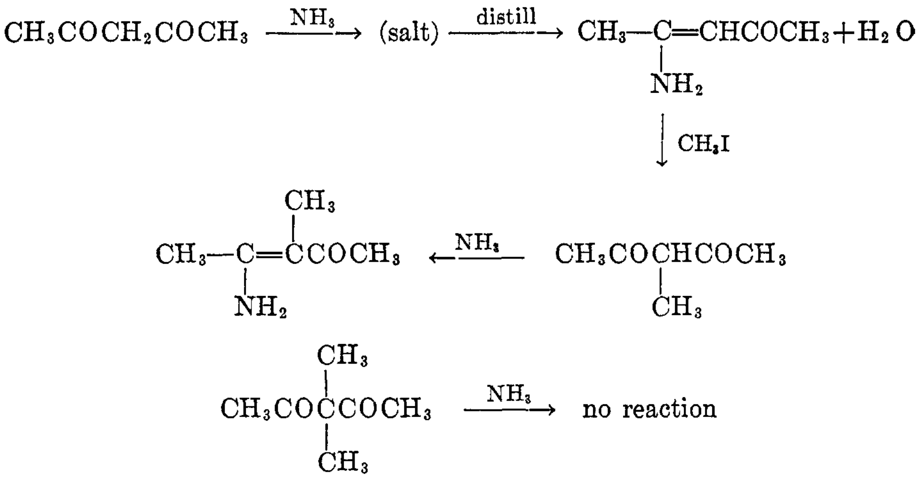
β-Amino ketones from β-hydroxy-α,β-unsaturated ketones (11)

AMINE	MELTING POINT OR BOILING POINT
	$CH_3COCH{=}CHN$
	°C.
Ammonia	96/14 mm.
Methylamine	93/17 mm.
Dimethylamine	118/19 mm.
Piperidine	162/16 mm.
	$CH_3CO{-}\underset{\displaystyle CH_3}{\underset{\vert}{C}}{=}CHN$
Ammonia	112
Methylamine	58
Dimethylamine	55
	$C_6H_5COCH{=}CHN$
Piperidine	81



3. Mechanism of reaction and structure of products

During his rather extensive investigations of such compounds Combes (26) carried out the following series of reactions:



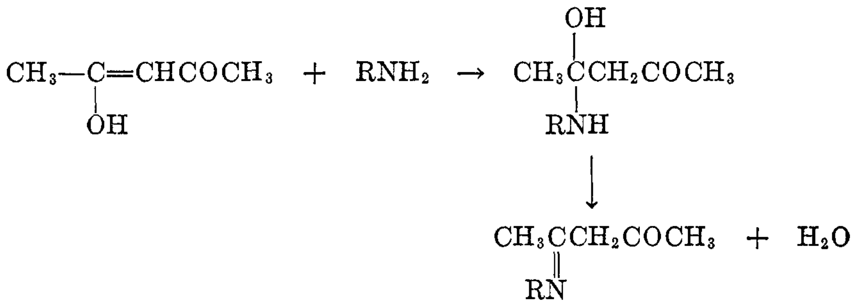
$$CH_3COCH_2COCH_3 \xrightarrow{NH_3} (\text{salt}) \xrightarrow{\text{distill}} CH_3\text{—}\underset{\underset{NH_2}{|}}{C}\text{=}CHCOCH_3+H_2O$$

$$\Big\downarrow CH_3I$$

$$CH_3\text{—}\underset{\underset{NH_2}{|}}{C}\text{=}\overset{\overset{CH_3}{|}}{C}COCH_3 \xleftarrow{NH_3} CH_3CO\underset{\underset{CH_3}{|}}{C}HCOCH_3$$

$$CH_3CO\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}COCH_3 \xrightarrow{NH_3} \text{no reaction}$$

Since the α,α-dimethylacetylacetone gave no reaction with ammonia, Combes interpreted this as meaning that reaction will take place only when the grouping $(\text{—}\underset{\underset{OH}{|}}{C}\text{=C—})$ is available. Rügheimer (103, 104) also considered the reaction of amines with β-diketones to depend upon the enol form but preferred the imine structure to the vinylamine one for the product.

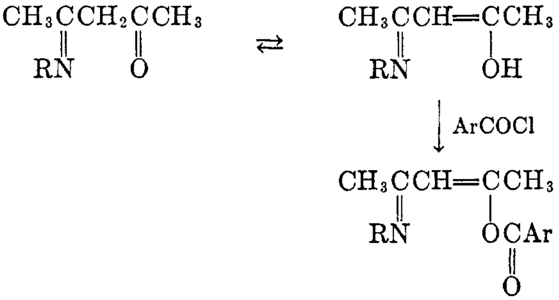


$$CH_3\text{—}\underset{\underset{OH}{|}}{C}\text{=}CHCOCH_3 + RNH_2 \rightarrow CH_3\overset{\overset{OH}{|}}{\underset{\underset{RNH}{|}}{C}}CH_2COCH_3$$

$$\Big\downarrow$$

$$CH_3\underset{\underset{RN}{\|}}{C}CH_2COCH_3 + H_2O$$

Furthermore, he believed these amino or imino ketones quite capable of enolization. He was able to prepare benzoyl derivatives (X) which hydrolyzed readily, as do *O*-derivatives. His findings that these amino or imino ketones often give a color with ferric chloride may or may not be of importance, since such compounds are rapidly hydrolyzed in acid solution to the 1,3-diketones, which would be expected to give color with this reagent.

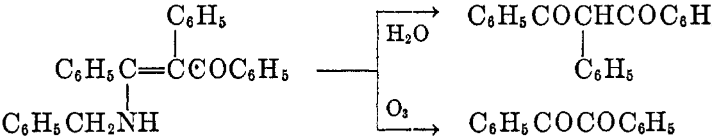


$$\mathrm{CH_3C(=NR)CH_2C(=O)CH_3} \rightleftarrows \mathrm{CH_3C(=NR)CH{=}C(OH)CH_3} \xrightarrow{\mathrm{ArCOCl}} \mathrm{CH_3C(=NR)CH{=}C(OC(=O)Ar)CH_3}$$

X

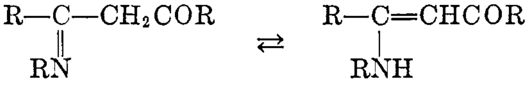
(a) Structure of products

Kohler and Blatt (75) studied the structure of β-benzylamino-α-phenylbenzalacetophenone and showed that hydrolysis resulted in the formation of dibenzoylphenylmethane, while ozonolysis gave benzil.



$$\mathrm{C_6H_5C(NHCH_2C_6H_5){=}C(C_6H_5)COC_6H_5} \xrightarrow{\mathrm{H_2O}} \mathrm{C_6H_5COCH(C_6H_5)COC_6H_5}; \quad \xrightarrow{\mathrm{O_3}} \mathrm{C_6H_5COCOC_6H_5}$$

This may be taken as evidence for the location of the β-benzylamino group, and the presence of the grouping $C_6H_5C{=}C(C_6H_5)COC_6H_5$. It must be admitted though, that such evidence is not particularly conclusive for the latter deduction because of the tautomeric relationship between the competitive structures and the possibility for rearrangement from one form to the other during reaction.



$$\mathrm{R{-}C({=}NR){-}CH_2COR} \rightleftarrows \mathrm{R{-}C(NHR){=}CHCOR}$$

XI XII

On the basis of an extensive study of the exaltation of molecular dispersions of such substances, v. Auwers and Susemihl (7) have stated that these compounds always have the enamine (XII) not the imine (XI) structures (see table 6). Similar evidence dependent on the conjugated unsaturated nature of such substances has been reported in a study of color and constitution made by Cromwell and Johnson (42, 43) (see table 7).

In most cases the possibility for conjugation, with its accompanying stabilizing resonance energy, may be expected to favor the enamine structure (XII). However, if the nature of the R groups in XI ⇄ XII allows for a competing conjugated system in which the imine structure in XI may be involved, then resonance may in such cases stabilize the imine structure (XI).

TABLE 6

Exaltations of β-amino-α,β-unsaturated ketones (7)

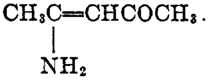
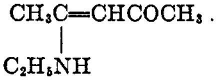
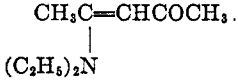
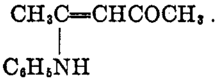
AMINO KETONES	$E(\Sigma_\beta - \Sigma_\alpha)$
	per cent
 $CH_3\underset{NH_2}{\underset{\vert}{C}}{=}CHCOCH_3$	185
 $CH_3\underset{C_2H_5NH}{\underset{\vert}{C}}{=}CHCOCH_3$	164
 $CH_3\underset{(C_2H_5)_2N}{\underset{\vert}{C}}{=}CHCOCH_3$	185
 $CH_3\underset{C_6H_5NH}{\underset{\vert}{C}}{=}CHCOCH_3$	198

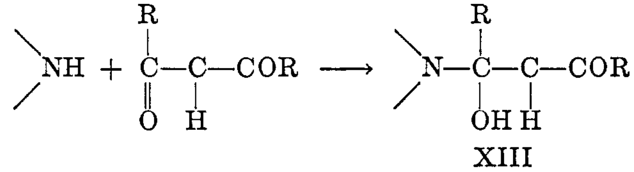
TABLE 7

Absorption spectra of β-amino-α,β-unsaturated ketones (42)

BENZALACETOPHENONES	MAXIMUM ABSORPTION BAND IN RANGE 3100–7000 Å. IN ABSOLUTE ALCOHOL	
	λ	$\epsilon \times 10^{-3}$
	Å.	
β-Diethylamino	3500	18.50
β-Morpholino	3500	20.48
β-Benzylamino	3450	14.58

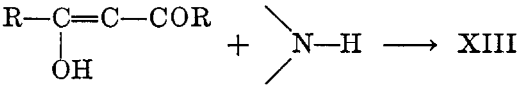
(b) The mechanism of the condensations

Very early in the study of the reactions of amines with 1,3-dicarbonyl compounds, it was shown that some intermediate compound was formed which then lost water to give the β-amino carbonyl substance (23, 26, 83). It is possible to write the formation of the intermediate compound in three different ways, one involving as the reactant the keto form, the other two the enol form.

(1) 

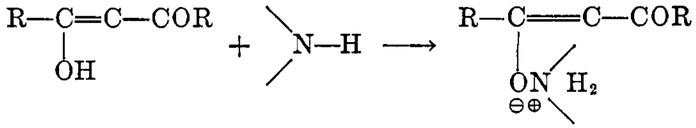
$$>NH + \underset{O}{\underset{\Vert}{\overset{R}{\overset{\vert}{C}}}}-\underset{H}{\underset{\vert}{C}}-COR \longrightarrow >N-\underset{OH}{\underset{\vert}{\overset{R}{\overset{\vert}{C}}}}-\underset{H}{\underset{\vert}{C}}-COR$$

XIII

(2) 

$$R-\underset{OH}{\underset{\vert}{C}}{=}C-COR + >N-H \longrightarrow \text{XIII}$$

(3)

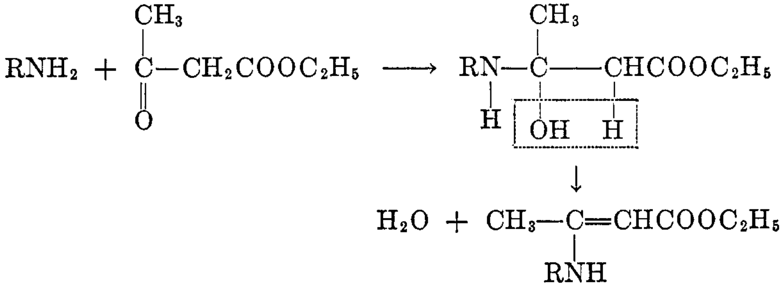


$$\mathrm{R{-}\underset{\underset{\displaystyle OH}{|}}{C}{=}C{-}COR} + {>}\mathrm{N{-}H} \longrightarrow \mathrm{R{-}\underset{\underset{\displaystyle \underset{\ominus\oplus}{ON}H_2}{|}}{C}{=}C{-}COR}$$

XIV

It is of course well known that many of the 1,3-diketones exist mainly in the enol form (121). Furthermore, it is evident that when such highly enolized β-diketones as acetylacetone (26), dibenzoylmethane, and benzoylacetone are mixed with strongly basic amines, the immediate formation of a salt-like solid is experienced which must have the structure XIV, since these substances are often quite water soluble. Whether or not the formation of the salt (XIV) is important as an intermediate in the formation of the β-amino-α,β-unsaturated ketone (XII) is not answered by such evidence. It is quite possible that XIV must decompose to the starting materials, and the more important intermediate (XIII) then be formed by either course 1 or course 2. Also, even though these β-diketones exist mainly in the enol form, the energy required to convert from nearly all enol into nearly all keto form is so small that the keto form could well be the reactant, as shown in course 1 (see pages 286–87 of reference 20; also reference 27).

Recently Décombe (49) in his studies with the analogous β-keto esters and amines has chosen the keto form as the reactant in such condensations. His investigations indicated that the pure enolic form of acetoacetic ester did not react immediately with dry ammonia, while the equilibrium mixture in dry ether at 0°C. gave an intermediate crystalline compound which decomposed rapidly above 0°C. He wrote the mechanism for these reactions then, as:



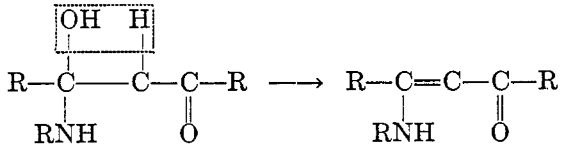
$$\mathrm{RNH_2} + \mathrm{\overset{\displaystyle CH_3}{\overset{|}{\underset{\underset{\displaystyle O}{\|}}{C}}}{-}CH_2COOC_2H_5} \longrightarrow \mathrm{R\underset{\underset{\displaystyle H}{|}}{N}{-}\overset{\displaystyle CH_3}{\overset{|}{\underset{\underset{\displaystyle OH}{|}}{C}}}{-}\underset{\underset{\displaystyle H}{|}}{C}HCOOC_2H_5}$$

$$\downarrow$$

$$\mathrm{H_2O} + \mathrm{CH_3{-}\underset{\underset{\displaystyle RNH}{|}}{C}{=}CHCOOC_2H_5}$$

If the intermediate is XIII, water might split out according to either course 4 or course 5.

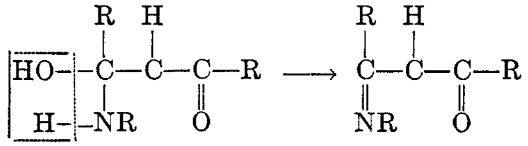
(4)



$$\mathrm{R{-}\overset{\displaystyle OH}{\overset{|}{\underset{\underset{\displaystyle RNH}{|}}{C}}}{-}\overset{\displaystyle H}{\overset{|}{C}}{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}R} \longrightarrow \mathrm{R{-}\underset{\underset{\displaystyle RNH}{|}}{C}{=}C{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}R}$$

XIII XII

(5)

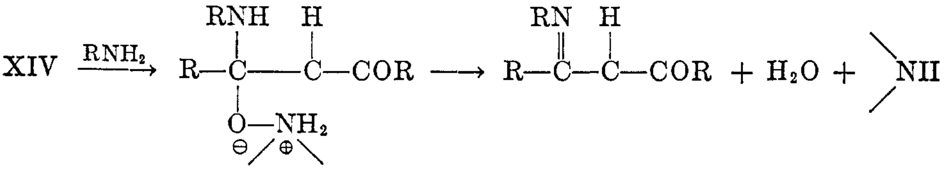


$$\boxed{\begin{matrix}\text{HO}-\\ \text{H}-\end{matrix}}\;\overset{\text{R}}{\overset{|}{\underset{\underset{\text{NR}}{|}}{\text{C}}}}-\overset{\text{H}}{\overset{|}{\text{C}}}-\underset{\underset{\text{O}}{\|}}{\text{C}}-\text{R} \longrightarrow \overset{\text{R}}{\overset{|}{\underset{\underset{\text{NR}}{\|}}{\text{C}}}}-\overset{\text{H}}{\overset{|}{\text{C}}}-\underset{\underset{\text{O}}{\|}}{\text{C}}-\text{R}$$

XIII XI

For course 4 to be possible it is necessary that an α-hydrogen be available. Course 5 would be possible with no α-hydrogen available, but would take place only when hydrogen was available on nitrogen. It is certain that course 5 is impossible when secondary amines are used in these reactions. Moreover, it is to be recalled that Combes (26) was unable to condense ammonia with α,α-dimethylacetylacetone. This latter reaction might be expected if the mechanism of such condensations may be represented by course 1 followed by course 5. This is strong negative evidence against such a mechanism. Furthermore, it should be pointed out that the amino ketones resulting from the addition of amines to acetylenic ketones (see table 2) are identical with those resulting from the condensation of the same amines with analogous β-diketones (see table 4). However, whether XI or XII is first formed, the resulting product might be the more stable tautomer.

The fact that β-alkoxy-α,β-unsaturated ketones react readily with amines to give β-amino-α,β-unsaturated ketones may be taken as evidence that amines can add to such conjugated systems, but the isolation of the intermediate addition compounds has not been reported for such reactions. If the salt intermediate (XIV) is not important in such condensations, it might be expected that the preparation of certain β-amino-α,β-unsaturated ketones from strong amines and highly enolized ketones would be difficult. Cromwell and Witt (45) were not able to condense piperidine with dibenzoylmethane (intermediate salt formation was noted) to give the known β-piperidinobenzalacetophenone prepared by André (3) (see table 2) from benzoylphenylacetylene. In a private communication, Lutz (89) has reported the preparation of this amino ketone from β-ethoxybenzalacetophenone and piperidine. Salt formation might, however, be expected to favor enolization. Also, addition of the amine to the carbon-to-carbon double bond of the salt (XIV) can conceivably take place (103).



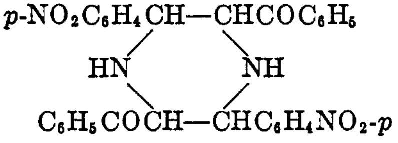
$$\text{XIV} \xrightarrow{\text{RNH}_2} \text{R}-\overset{\text{RNH}}{\overset{|}{\underset{\underset{\overset{\ominus}{\text{O}}-\overset{\oplus}{\text{NH}_2}\diagdown}{|}}{\text{C}}}}-\overset{\text{H}}{\overset{|}{\text{C}}}-\text{COR} \longrightarrow \text{R}-\overset{\text{RN}}{\overset{\|}{\text{C}}}-\overset{\text{H}}{\overset{|}{\text{C}}}-\text{COR} + \text{H}_2\text{O} + \rangle\text{NH}$$

Although no definite conclusion concerning the mechanism for these condensations of β-diketones with amines can yet be reached, the experimental results now available favor the following mechanism: 1,4-addition of the amine to the enol according to the scheme outlined for all α,β-unsaturated ketones in section II,C, followed by the loss of water from the intermediate (XIII) according to course 4.

B. REACTION OF AMINES WITH BROMO DERIVATIVES OF UNSATURATED KETONES

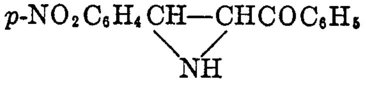
1. Introduction

The first reported reaction of a bromo derivative of an unsaturated ketone with an amino compound seems to have been the reaction of a dibromobenzalacetophenone with ammonia, carried out by Wieland in 1904 (122). The dibromide of *p*-nitrobenzalacetophenone reacted with alcoholic ammonia to give a colorless base melting at 141°C., for which Wieland wrote the structure



I

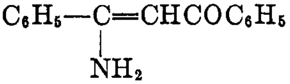
or



II

with preference expressed for formula I. No evidence was given to point to either structure. As will be brought out later (Section III,B,3), this actually was the first preparation of an ethylenimine of this type (II).

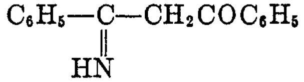
In the same year Ruhemann and Watson (106) reported the reaction of alcoholic ammonia with α,β-dibromobenzylacetophenone. They obtained a new, colorless base, m.p. 97°C., to which they assigned the structure:



$C_6H_5-C(NH_2)=CHCOC_6H_5$

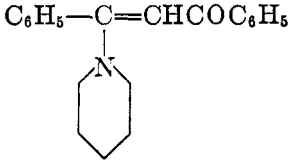
III

or



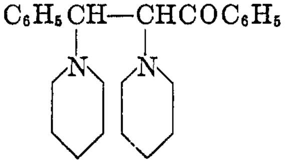
$C_6H_5-C(=NH)-CH_2COC_6H_5$

This product was shown to have a molecular weight corresponding to the indicated composition, and they pointed out that Wieland's product also probably contained only one benzalacetophenone residue. In a further extension of this work, Watson (118) obtained the same base, m.p. 97°C., from the reaction of alcoholic ammonia with the related α-bromobenzalacetophenone (he thought the structure was β-bromobenzalacetophenone). Furthermore, it was reported that piperidine reacted with such bromo derivatives. From the reaction of α-bromobenzalacetophenone with piperidine in alcohol solution two colored products were isolated which were described as follows:



IV

(red; m.p., 100°C.)

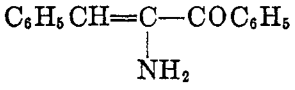


V

(yellow; m.p., 157°C.)

No evidence for these structures was presented.

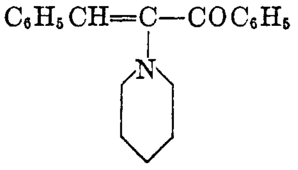
Much later, in 1927, Dufraisse and Moureu (50) began a series of investigations with bromo derivatives of unsaturated ketones with the apparent purpose of developing a method for preparing 1,2-diketones. The earlier work of Watson (118) was repeated, and on the basis of certain structure studies the formulas of Watson's products were changed to read:



$C_6H_5CH{=}\underset{\displaystyle NH_2}{C}{-}COC_6H_5$

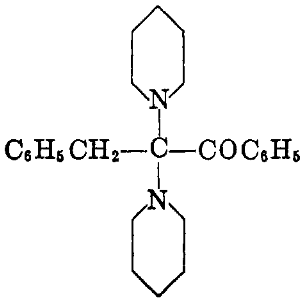
VI

(colorless; m.p., 95–97°C.)



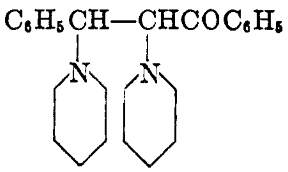
VII

(red; m.p., 100–101°C.)



VIII

or

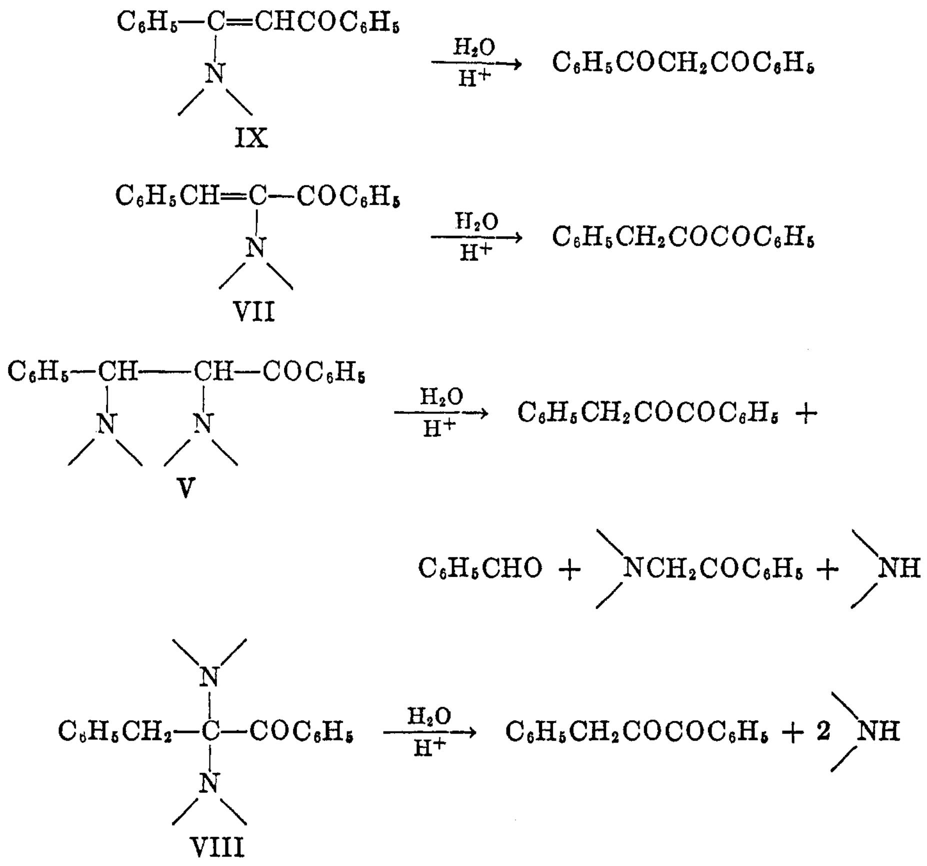


V

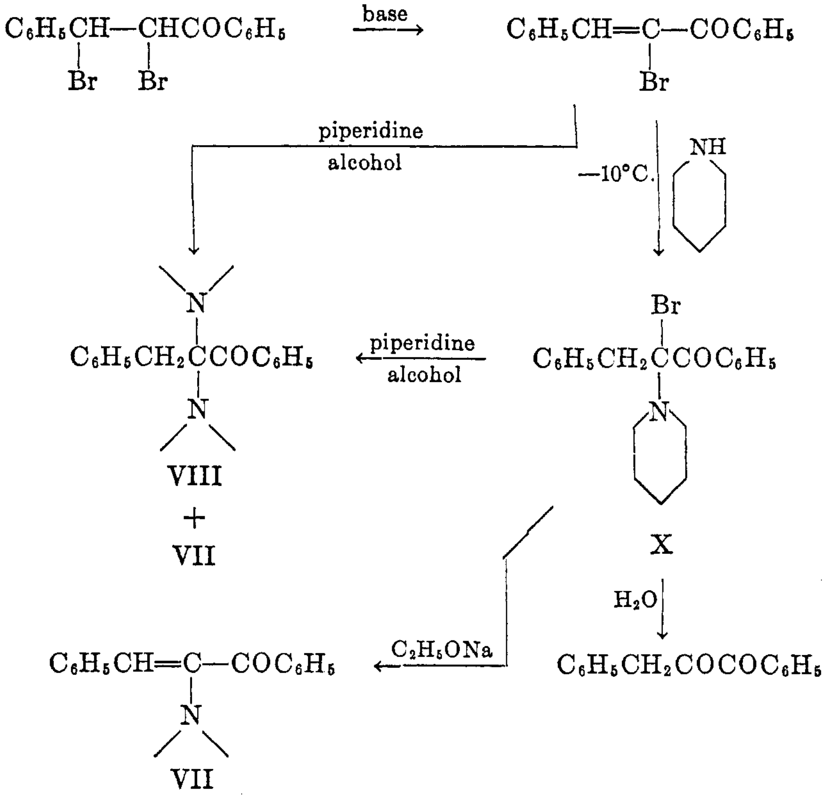
(yellow; m.p.,174°C.)

The red piperidino derivative (VII) was shown to hydrolyze readily with dilute acid to give 90 per cent yields of benzyl phenyl diketone. It was pointed out that André (3) had obtained β-piperidinobenzalacetophenone by adding piperidine to benzoylphenylacetylene. Such products of structure IX give only dibenzoylmethane when hydrolyzed with dilute acids. Furthermore, Dufraisse and Moureu found that acid hydrolysis of the aminobenzalacetophenone (structure III or VI) gave no dibenzoylmethane but did give small amounts of benzyl phenyl diketone and thus it was assigned structure VI. The evidence in this latter case was misleading, as will be brought out later (Section III,B,3).

The structure of the dipiperidinobenzylacetophenone (structure V or VIII) was also studied by acid hydrolysis. Dufraisse and Moureu showed this substance to hydrolyze to give small amounts of benzyl phenyl diketone and larger amounts of benzaldehyde and ω-piperidinoacetophenone. Although this evidence definitely favors structure V for this substance, these investigators apparently preferred structure VIII, which should have given much larger amounts of benzyl phenyl diketone on such treatment.



An important intermediate product of these reactions containing bromine and the piperidino group was isolated by Dufraisse and Moureu. When 1 mole of piperidine was added to a dry ether solution of 1 mole of α-bromobenzalacetophenone at −10°C., there resulted in 90 per cent yield a white product (X), m.p. 164°C., which gave a hydrobromide, m.p. 192°C. This substance was not very stable in air and reacted readily with sodium ethoxide to give 90 per cent yields of the red α-piperidinobenzalacetophenone (VII), m.p. 100–101°C., which had been obtained directly from either α-bromobenzalacetophenone or α,β-dibromobenzylacetophenone. With excess piperidine in alcohol solution X gave a mixture of the red monopiperidino compound (VII) and the yellow dipiperidino product (VIII). Furthermore, X was hydrolyzed by aqueous bases to give, along with other products, some benzyl phenyl diketone. On the basis of this evidence, Dufraisse and Moureu wrote reactions to explain all of these various changes as follows:



These investigators showed the action of piperidine on bromo derivatives of other unsaturated ketones to be analogous to the reactions described above, although the isolation of other intermediate bromo amino ketones of type X was not realized. According to the nature of the ketone, the reaction products were found to be made up of varying amounts of the monopiperidino and the dipiperidino products. No decision was reached with regard to the structures of the dipiperidino products, since they gave varying amounts of α-amino ketones and the 1,2-diketones on hydrolysis, depending on the nature of the starting bromo ketone. The various α-amino-α,β-unsaturated ketones and diamino ketones obtained from these studies are included in tables 8 and 9, respectively. Since the α-amino-α,β-unsaturated ketones are so readily hydrolyzed to 1,2-diketones, this constitutes an excellent method for preparing these substances (94).

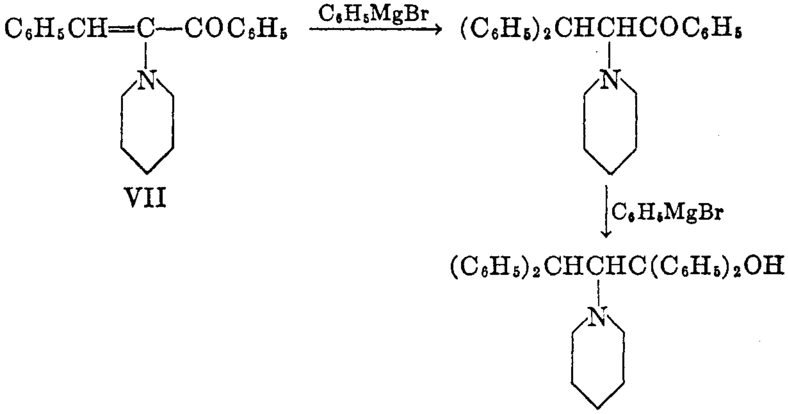
Kohler and Addinall (74) expressed the opinion that the structure VII for the α-piperidinobenzalacetophenone was incorrect. This view was revised in a subsequent communication (76), in which further evidence was offered for the structure (VII) of the α-piperidinobenzalacetophenone as described by Dufraisse and Moureu. This α-amino-α,β-unsaturated ketone was shown to react with the Grignard reagent in the normal way to give first a 1,4-addition product. The

TABLE 8

α-Amino-α,β-unsaturated ketones

AMINE	MELTING POINT	YIELD	REFERENCES
$C_6H_5CH{=}\underset{\substack{\vert \\ N}}{C}{-}COC_6H_5$			
	°C.	*per cent*	
Dimethylamine	62		(112)
Diethylamine	53	89	(28)
Piperidine	102	81	(50)
Morpholine	96	75	(29)
Pyrrolidine	98	60	(32)
N-Methylbenzylamine	75	50	(45)
p-Methoxy-*N*-methylbenzylamine	82	74	(41)
$C_6H_5CH{=}\underset{\substack{\vert \\ N}}{C}{-}COCH_3$			
Piperidine	58	20	(45)
Morpholine	76	60	(30)
Tetrahydroisoquinoline	91	84	(37)
$p\text{-}CH_3OC_6H_4CH{=}\underset{\substack{\vert \\ N}}{C}{-}COC_6H_5$			
Piperidine	79	70	(50)

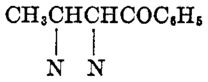
resulting saturated ketone then could be made to add a second mole of the Grignard reagent to give an amino carbinol.



Reduction of α-piperidinobenzalacetophenone (VII) gave α-piperidinobenzylacetophenone (XI), which was also prepared from α-bromobenzylacetophenone. This saturated α-amino ketone reacted with phenylmagnesium bromide to give

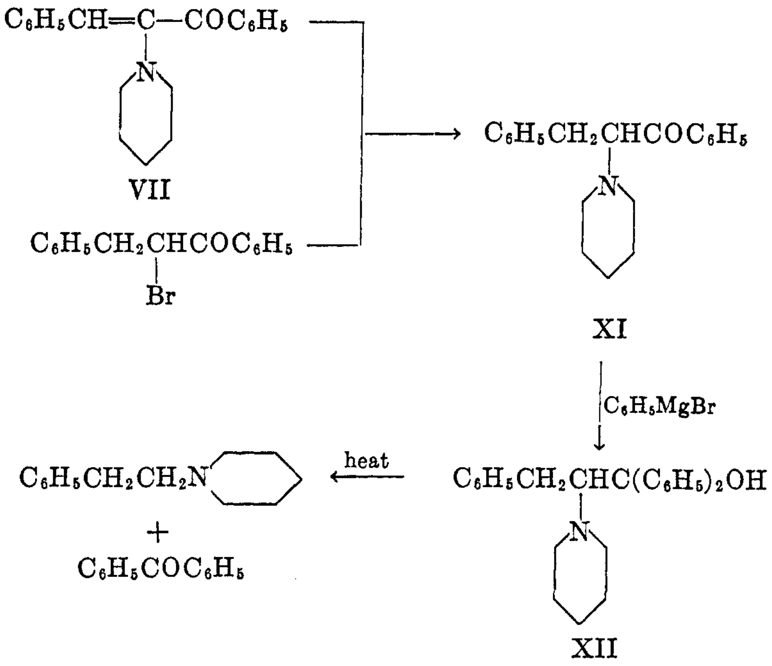
TABLE 9

α,β-Diamino ketones from α,β-dibromoketones

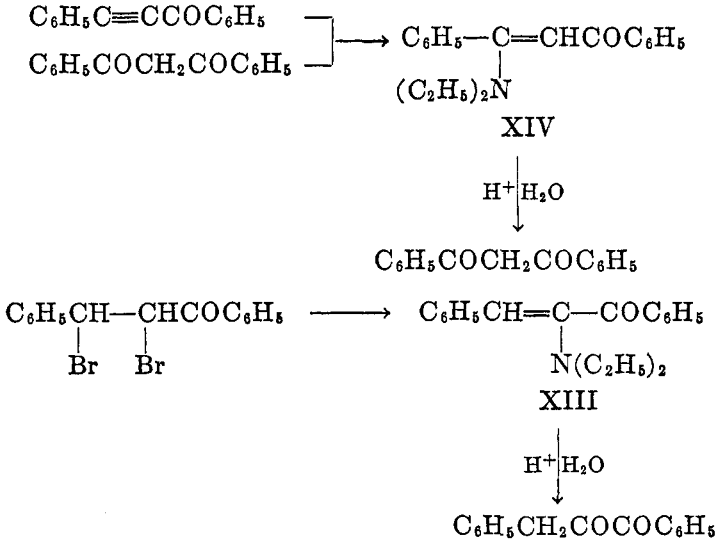
AMINE	MELTING POINT	YIELD	REFERENCES
 $C_6H_5\underset{\substack{\vert\\ N}}{CH}\underset{\substack{\vert\\ N}}{CH}COC_6H_5$			
	°C.	*per cent*	
Piperidine	174	32	(50)
Morpholine	175		
	156	70	(29)
Pyrrolidine	123	22	(32)
Tetrahydroisoquinoline	187	51	(38)
N-Methylbenzylamine	144		
	103	10	(45)
 $C_6H_5\underset{\substack{\vert\\ N}}{CH}\underset{\substack{\vert\\ N}}{CH}COCH_3$			
Piperidine	122	35	(94, 45)
Morpholine	160	63	(30)
Tetrahydroisoquinoline	170	75	(37)
N-Methylbenzylamine	108	30	(45)
o-Hydroxy-*N*-methylbenzylamine	163	20	(41)
o-Methoxy-*N*-methylbenzylamine	114	80	(41)
p-Methoxy-*N*-methylbenzylamine	103	75	(41)
 $CH_3\underset{\substack{\vert\\ N}}{CH}\underset{\substack{\vert\\ N}}{CH}COC_6H_5$			
Piperidine	114	65	(50)
 $\underset{\substack{\vert\\ N}}{CH_2}\underset{\substack{\vert\\ N}}{CH}COC_6H_5$			
Piperidine	73	90	(50)

an α-amino carbinol (XII), which on pyrolysis formed benzophenone and ω-piperidinoethylbenzene.

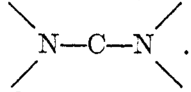
In 1940 a series of investigations was begun by Cromwell and his coworkers on the reactions of various amines with α,β-dibromo ketones and α-bromo-α,β-unsaturated ketones. In the first paper in the series (28), α,β-dibromobenzylacetophenone was shown to react with excess diethylamine in alcohol solution to give good yields of a red compound melting at 51–53°C., which was shown to be α-*N*-diethylaminobenzalacetophenone (XIII). Acid hydrolysis gave benzyl phenyl diketone.

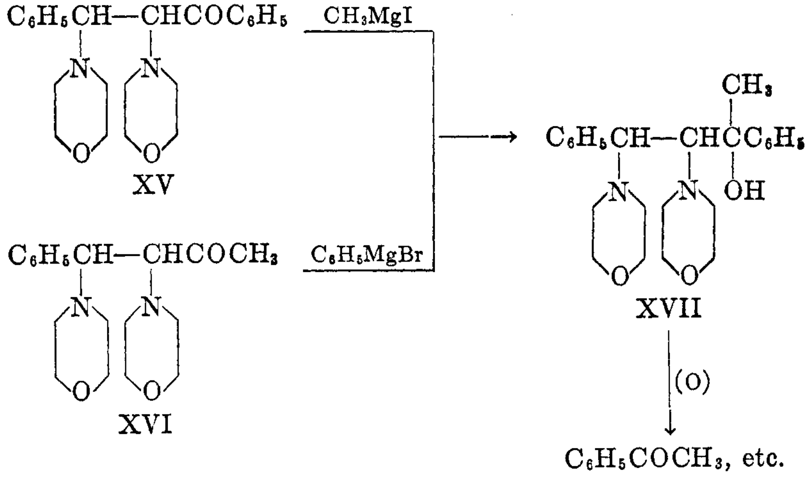


In this same communication the preparation of β-*N*-diethylaminobenzalacetophenone (XIV) by condensing dibenzoylmethane with diethylamine was also reported. This latter product was almost colorless, melted at 61–62°C., and was identical with the product previously obtained by André (3) by adding diethylamine to benzoylphenylacetylene. This definitely established the relationship between these two isomeric types of unsaturated amino ketones obtained by three different reactions.



It was not possible to obtain a bis-*N*-diethyl amino ketone similar to the dipiperidinoketone reported by Dufraisse in his studies. Subsequent investigations using morpholine, as Dufraisse had used piperidine, revealed the parallel nature of the behavior of these two heterocyclic secondary amines in these reactions (29, 30).

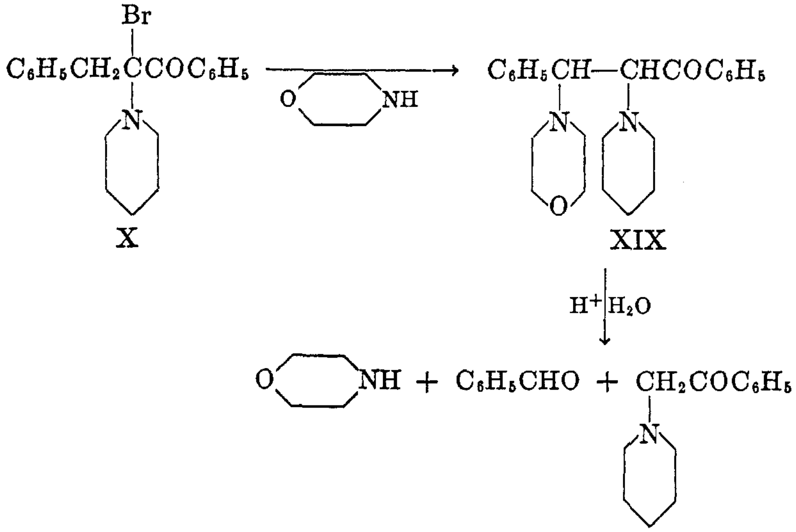
The α,β-dimorpholinobenzylacetophenone (XV) was obtained in a high (m.p. 175°C.) and a low (m.p. 154–156°C.) melting form, from α,β-dibromobenzylacetophenone. These were probably the two possible racemic mixtures (two dissimilar asymmetric carbon atoms are present). Both of these products hydrolyzed to give benzaldehyde, ω-morpholinoacetophenone, and only traces of benzyl phenyl diketone, indicating the structure to be that assigned, instead of the α,α-diamino ketone type of structure. α,β-Dibromobenzylacetone reacted with morpholine to give good yields of α,β-dimorpholinobenzylacetone (XVI). The structure of this product was shown to be analogous to that obtained in the benzylacetophenone series by application of the Grignard reaction as indicated. The products obtained from the two reactions were identical. This α,β-diamino carbinol (XVII) was stable to long boiling with dilute acid solutions, indicating the improbability of the presence of the structural unit  . Furthermore, oxidation of the diamino carbinol (XVII) with dilute ammonium persulfate gave acetophenone, as expected.



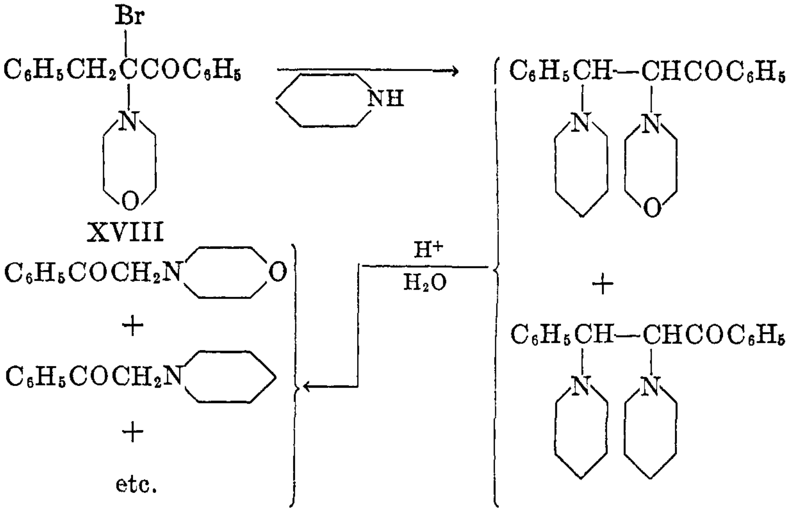
α-Bromobenzalacetophenone and the benzalacetone analogue both reacted with morpholine in dry ether solutions at low temperature to give (29, 30) excellent yields of bromo morpholino ketones, which showed the same properties as the analogous bromopiperidinobenzylacetophenone obtained by Dufraisse and Moureu and discussed previously in this review. Without further evidence, these structures were written by Cromwell as α,α-disubstituted ketones, analogous to the structure assigned by Dufraisse to his product.

In a following communication (31), the reactions of α-bromo-α-piperidinobenzylacetophenone (X) and the morpholino analogue (XVIII) with morpholine and piperidine, respectively, were reported. The first reaction was shown to give mainly α-piperidino-β-morpholinobenzylacetophenone (XIX), while the second reaction gave a mixed product which apparently contained several diaminobenzylacetophenones, as shown by acid hydrolysis and analysis. These reactions were written as follows:

(1)



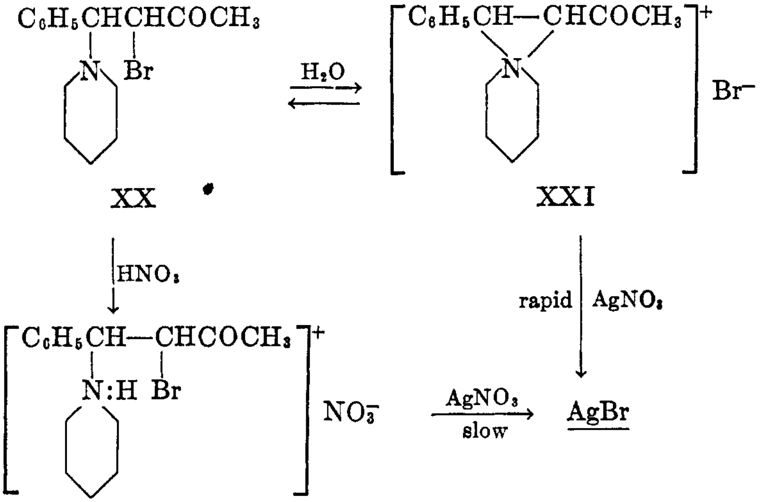
(2)



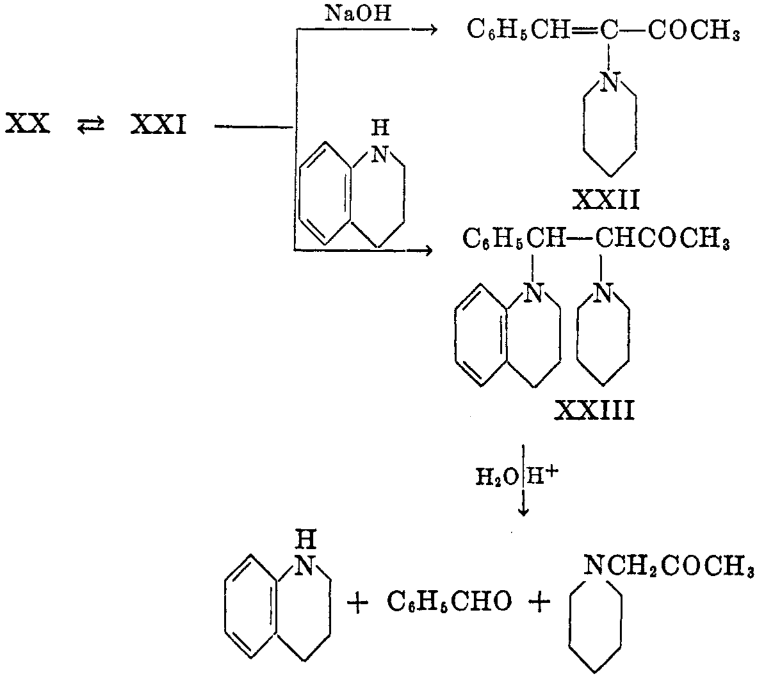
The reactions of series 1, especially, were offered as evidence for the location of the piperidino group on the α-carbon atom in the bromo amino ketones. These experiments did not explain how the second amino group arrived on the β-carbon. It was pointed out that it was not possible to add amines to either α-amino- or β-amino-α,β-unsaturated ketones to obtain α,β-diamino ketones.

2. Structure of the bromo amino ketones

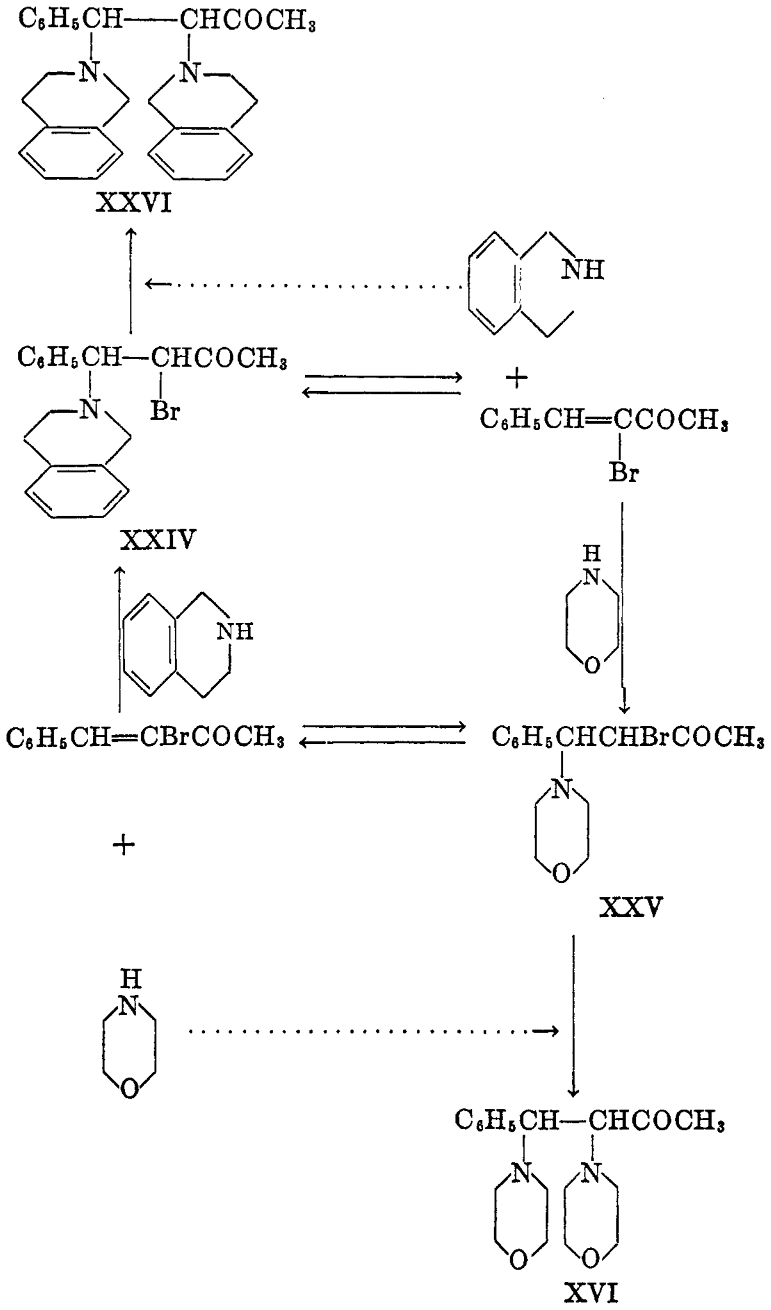
In 1943, after a more extensive investigation, evidence was presented to clarify these complex reactions. It was shown by Cromwell and Witt (45) that the intermediate bromo amino ketones were α-bromo-β-amino ketones (XX) which rearranged in neutral or basic solutions to form quaternary immonium salts (XXI) of the little-known ethylenimines. When XX was dissolved in dilute nitric acid and alcoholic silver nitrate added, only a very slow precipitation of silver bromide ensued. However, if XX was dissolved in aqueous alcohol, allowed to stand a few minutes, and then dilute nitric acid and silver nitrate added, an immediate precipitation of silver bromide took place. The initial presence of the acid involved the unshared electrons of the amino nitrogen and prevented the intramolecular attack on the α-carbon to displace the bromine as an ion and form XXI.



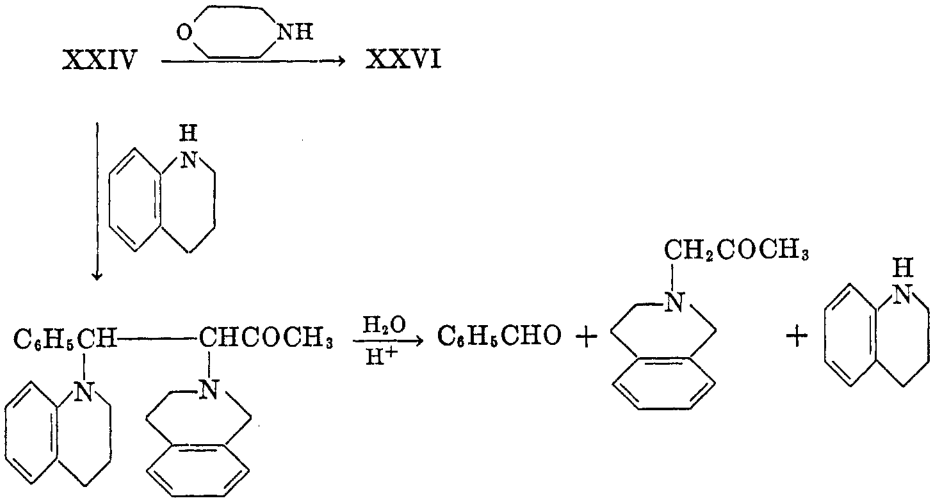
XX was shown to dissolve in water on long shaking to give a solution of XXI, which conducted the electric current and which reacted with sodium hydroxide to give α-piperidinobenzalacetone (XXII), and with tetrahydroquinoline to form α-piperidino-β-tetrahydroquinolinobenzylacetone (XXIII), the structure of which was shown by acid hydrolysis. These experiments served as further evidence for the α-bromo-β-amino ketone type of structure (XX) for these compounds.



In a parallel investigation, Cromwell and Cram (37) reported the preparation of many amino derivatives of benzalacetone and shed further light on the mechanisms of these reactions and the structures of the products. The nature of the important bromo amino ketones was studied further by an interesting series of experiments. If such compounds, XXIV and XXV, were allowed to stand in alcohol solution, a slow decomposition took place to re-form the amine and the α-bromo-α,β-unsaturated ketone. The released amine then reacted with the unchanged α-bromo-β-amino ketone, XXIV or XXV, respectively, to give the corresponding α,β-diaminoketone, XXVI and XVI, respectively. The filtrates from these solutions were then treated with some other amine to cause the released α-bromo-α,β-unsaturated ketone to react to form a different α,β-diamino ketone. These changes are shown in graphical form as follows:



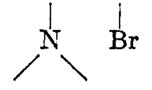
This series of experiments explained why it was possible to obtain complex products when bromo amino ketones were treated with certain amines, especially ones of the same or stronger basic strength compared with that of the amine used to prepare the bromo amino ketone. For example, the main product from the reaction of α-bromo-β-tetrahydroisoquinolinobenzylacetone (XXIV) with morpholine was α,β-ditetrahydroisoquinolinobenzylacetone (XXVI). The same bromo amino ketone reacted with a much weaker base, tetrahydroquinoline, to give excellent yields of the expected α-tetrahydroisoquinolino-β-tetrahydroquinolinobenzylacetone (XXVII), the structure of which was proven by acid hydrolysis.



XXVII

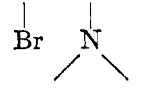
Moreover, the main product obtained by treating α-bromo-β-morpholinobenzylacetone with tetrahydroisoquinoline was also α,β-ditetrahydroisoquinolinobenzylacetone. When α-bromo-β-piperidinobenzylacetone was treated with tetrahydroisoquinoline (a weaker base than piperidine), a good yield of the expected α-piperidino-β-tetrahydroisoquinolinobenzylacetone resulted. On the other hand, when α-bromo-β-tetrahydroisoquinolinobenzylacetone was treated with piperidine (a stronger base than tetrahydroisoquinoline), the main product was again α,β-ditetrahydroisoquinolinobenzylacetone. Several other comparative reactions in the benzalacetone series were discussed by Cromwell and Cram (37), and in the benzalacetophenone series by Cromwell, Harris, and Cram (38).

In an attempt to gain further evidence for the structure of these important bromo amino ketone intermediates, Cromwell and Cram (37) subjected α-bromo-β-piperidinobenzylacetophenone to mild catalytic reduction with the hope that the compound might be reduced to the known β-piperidinobenzylacetophenone. However, both the bromine atom and the piperidino group were removed, to give a 71 per cent yield of benzylacetophenone. This experiment favored the assigned, α-bromo-β-amino ketone structure (XXVIII).



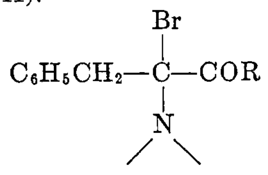
$$C_6H_5\text{—}\underset{\underset{\diagup\;\diagdown}{N}}{CH}\text{—}\underset{Br}{CH}COR$$

XXVIII



$$C_6H_5\text{—}\underset{Br}{CH}\text{—}\underset{\underset{\diagup\;\diagdown}{N}}{CH}COR$$

XXIX



$$C_6H_5CH_2\text{—}\overset{Br}{\underset{\underset{\diagup\;\diagdown}{N}}{C}}\text{—}COR$$

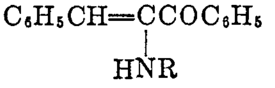
XXX

XXIX or XXX might be expected to reduce to the known α-piperidinobenzylacetophenone, which should be more stable under these conditions, while the product from XXVIII would be a β-amino ketone of a type which has been shown to be unstable to even mild catalytic reduction (44).

3. Reaction with primary amines. Ethylenimine ketones

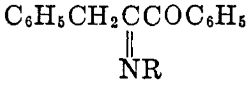
In Section III,B,1 ammonia, which may be looked upon as a primary amine, was mentioned as reacting with bromine derivatives of benzalacetophenone. Doubt was expressed as to the similarity in structure between these products and the products from the reactions of secondary amines with bromine derivatives of α,β-unsaturated ketones.

In 1943, Cromwell, Babson, and Harris (33) reported the reactions of two primary amines, benzylamine and cyclohexylamine, with α-bromobenzalacetophenone and α,β-dibromobenzylacetophenone as leading to the formation of ethylenimine ketones of the type shown in XXXIII:



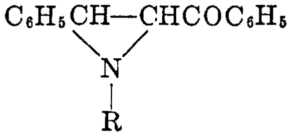
$$C_6H_5CH{=}\underset{\displaystyle HNR}{\underset{|}{C}}COC_6H_5$$

XXXI



$$C_6H_5CH_2\underset{\displaystyle NR}{\underset{\|}{C}}COC_6H_5$$

XXXII



XXXIII

Since the isomeric β-aminobenzalacetophenones had been prepared from dibenzoylmethane and by other means (3, 51) and found to possess entirely different properties (see Sections II,B and III,A,1) than these products resulting from bromine derivatives of benzalacetophenone, only structures XXXI, XXXII, and XXXIII needed to be considered.

It was shown (33) that products of structure XXXIII did not decolorize chloroform solutions of bromine as did the isomeric β-aminobenzalacetophenones. Also, the products having structure XXXIII were stable to catalytic hydrogenation with Raney nickel catalyst at room temperature, using hydrogen at 50 lb. per square inch.

The observation that all of the secondary amine reaction products of bromobenzalacetophenones possessed visible color, while the primary amine reaction products were colorless, led Cromwell and Johnson (42, 43) to carry out a study of color and constitution. As shown in table 10, the absorption spectra of compounds having the ethylenimine ketone structure (XXXIII) resemble that of the parent saturated ketone, benzylacetophenone.

As in the case of the reactions with secondary amines, it was possible (33) to add 1 mole of benzylamine to α-bromobenzalacetophenone to give α-bromo-β-benzylaminobenzylacetophenone (XXXIV), which possessed the general solubility properties of the previously discussed α-bromo-β-*sec*-amino ketones. This product reacted with various bases to produce the ethylenimine ketone (XXXV), which was also obtained directly from either α-bromobenzalacetophenone or α,β-dibromobenzylacetophenone.

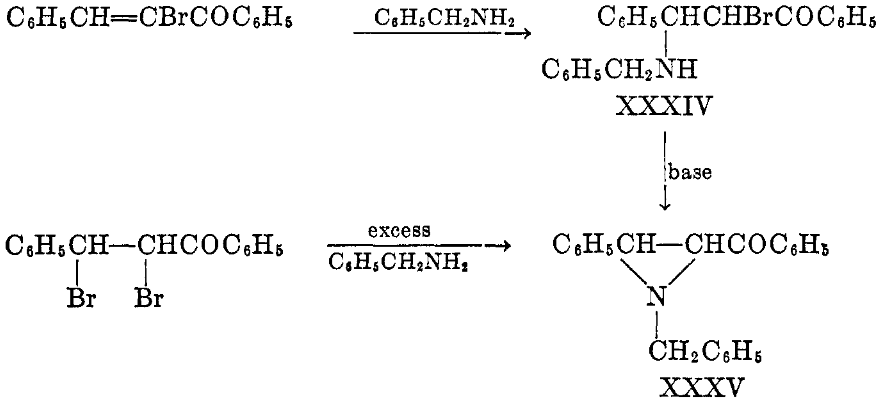


TABLE 10

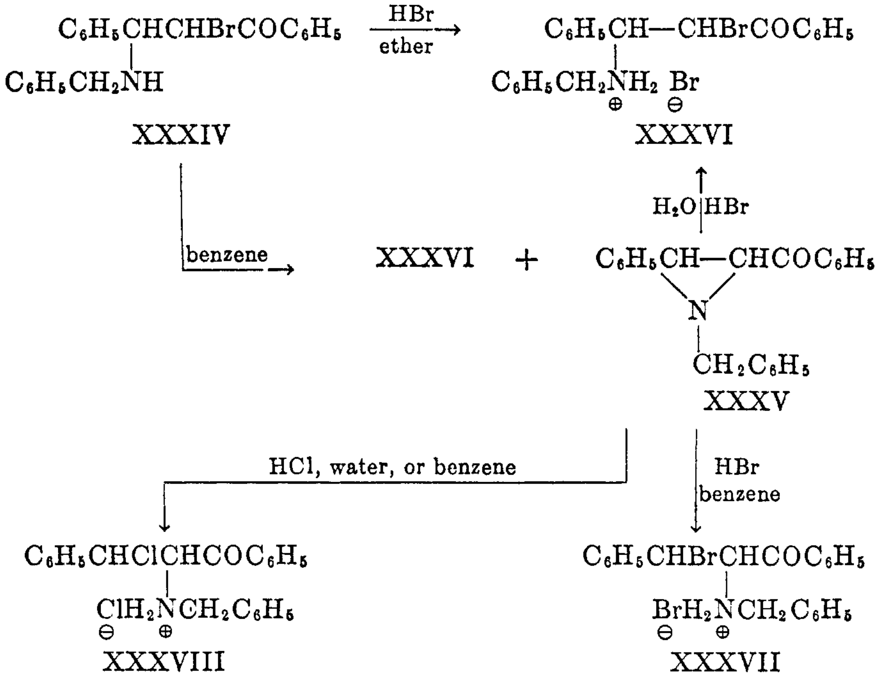
Absorption maxima of amino ketones (42)

KETONE	MELTING POINT	MAXIMUM ABSORPTION BAND IN RANGE FROM 3100–7000 Å.			
		Absolute alcohol		Dry benzene	
		λ	ε × 10⁻³	λ	ε × 10⁻³
	°C.	Å.		Å.	
Benzylacetophenone	72	3275	0.0418	3275	0.0331
2-Phenyl-3-benzoylethylenimine	101	3250	0.0430	3250	0.0465
1-Benzyl	108	3275	0.0623	3325	0.0686
1-Cyclohexyl	107	3300	0.0700	3350	0.0745
1-Methyl*	89			3325	0.0564
Benzalacetophenone	59	3350	2.040	3275	1.468
α-Diethylamino	54	4000	2.017	4000	2.820
α-Piperidino	102	3850	3.024		
α-*N*-Methylbenzylamino	75	4000	2.552		
β-Diethylamino	62	3500	18.50	3425	15.10
β-Benzylamino	101	3450	14.58		

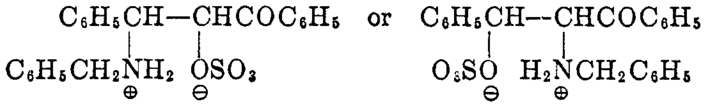
* See reference 35.

Ethylenimines have been prepared and studied by several investigators (47, 117, 119, 120). One of the most important reactions that such compounds undergo is their addition of 2 moles of hydrogen halide to form the hydrohalides of α-halo amino compounds. It was shown (33) that ethylenimine ketones of type XXXIII react with either dry or aqueous hydrogen halides to produce such products. Since the ethylenimine ring could open in two possible ways, it was necessary that some way be found to prove the structures of the resulting dihalides. In a recent paper, Cromwell and Caughlan (35) have found that such structures can be assigned on the basis of the relative rates of reactions of these hydrohalides of halo amino ketones with acidified potassium iodide solutions (see table 11).

These various dihalides were prepared in several ways (33, 35), as indicated in the following reactions:



These ethylenimine ketones also react (33) with dilute sulfuric acid to form an interesting type of aminosulfonic acid (XXXIX) (120):

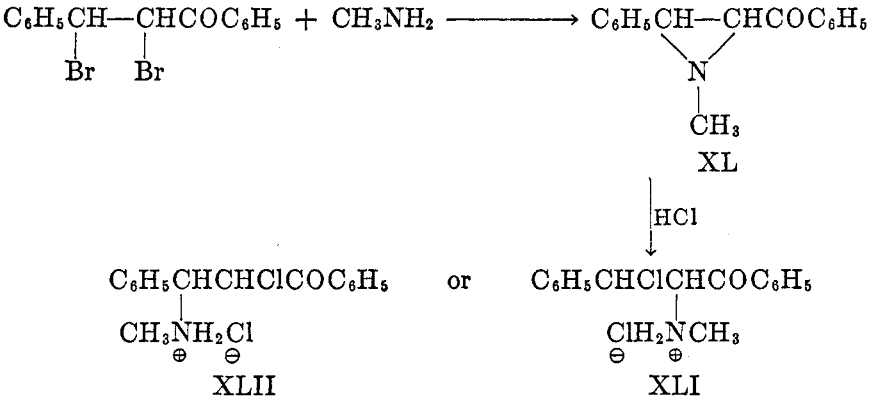


$$\underset{\substack{|\\ C_6H_5CH_2\underset{\oplus}{N}H_2}}{C_6H_5CH}-\underset{\substack{|\\ \underset{\ominus}{O}SO_3}}{CHCOC_6H_5} \quad \text{or} \quad \underset{\substack{|\\ O_3S\underset{\ominus}{O}}}{C_6H_5CH}-\underset{\substack{|\\ H_2\underset{\oplus}{N}CH_2C_6H_5}}{CHCOC_6H_5}$$

XXXIX

In 1943, shortly after the paper by Cromwell, Babson, and Harris (33) had appeared, Algar, Hickey, and Sherry published an article (1) in which they described some interesting experiments involving the reactions of ammonia and methylamine with α,β-dibromobenzylacetophenone. These investigators did not isolate the intermediate products from these reactions but treated the crude products with alcoholic hydrogen chloride to obtain, as isolable products, the hydrochlorides of chloroaminobenzylacetophenones, apparently similar to those reported by Cromwell, Babson, and Harris (33).

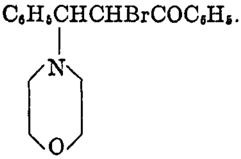
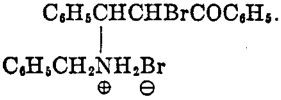
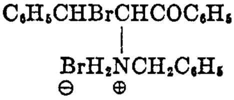
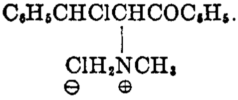
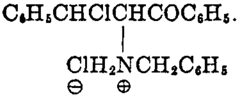
In a recent reinvestigation of some of these reactions, Cromwell and Caughlan (35) have shown that methylamine behaves in the same manner as benzylamine and cyclohexylamine, giving 1-methyl-2-phenyl-3-benzoylethylenimine (XL), as shown graphically here:


XL

XLII or XLI

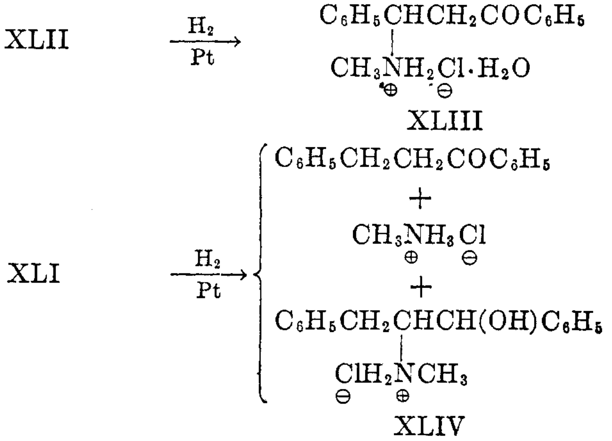
TABLE 11

Release of iodine from potassium iodide solutions by halogenated ketones (35)

HALOGENATED KETONES	PER CENT REACTING IN 30 MIN.
$C_6H_5CH_2CHBrCOC_6H_5$	27
	79
 $\underset{\overset{\oplus\ \ominus}{C_6H_5CH_2NH_2Br}}{C_6H_5CHCHBrCOC_6H_5}$	97
 $\underset{\overset{\ominus\ \oplus}{BrH_2NCH_2C_6H_5}}{C_6H_5CHBrCHCOC_6H_5}$	0.87
 $\underset{\overset{\ominus\ \oplus}{ClH_2NCH_3}}{C_6H_5CHClCHCOC_6H_5}$	0.93
 $\underset{\overset{\ominus\ \oplus}{ClH_2NCH_2C_6H_5}}{C_6H_5CHClCHCOC_6H_5}$	0

The Irish workers wrote the structure for the dichloride as indicated by XLII rather than as XLI on the basis of the behavior of this product on catalytic hydrogenation. They reported that the dichloride could be reduced to give the hydrate of β-methylaminobenzylacetophenone hydrochloride (XLIII), m.p.

191°C. Cromwell and Caughlan (35) repeated this work and obtained a hydrochloride product melting in this range. The latter investigators, however, showed this product to contain methylamine hydrochloride and α,γ-diphenyl-β-methylaminopropanol hydrochloride (XLIV), and were not able to demonstrate the presence of XLIII.



$$\text{XLII} \xrightarrow[\text{Pt}]{\text{H}_2} \underset{\overset{\oplus}{}\mathrm{CH_3NH_2}\overset{\ominus}{\mathrm{Cl}}\cdot\mathrm{H_2O}}{\mathrm{C_6H_5CHCH_2COC_6H_5}}$$

XLIII

$$\text{XLI} \xrightarrow[\text{Pt}]{\text{H}_2} \left\{ \begin{array}{c} \mathrm{C_6H_5CH_2CH_2COC_6H_5} \\ + \\ \overset{\oplus}{\mathrm{CH_3NH_3}}\,\overset{\ominus}{\mathrm{Cl}} \\ + \\ \mathrm{C_6H_5CH_2CHCH(OH)C_6H_5} \\ \overset{\ominus}{\mathrm{Cl}}\overset{\oplus}{\mathrm{H_2N}}\mathrm{CH_3} \end{array} \right.$$

XLIV

Any of the structures XXXI, XXXII, and XXXIII might be expected to give varying amounts of 1,2-diketones when warmed with acids. It will be recalled (Section III,B,1) that α-amino-α,β-unsaturated ketones give almost quantitative yields of 1,2-diketones on such treatment. Thus the isolation of small amounts of 1,2-diketones from the hydrolysis of the reaction products of ammonia and primary amines with bromo derivatives of α,β-unsaturated ketones can not be taken as evidence for their structures.

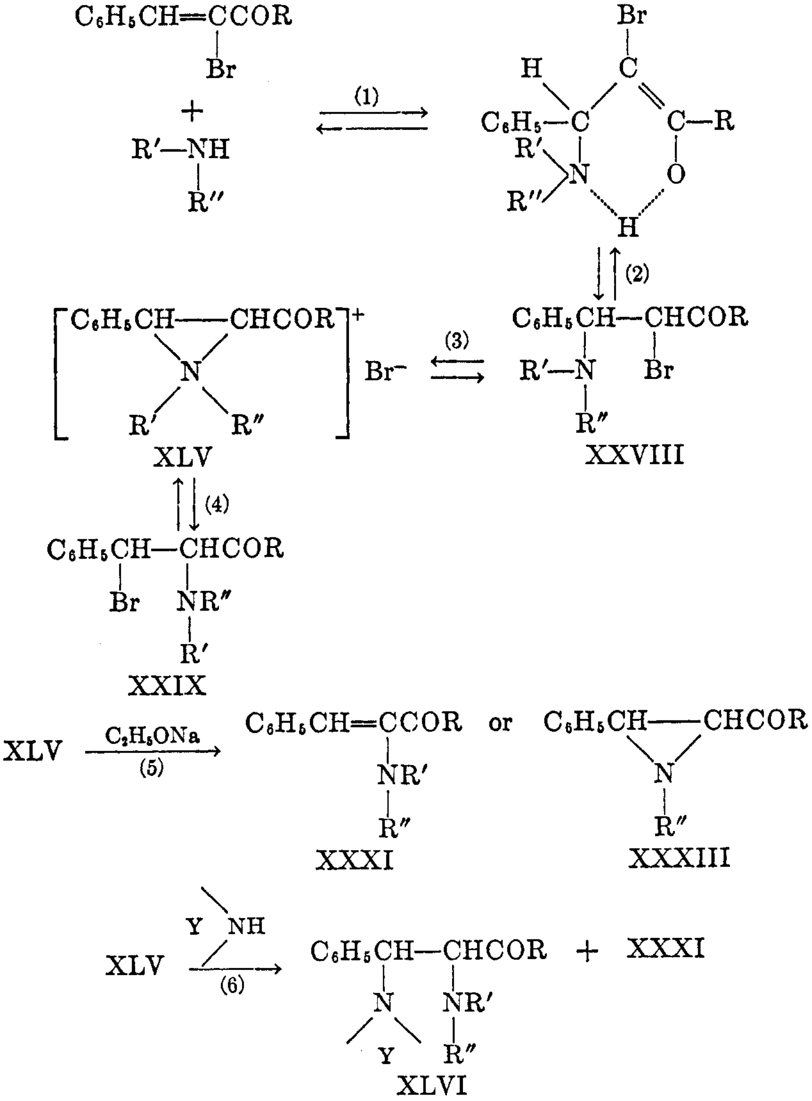
It seems evident that ammonia and primary amines react with α-bromo-α,β-unsaturated ketones and α,β-dibromoketones to give ethylenimine ketones of type XXXIII.

4. Mechanisms of the reactions

(a) With α-bromo-α,β-unsaturated ketones

The mechanism of the reaction of secondary amines with α-bromo-α,β-unsaturated ketones as assigned by Dufraisse (50) and elaborated by Cromwell (29) was incorrect. This first mechanism was based upon the assumption of the addition of the amine to the unsaturated ketone in such a manner as to form, as an intermediate, an α-bromo-α-amino ketone. Although such a structure for these intermediates could be expected to give the α-amino-α,β-unsaturated ketones, it could not be used to explain properly the formation of the α,β-diamino ketones, especially of the mixed type.

The evidence offered by the later investigations of Cromwell *et al.* (33, 35, 37, 38, 45) shows the structure of the addition products formed by the addition of amines to α-bromo-α,β-unsaturated ketones to be of the α-bromo-β-amino ketone type, as has been discussed previously (Section III,B,2). These active intermediates, which can often be isolated in almost quantitative yields, can then engage in various reactions in which the neighboring amino group participates during the removal or replacement of the halogen atom. Such a mechanism has been given by Cromwell and Cram (37).

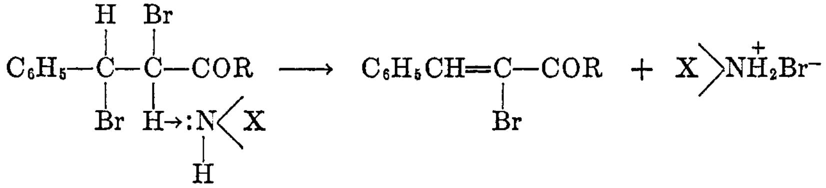


The addition of the amine to the α,β-unsaturated carbonyl system is usually quite rapid even at low temperatures and probably proceeds by some such mechanism as outlined in steps 1 and 2. Compounds of structure XXVIII are most readily obtained when the amine R′R″NH is of relatively high molecular weight and of considerable basic strength (morpholine, piperidine, pyrrolidine, tetrahydroisoquinoline, benzylamine, and *N*-methylbenzylamines). Furthermore, compounds XXVIII must be prepared in solvent media from which they will precipitate as rapidly as they are formed. In neutral or basic solutions XXVIII rearranges to form the important quaternary immonium salts, XLV, which under certain conditions may rearrange further to β-bromo-α-amino ketones (XXIX). That reactions 1 and 2 are reversible has been shown (37, 38) by allowing XXVIII to stand in solution to give "abnormal" products (see Section III,B,2).

Solutions of compounds of type XLV react almost quantitatively with a strong base such as sodium ethoxide to lose hydrogen bromide and give XXXI when R′R″NH is a secondary amine, and XXXIII when R′R″NH is ammonia or a primary amine. When solutions of XLV are treated with amines $\mathrm{Y}{>}\mathrm{NH}$ (primary or secondary) which are weaker bases than the amine R′R″NH (secondary amine) previously used to form XXVIII, then good yields of XLVI are to be expected, if no steric factor is involved. It has been reported (36) that when $\mathrm{Y}{>}\mathrm{NH}$ is an open-chain secondary amine (*N*-methylbenzylamine or dibenzylamine) the formation of XLVI is slowed because the approach of the amino nitrogen to the β-carbon atom in XLV is hindered to such an extent that larger amounts of XXXI are formed. The formation of XXXI is less dependent on the structure of the base $\mathrm{Y}{>}\mathrm{NH}$ and more dependent on its basic strength than is the formation of XLVI. In XLV the α-carbon–nitrogen bond should be the strongest, and thus the incoming amino group $\mathrm{Y}{>}\mathrm{N}$ would be expected to take the β-position, especially when $\mathrm{Y}{>}\mathrm{NH}$ is a weaker base than R′R″NH. Ethylenimines (XXXIII) are to be expected from the treatment of XLV with amines $\mathrm{Y}{>}\mathrm{NH}$ when R′R″NH is a primary amine (33).

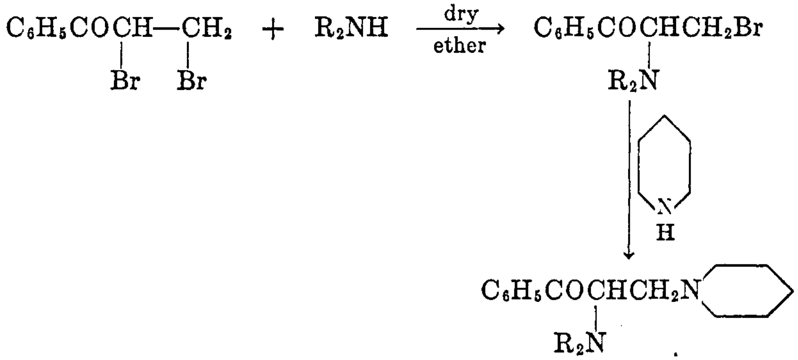
(b) With α,β-dibromo ketones

The dibromo ketones react with secondary amines to give mixtures of the α,β-diamino ketones and the α-amino-α,β-unsaturated ketones in varying proportions. In general, the best yields of the α,β-diamino ketones result when the amine used is of moderate strength (morpholine, tetrahydroisoquinoline, and methoxybenzylamines) (see table 9). With stronger amines (diethylamine and piperidine) the α-amino-α,β-unsaturated ketones are formed in larger amounts. The first step in the reactions of the α,β-dibromo ketones with amines in some cases is probably the loss of hydrogen bromide to form the α-bromo-α,β-unsaturated ketone, which then reacts further according to the mechanisms outlined above.



$$C_6H_5-\underset{Br}{\overset{H}{C}}-\underset{H\rightarrow :\underset{H}{N}\langle X}{\overset{Br}{C}}-COR \longrightarrow C_6H_5CH{=}\underset{Br}{C}-COR + X\rangle \overset{+}{N}H_2Br^-$$

An alternative mechanism, possibly parallel in some cases and exclusive in others, is one involving direct attack of the amine at the carbon atoms holding the bromine atoms. Davis (48) has reported an investigation in which the amine has been indicated as attacking the α-carbon atom first in such compounds. A series of mixed α,β-diamino ketones was prepared, the structures for which were reported without proof, as shown below:



(R = CH_3; C_2H_5; n-C_3H_7; n-C_4H_9; n-C_5H_{11})

The limitations of this method of preparing mixed α,β-diamino ketones from α,β-dibromo ketones of the type $C_6H_5COCHBrCHBrR$, where R is alkyl or aryl, have not been reported. The nature of R would be expected to influence the course of such reactions.

5. *The preparation of mixed α,β-diamino ketones*

A wide variety of mixed diamino ketones may be prepared starting with α-bromo-α,β-unsaturated ketones. From a knowledge of the mechanisms of these reactions it became possible to arrange the experimental conditions in such a manner as to allow for the maximum yields. In general, the α-bromo-β-amino ketones are prepared in dry ether solutions at low temperatures, isolated, and used immediately in the next step of the preparation. The formation of the mixed diamino ketone from the α-bromo-β-amino ketone is usually carried out in absolute alcohol, although better yields have been obtained in a few cases in dry ether solutions when the amine being used was of almost the same basic strength as that of the amine used to form the α-bromo-β-amino ketone.

The structures of the mixed α,β-diamino ketones have been proven for various typical types by hydrolysis, as shown in Sections III,B,1 and III,B,2. A different method for preparing certain mixed α,β-diamino ketones has been reported by Davis (48) and is discussed at the end of Section III,B,4b. In table 12 are listed the various mixed α,β-diamino ketones that have been prepared by the former method.

IV. REACTION WITH CARBONYL REAGENT TYPE OF AMINO COMPOUNDS

As has been shown in the preceding sections, ammonia and amines can usually be expected to react exclusively with the ethylenic linkage in α,β-unsaturated ketones. With amino compounds that are usually considered to be carbonyl reagents, α,β-unsaturated ketones show reactivity at both the ethylenic and the carbonyl linkages, as they do with other carbonyl reagents such as sodium bisulfite, the Grignard reagent, etc.

In acidic media α,β-unsaturated ketones react with carbonyl reagent types of amino compounds to give hydrazones, phenylhydrazones, semicarbazones, and oximes. In alkali media the reactions are more complex and products result from the addition at both the carbonyl and the ethylenic linkages. Furthermore, in alkali media, secondary products result from reactions involving active hydrogen in the primary addition products and also from oxidation–reduction reactions. In an excellent series of three review papers (4, 5, 6), v. Auwers and Muller have reviewed the earlier work on the reactions of hydroxylamine with benzalacetophenone and dibenzoylmethane, and with benzalacetone, benzoylacetone, and ethylideneacetone. Also, detailed directions are given for the preparation of the great variety of products possible from these reactions.

Blatt (18) has shown that, in contrast to hydroxylamine, methoxylamine adds only at the ethylenic bond in α,β-unsaturated ketones. Benzalacetophenone reacted to give β-methoxyaminobenzylacetophenone, m.p. 54–55°C. The hydrochloride of I was oxidized with hypochlorous acid to II, which was also obtained from dibenzoylmethane and from benzoylphenylacetylene.

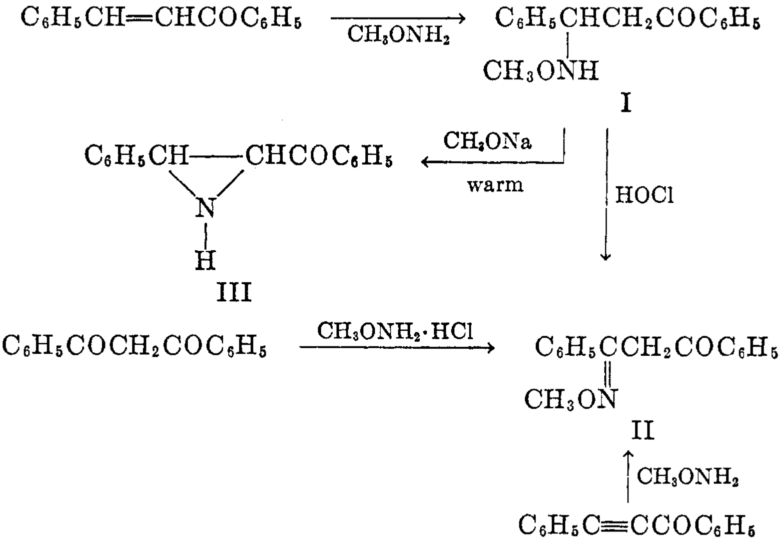
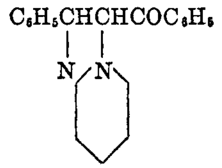
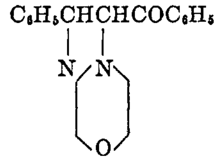


TABLE 12

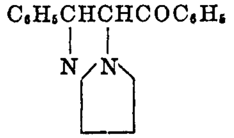
Mixed α,β-diamino ketones



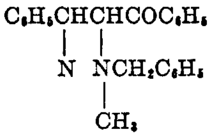
β-AMINE	MELTING POINT	YIELD	REFERENCES
	°C.	*per cent*	
Morpholine	175 157	50	(31)
Tetrahydroquinoline	167	80	(32)
Tetrahydroisoquinoline	165	37	(38)
Cyclohexylamine	155	20	(38)
Thalline	160	85	(36)
N-Methylbenzylamine	140	36	(36)
Dibenzylamine	175	13	(36)
N-Methylethanolamine	108	10	(36)
8-Amino-6-methoxyquinoline	183	87	(40)



β-AMINE	MELTING POINT	YIELD	REFERENCES
Piperidine	Impure product		(31)
Tetrahydroquinoline	154	50	(32)
Tetrahydroisoquinoline	163	15	(38)
Thalline	143	68	(36)
8-Amino-6-methoxyquinoline	194	77	(40)
o-Methoxy-*N*-methylbenzylamine	174	10	(41)



β-AMINE	MELTING POINT	YIELD	REFERENCES
Tetrahydroquinoline	149	35	(32)



$$C_6H_5\underset{\text{N}}{\text{CH}}\underset{\substack{\text{NCH}_2\text{C}_6\text{H}_5\\ \text{CH}_3}}{\text{CH}}COC_6H_5$$

β-AMINE	MELTING POINT	YIELD	REFERENCES
Tetrahydroquinoline	153	50	(45)
8-Amino-6-methoxyquinoline	192	44	(40)

TABLE 12—*Continued*

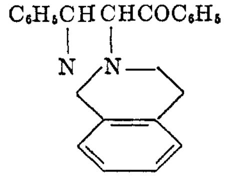
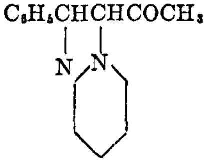
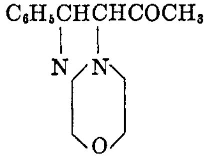
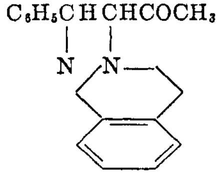
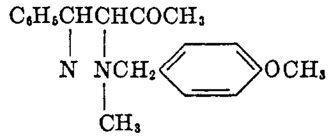
β AMINE	MELTING POINT	YIELD	REFERENCES
			
	°C.	*per cent*	
Morpholine	177	30	(38)
Tetrahydroquinoline	164	47	(38)
			
Morpholine	101 117	32	(38)
Tetrahydroquinoline	127	48	(37, 45)
Tetrahydroisoquinoline	148	40	(37)
6-Methoxytetrahydroquinoline	124	39	(36)
N-Methylbenzylamine	111	14	(36)
Dibenzylamine	160	4	(36)
N-Methylethanolamine	132	5	(36)
8-Amino-6-methoxyquinoline	160	66	(40)
			
Piperidine	123	10	(38)
Tetrahydroquinoline	173	51	(38)
Tetrahydroisoquinoline	135	<5	(37)
6-Methoxytetrahydroquinoline	126	40	(36)
8-Amino-6-methoxyquinoline	159	51	(40)
			
Piperidine	151	5	(37)
Morpholine	Impure product		(37)
Tetrahydroquinoline	109	44	(37)

TABLE 12—*Concluded*

β-AMINE	MELTING POINT	YIELD	REFERENCES
			
8-Amino-6-methoxyquinoline	173	90	(41)

The most interesting reaction of the addition products of type I is their loss of methyl alcohol on heating with sodium methoxide. Blatt wrote the resulting products as derivatives of α-aminobenzalacetophenone, $C_6H_5CH{=}C(NH_2)COC_6H_5$. These products were identical with the products resulting from the reaction of ammonia with α,β-dibromobenzylacetophenones. For the reasons that have been presented in Section III,B,3, it now seems that these products have the ethylenimine type of structure (III).

The reactions of α,β-unsaturated ketones and their derivatives with amines of the carbonyl reagent type would seem to warrant a separate comprehensive review.

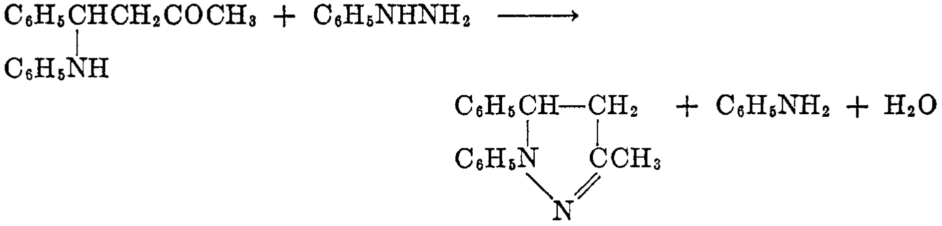
V. PROPERTIES OF AMINO KETONES

The amino ketones often serve as starting materials, or occur as intermediates, in the preparation of many interesting and valuable amino alcohols, diamines, heterocyclic nitrogen compounds, etc. Many of the reactions of α,β-unsaturated ketones and derivatives with amino compounds to form nitrogen ring compounds have been reviewed by Hollins in his excellent book (66). It is not the purpose of this review to survey completely all of such studies that have been reported, but merely to point out the various types of reactions, and to compare and contrast the properties of the various types of saturated and unsaturated amino ketones that have been mentioned previously in this review. Some of these reactions and properties already have been discussed in connection with structure proofs of the products.

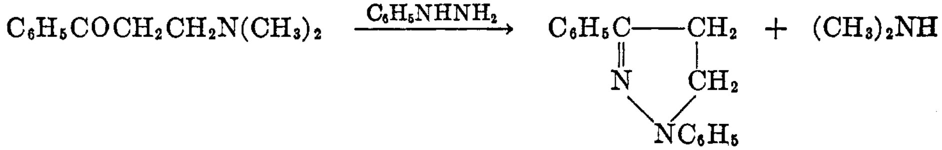
A. SATURATED AMINO KETONES

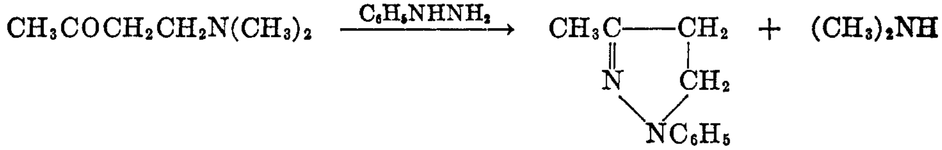
1. Monoamino ketones

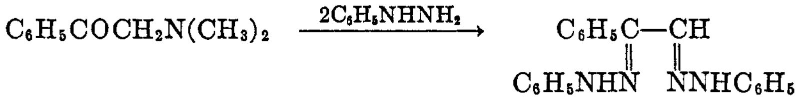
Because these molecules contain two reactive functional groups which are also activating groups, reactions dependent on active hydrogen as well as the usual reactions of the keto and amino groups are to be expected with such substances. In general, the α-aminoketones are more stable than the β-aminoketones at elevated temperatures or in the presence of acids, etc. The β-aminoketones, like β-amino acids, show a tendency to split out the amine and re-form the α,β-unsaturated carbonyl compound (34, 44). In attempting to prepare the phenylhydrazone of β-anilinobenzylacetone, Macovski and Silberg (90) obtained only 3-methyl-1,5-diphenylpyrazoline.



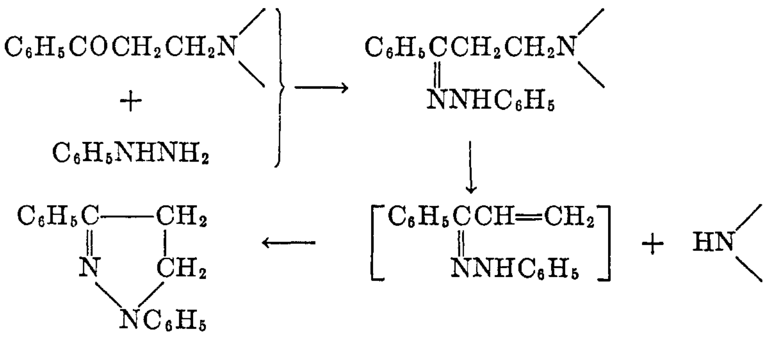
Similar results have been reported by Jacob and Madinaveitia (68) with ω-dimethylaminopropiophenone, which reacted with phenylhydrazine in warm acetic acid to form 1,3-diphenylpyrazoline. β-Dimethylaminoethyl methyl ketone under these conditions gave 1-phenyl-3-methylpyrazoline. These workers also found the dimethylamino group to be labile even in the α-position. ω-Dimethylaminoacetophenone under the above conditions gave phenylglyoxal osazone.







Recently, Nisbet (95) has succeeded in preparing the intermediate phenylhydrazones of such compounds, using the mild conditions outlined by v. Auwers and Voss (8). Furthermore, Nisbet showed that such phenylhydrazones could be converted, by heating with sodium acetate in a 50 per cent acetic acid solution, into the 1,3-diphenylpyrazoline obtained by Jacob and Madinaveitia (68). The postulated intermediate phenylhydrazones of the α,β-unsaturated ketones were not isolated, however.



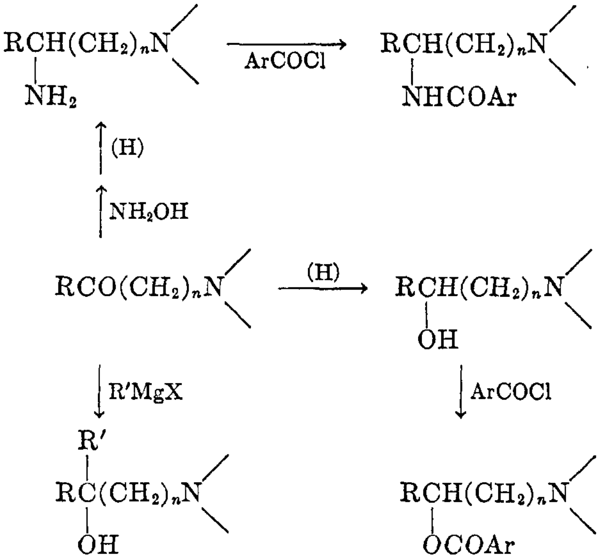
Several investigators have reduced certain α-amino and β-amino ketones to the corresponding amino alcohols, using sodium amalgam (44, 62, 77, 79), aluminum isopropoxide (21), or various catalytic methods (2, 67, 102) in attempts to produce pharmacologically active substances. Hartung (58, 59) has discussed the pressor activity of certain α-amino ketones and alcohols in two review articles.

Because of the unstable nature of some β-amino ketones toward catalytic reduction, better yields may often be obtained by reducing the β-amino ketone hydrochloride with sodium amalgam in water solution at −3°C. (44, 79).

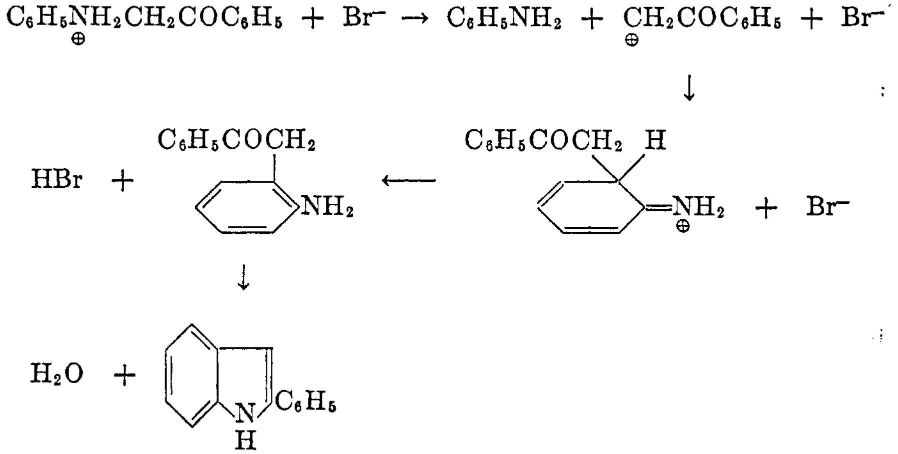
Amino alcohols of possible pharmacological interest may be prepared by adding Grignard reagents to either α-amino (76, 112, 115) or β-amino ketones (34, 80) to obtain the corresponding amino tertiary alcohols.

The keto group in the amino ketones often reacts readily with hydroxylamine to give oximes which may be reduced to the corresponding diamines (34, 39, 44, 57, 82). It has been pointed out by Cromwell and Hoeksema (39) that better yields are obtained from these reductions by the use of sodium and alcohol than by catalytic hydrogenation. These workers reported that such diamines are unstable at elevated temperatures and undergo self-condensation through loss of ammonia during distillation.

The amino alcohols and the diamines prepared from the amino ketones have been converted by aroyl chlorides into amino benzoates (44, 58) and amino benzamides (34, 39, 44), several of which have shown activity as local anesthetics.



It has long been known that phenacyl halides react with aromatic primary amines to give not only α-amino ketones, but indoles as well. The indoles apparently result from the further reaction of the primary product, the α-amino ketone. The formation of indoles from such reactions has been reinvestigated and the earlier work reviewed recently by Crowther and Mann (46). These investigators have offered some evidence for the following mechanism[1], but they did not isolate the important postulated intermediate, o-aminobenzyl phenyl ketone.



$$C_6H_5\underset{\oplus}{N}H_2CH_2COC_6H_5 + Br^- \rightarrow C_6H_5NH_2 + \underset{\oplus}{C}H_2COC_6H_5 + Br^-$$

Stevens and his coworkers (110, 111, 112, 113) have carried out an interesting series of investigations, starting with phenacyl bromide and ending with an α-amino-α,β-unsaturated ketone. Phenacyl bromide reacted with N-dimethylbenzylamine to give a quaternary ammonium bromide which was rearranged with sodium hydroxide to form α-dimethylaminobenzylacetophenone. This latter compound underwent a remarkable oxidation. In an alcohol solution containing sodium ethoxide, α-dimethylaminobenzylacetophenone was oxidized by air at 70°C. to α-dimethylaminobenzalacetophenone. The structures of all of these products were proved and mechanisms offered for these reactions.

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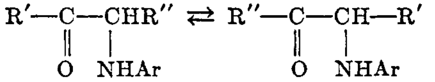
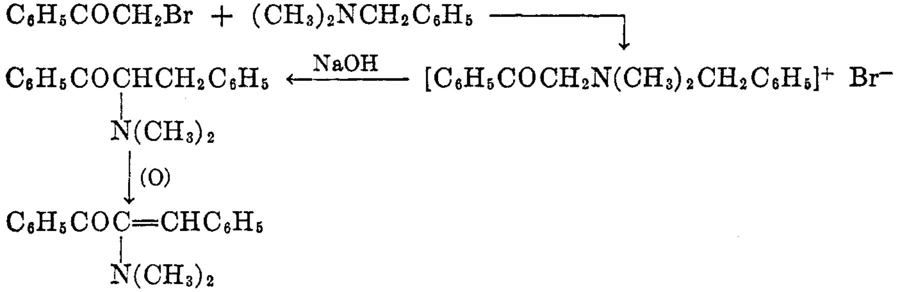
[1] Just after this review was submitted to the Editor there appeared an interesting paper by P. L. Julian *et al.* (J. Am. Chem. Soc. **67**, 1203 (1945)), disputing the mechanism proposed by Crowther and Mann and surveying the various proposals of others. The complete explanation of these complex reactions is not yet at hand and must await further definitive experimentation. Julian points out that the reaction of an α-bromo ketone and an arylamine is a complicated system in the presence of oxygen and may involve any or all of the following: (*a*) direct replacement of the bromine; (*b*) addition to the carbonyl double bond; (*c*) rearrangement of the anilino ketones

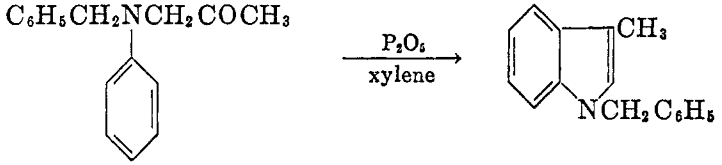


$$R'\text{—}\underset{\underset{O}{\|}}{C}\text{—}\underset{\underset{NHAr}{|}}{C}HR'' \rightleftarrows R''\text{—}\underset{\underset{O}{\|}}{C}\text{—}\underset{\underset{NHAr}{|}}{C}H\text{—}R'$$

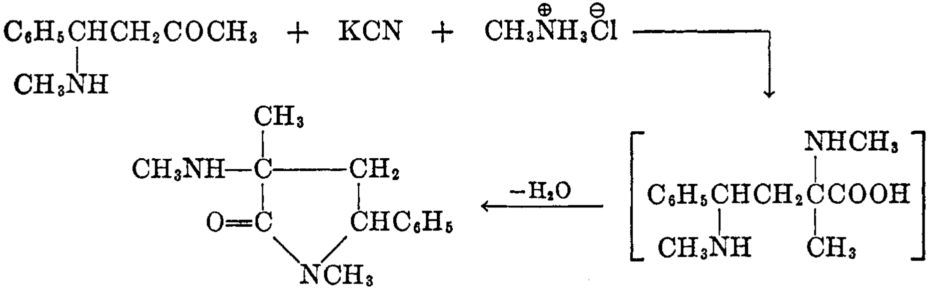
(*d*) monoanil formation; (*e*) dianil formation; (*f*) anilineanil or diamine formation; (*g*) cleavage of arylamine from the diamine to form the indole.



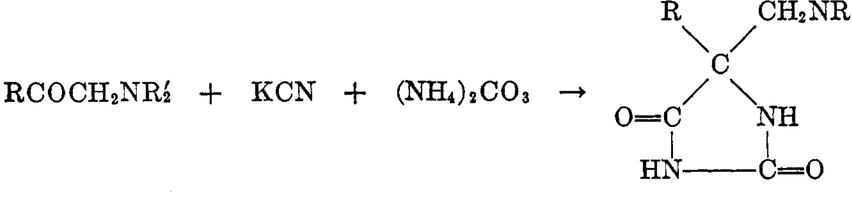
Bauer and Buhler (10) have reported an interesting cyclization of α-*N*-benzylanilinoacetone to form an indole.



Kohn (81) reported the formation of amino lactams from a Strecker type of reaction with β-amino ketones.



Another modification of the Strecker process, known as the Bucherer method for preparing hydantoins, has been used by Henze with α-amino ketones (63, 64, 91).



2. Diamino ketones

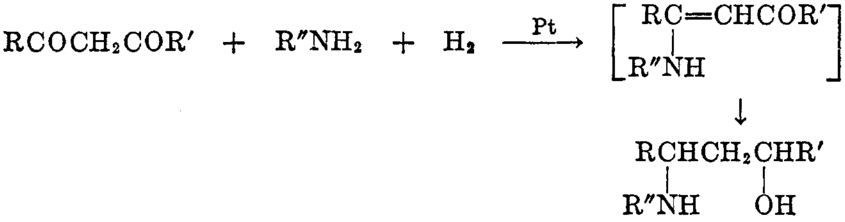
The diamino ketones do not appear to be as reactive as either the α- or β-amino ketones. The presence of the comparatively large hindering amino groups on both the α- and β-positions in the same molecule seems to hinder some of the usual carbonyl reactions of such substances (40, 41). As was pointed out in Section III,B,1, certain of these compounds will add Grignard reagents to form α,β-diamino tertiary alcohols. The hydrolysis of the α,β-diamino ketones in acid solution to form α-amino ketones was mentioned in Sections III,B,1 and III,B,2.

Some of these diamino ketones have been found to possess mild avian antimalarial activity (40).

B. UNSATURATED AMINO KETONES

Both the α-amino- and the β-amino-α,β-unsaturated ketones are readily hydrolyzed by acid solutions to diketones. The former give 1,2-diketones, while the latter yield 1,3-diketones as discussed in Section III,B,1. The reduction of an α-amino-α,β-unsaturated ketone to a saturated α-amino ketone and the reactions of both of these ketones with a Grignard reagent were also discussed in Section III,B,1.

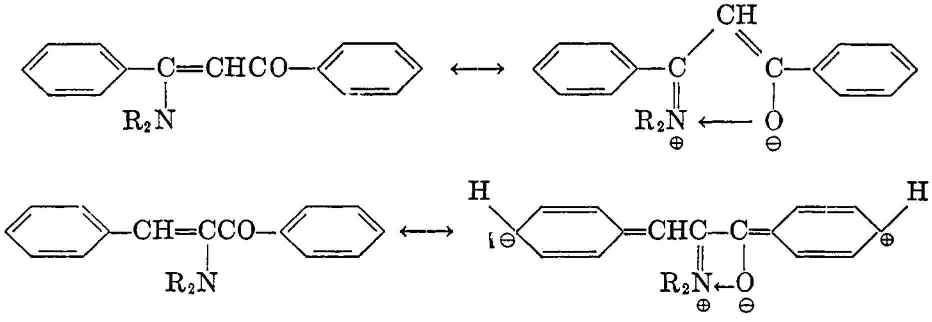
Skita and Keil (107) have reported the preparation of β-amino alcohols by a method that seems to involve the intermediate formation of β-amino-α,β-unsaturated ketones. A mixture of a 1,3-diketone and an amine was reduced with hydrogen in the presence of platinum.



$$\mathrm{RCOCH_2COR'} + \mathrm{R''NH_2} + \mathrm{H_2} \xrightarrow{\mathrm{Pt}} \left[\begin{array}{l} \mathrm{RC{=}CHCOR'} \\ \;| \\ \mathrm{R''NH} \end{array}\right] \; \begin{array}{c} \downarrow \\ \begin{array}{c} \mathrm{RCHCH_2CHR'} \\ |\qquad\quad | \\ \mathrm{R''NH} \quad \mathrm{OH} \end{array} \end{array}$$

It has been pointed out at the beginning of Section III,A,3 that β-amino-α,β-unsaturated ketones undergo alkylation and acylation. More extensive studies, such as those that have been carried out with β-amino-α,β-unsaturated esters (84, 85), would be of interest and are contemplated.

A comparison of the color and constitution of α-amino- and β-amino-α,β-unsaturated ketones has been made by Cromwell and Johnson (42, 43). The β-amino-α,β-unsaturated ketones are colorless and show maximum absorption bands at about 3500 Å. with extinction coefficients of about 15–20 × 10^3. For the α-amino-α,β-unsaturated ketones, which range in color from yellow to deep red, the maximum absorption band was found at about 4000 Å. and with extinction coefficients of about 2–3 × 10^3 (see table 10). This difference in the absorption spectra was attributed to a difference in the nature of the resonance oscillators of such substances, approximated as follows:



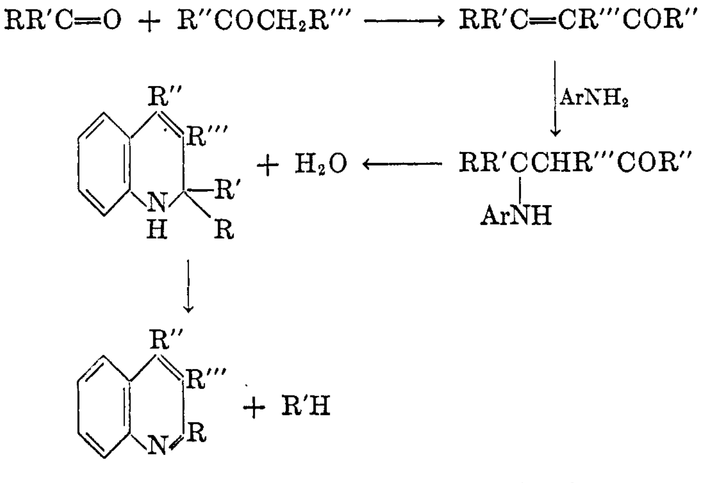
C. QUINOLINE SYNTHESES

One of the most important properties of the β-arylamino carbonyl compounds is their ability to cyclize to form substituted quinolines. Many reviews dealing with the various methods of preparing quinolines are available, and several of them include methods involving the cyclization of saturated and unsaturated β-arylamino ketones (12, 66, 69, 70, 92, 100).

1. From vinyl ketones

In 1885 Reed (98) heated a mixture of β-naphthylamine hydrochloride, acetone, and paraldehyde to obtain a dimethylnaphthoquinoline melting at 126–127°C. During the next few years Beyer (13) extended this method, using many various aldehydes, ketones, and arylamines to obtain several substituted quinolines. At about the same time, Engler and Riehm (54) reported the synthesis of 2,4-dimethylquinoline by heating a mixture of aniline hydrochloride with acetone for several days. The reaction may also be carried out by heating mesityl oxide with aniline hydrochloride. It is remarkable that in these reactions water and a hydrocarbon (in this case, methane) are eliminated during cyclization.

Beyer (13) did not isolate the intermediates in these reactions but postulated the intermediate formation of α,β-unsaturated ketones which then added the arylamine to form a β-arylamino ketone, which finally cyclized with loss of water and hydrogen or a hydrocarbon.



Since these early studies, the so-called Beyer method and its various modifications have been applied to the synthesis of many substituted quinolines (see page 262 of reference 66). The yields are usually not high, because of the requirement for high temperatures to cause hydrogen or the hydrocarbon to split out. John and his coworkers (69, 70) obtained very low yields of the expected 2-phenyl-4-methylquinolines on heating benzalacetone with various substituted aniline hydrochlorides at 135°C. for 5 hr. (see table 13). These workers reported that addition of an oxidant to facilitate removal of the hydrogen did not increase the yields.

Recently Campbell and Schaffner (22) have reported that the addition of an oxidant and the employment of milder conditions does give better yields in such syntheses. These workers refluxed for 2 hr. alcohol solutions of 0.625 mole of the arylamine hydrochloride with 1 mole of ferric chloride hexahydrate, 10 g. of zinc chloride, and 0.5 mole of either methyl vinyl ketone, or 4-methoxy-2-butanone, or trimethoxybutane to obtain very good yields of lepidines (see table 14). The relationship between these latter reagents is readily seen.

TABLE 13

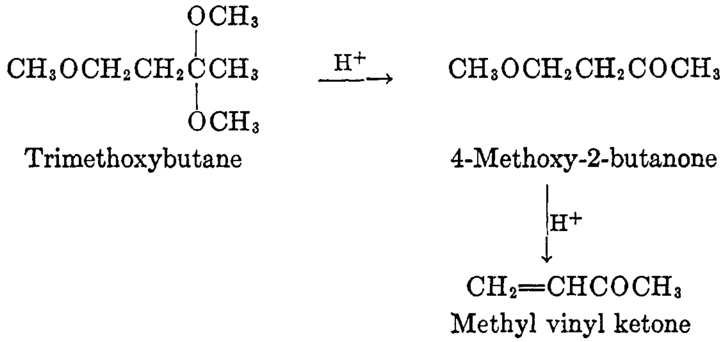
2-Phenyl-4-methylquinolines from benzalacetone (69, 70)

ARYLAMINE	2-PHENYL-4-METHYLQUINOLINES	MELTING POINT	YIELD
		°C.	*per cent*
Anisidine	6-Methoxy	129	8.8
Phenetidine	6-Ethoxy	153	5.3
p-Aminophenol	6-Hydroxy	212	7.7
p-Toluidine	6-Methyl	93	8.2
o-Toluidine	8-Methyl	91.5	14.3
o-Aminophenol	8-Hydroxy	58	10.6
o-Anisidine	8-Methoxy	98	13
o-Phenetidine	8-Ethoxy	98	14.4
p-Chloroaniline	6-Chloro	91.5	2.8
p-Bromoaniline	6-Bromo	100	3.8
p-Iodoaniline	6-Iodo	50	<2
p-Aminoethylbenzene	6-Ethyl	74	15
p-Xylidine	5,8-Dimethyl	111.5	7.1
ψ-Cumidine	5,6,8-Trimethyl	128	6.2
p-Dimethylaminoaniline	6-Dimethylamino	132	1.4
o-Aminobenzoic acid	8-Carboxy	202	8.7
p-Aminobenzoic acid	6-Carboxy	225	5

TABLE 14

Lepidines from vinyl ketones and derivatives (*22*)

ARYLAMINE	KETONE OR DERIVATIVE	LEPIDINES	BOILING POINT OR MELTING POINT	YIELD
			°C.	*per cent*
Aniline	Methylvinyl ketone	Lepidine	266/760 mm.	73
p-Anisidine	Methylvinyl ketone or Trimethoxybutane	6-Methoxy	122/2 mm.	52
p-Toluidine	Methylvinyl ketone	6-Methyl	104/2 mm.	65
o-Chloroaniline	Trimethoxybutane	8-Chloro	107	23
β-Naphthylamine	Trimethoxybutane	5,6-Benzo	101	58
Aniline	3-Penten-2-one	2-Methyl	105/4 mm.	62



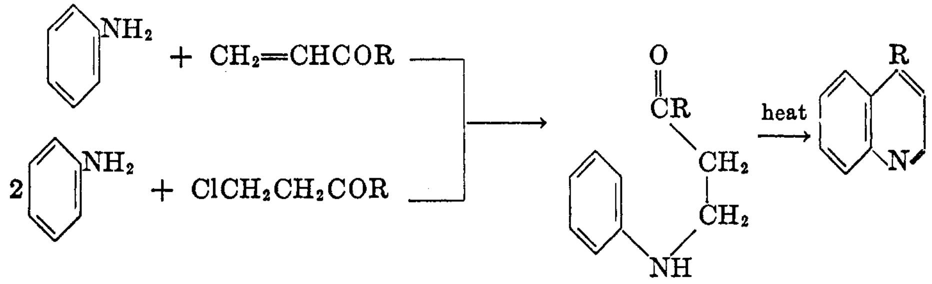
$$CH_3OCH_2CH_2\overset{OCH_3}{\underset{OCH_3}{C}}CH_3 \xrightarrow{H^+} CH_3OCH_2CH_2COCH_3 \xrightarrow{H^+} CH_2{=}CHCOCH_3$$

Trimethoxybutane

4-Methoxy-2-butanone

Methyl vinyl ketone

Blaise and Maire (17) isolated the β-amino ketones from the reactions of aniline, aniline hydrochloride mixtures with either vinyl alkyl ketones or the β-chloro derivatives, and then cyclized these products by heating them in the presence of aniline hydrochloride, to form the substituted quinolines:



2. *From β-diketones*

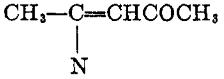
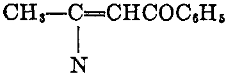
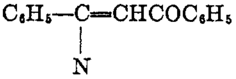
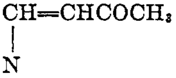
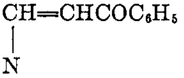
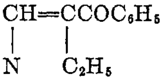
Earlier in this review (Section III,A,1) it was pointed out that almost the first reactions studied of amines with 1,3-diketones involved the use of arylamines. As has been indicated in Section III,A,1, Beyer (14) was actually the first to report the synthesis of quinolines by the cyclization of the resulting β-arylamino-α,β-unsaturated ketones. This excellent method for preparing 2,4-disubstituted quinolines has come to be known as the Combes method, but Combes (25) did not report the cyclization of his anilide of acetylacetone to give 2,4-dimethylquinoline until after the previous publication by Beyer (14) had appeared.

Since cyclization involves only the loss of water, and removal of hydrogen as in the Beyer method is not required, the yields reported from quinoline syntheses by the Combes method are often quite high. This method for preparing quinolines has been discussed by Hollins (66), and on page 269 of his book are listed the various 2,4-disubstituted quinolines prepared in this way through 1923.

In 1927, Roberts and Turner (100) published an excellent review of previous experiences with the Combes method and reported on an extensive series of investigations of the factors which affect the yields of substituted quinolines from these reactions. These investigations brought out the fact that, while most simple substituted anilines condense readily with acetylacetone to give good yields of the intermediate β-arylamino-α,β-unsaturated ketones, the second stage of the Combes quinoline synthesis (ring closure) is more definitely affected by the nature of the substituents present on the aniline benzene ring.

TABLE 15

Quinolines from β-arylamino-α,β-unsaturated ketones

AMINE	MELTING POINT OR BOILING POINT	QUINOLINES	MELTING POINT OR BOILING POINT	YIELD	REFERENCES
	 $CH_3\text{—}\underset{\substack{\vert\\ N}}{C}{=}CHCOCH_3$				
	°C.		°C.	per cent	
m-Anisidine	178/10 mm.	2,4-Dimethyl-7-methoxy	185/25 mm.	50	(86)
2,3,4-Trimethoxy-aniline	70	2,4-Dimethyl-6,7,8-tri-methoxy	59.5	>90	(87)
3,4,5-Trimethoxy-aniline	101	2,4-Dimethyl-5,6,7-tri-methoxy	59	>90	(87)
8-Aminoquinoline	95	Would not cyclize			(60)
	 $CH_3\text{—}\underset{\substack{\vert\\ N}}{C}{=}CHCOC_6H_5$				
3,4-Dimethoxy-aniline	100	2-Methyl-4-phenyl-6,7-dimethoxy	142	80–90	(88)
	 $C_6H_5\text{—}\underset{\substack{\vert\\ N}}{C}{=}CHCOC_6H_5$				
m-Anisidine	76	2,4-Diphenyl-7-methoxy	102	77	(86)
	 $\underset{\substack{\vert\\ N}}{CH}{=}CHCOCH_3$				
Aniline	Not isolated	2-Methyl	246/760 mm.		(101)
p-Toluidine	Not isolated	2,6-Dimethyl	55		(101)
	 $\underset{\substack{\vert\\ N}}{CH}{=}CHCOC_6H_5$				
Aniline	Not isolated	2-Phenyl	62	25	(93)
	 $\underset{\substack{\vert\\ N}}{CH}{=}\underset{\substack{\vert\\ C_2H_5}}{C}COC_6H_5$				
Aniline	Not isolated	2-Phenyl-3-ethyl	63	40	(93)

In agreement with the predictions of Roberts and Turner (100), several other investigators have since reported the preparation of various substituted quinolines using anilines with alkoxy substituents on the benzene ring in certain favorable arrangements. When only one alkoxy group is present in the ortho- or para-position of the aniline, the β-arylamino-α-β-unsaturated ketones (which can be obtained in good yields) cannot be induced to cyclize to the expected quinolines (100). The presence of at least one methoxyl group in the meta-position, however, seems to greatly facilitate ring closure (see table 15).

A modification (93, 101) of the Combes method involves the use of β-hydroxy-α,β-unsaturated ketones of the type RCOCR=CHOH (see table 15).

Borsche (19) has prepared certain tricyclic quinolines, using arylamines and β-diketones in which one ketone group is in an alicyclic ring (see reference 66, pages 372–4 and 387 for discussion).

Some of the material covered by this review has become available to the author during the past six years at the University of Nebraska, through the efforts of his several graduate research students whose names appear as coauthors of the papers mentioned here. The author is particularly indebted to his wife, Mary K. Cromwell, who helped in the literature search and typed the manuscript.

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