THE CHEMISTRY OF THE AMIDINES

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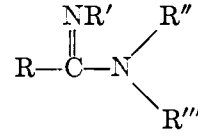
1. Introduction

Amidines are monacid bases characterized by the structural grouping:

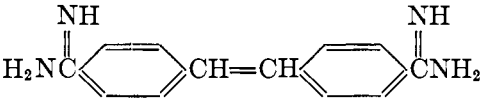


This review will be limited to the simple amidines in which R, R′, R″, R‴ are hydrogen, alkyl or aryl radicals and their substitution products. Molecules in which the two nitrogen atoms are part of a heterocyclic structure, or are

attached to elements other than hydrogen or carbon, will not be considered except when such compounds are formed as reaction products from simple amidines.

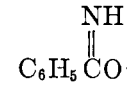
II. Nomenclature and Classification

Amidines have been designated as carbazylic acids, acid amidines, ammonocarboxylic acids, amimides, and imidoamides. The nomenclature used to designate specific amidines has varied somewhat; in this review the systems employed in *Chemical Abstracts* will be used in naming these compounds. In general, an amidine is named after the acid or amide which may be obtained from it by hydrolysis; thus $CH_3C(=NH)NH_2$ is *acetamidine*. The consecutive carbon atoms adjacent to the amidine carbon atom are designated in the same manner as those adjacent to a carbonyl group (α, β, γ, δ, . . . etc.); thus $C_6H_5CH_2CH_2C(=NH)NH_2$ is named *β-phenylpropionamidine*. The two nitrogen atoms are referred to as *N* and *N'*; $C_6H_5C(=NCH_3)NHCH_3$ is *N,N'-dimethylbenzamidine*. The imino nitrogen and amino nitrogen atoms are not differentiated by this system. In cases where the compound is difficult to name as a derivative of an acid, the amidine group is referred to as *carboxamidine*. For example, $NH_2C(=NH)(CH_2)_{12}C(=NH)NH_2$ may be named *dodecane-1,12-dicarboxamidine* and

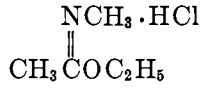


frequently called *p,p'-diamidinostilbene*, is more properly named *stilbene-4,4'-dicarboxamidine*.

The nomenclature of two types of compounds which are important intermediates in the synthesis of amidines may also be mentioned. The products obtained by the addition of alcohols to nitriles have been called imino ethers, imido ethers, imino esters, and imido esters. According to the *Chemical Abstracts* system these compounds are esters of imidic acids and are named after the parent acid. Two examples are:

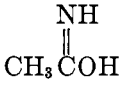


Ethyl benzimidate hydrochloride

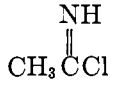


Ethyl *N*-methylacetimidate hydrochloride

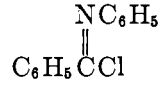
The compounds commonly called imino chlorides or imido chlorides are more properly named as the acid chlorides derived from the imidic acids. For example:



Acetimidic acid

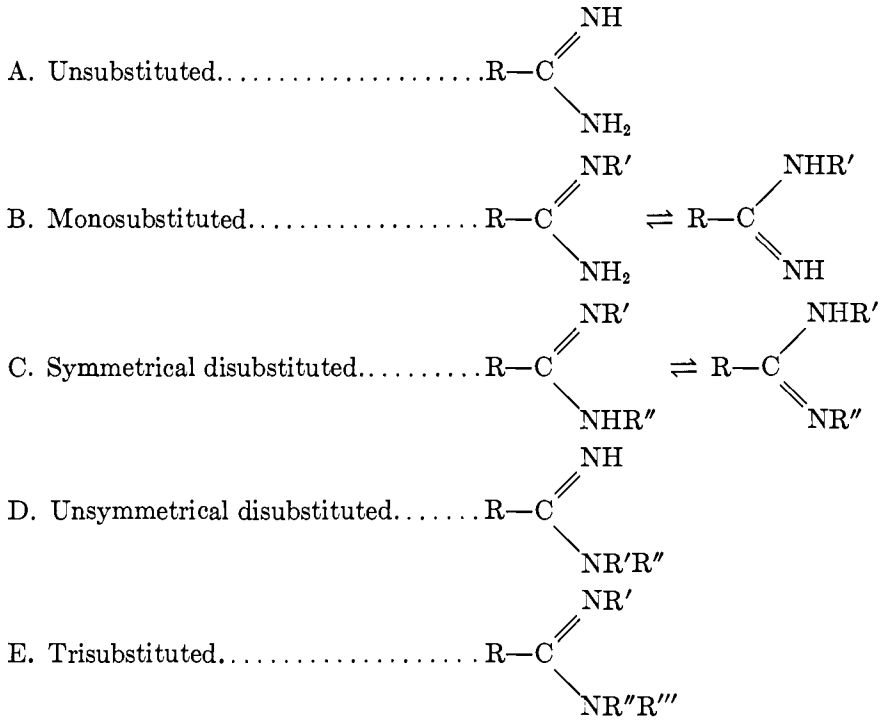


Acetimidyl chloride



N-Phenylbenzimidyl chloride

Amidines may be classified into five general types depending on the number and distribution of the substituents on the nitrogen atoms.

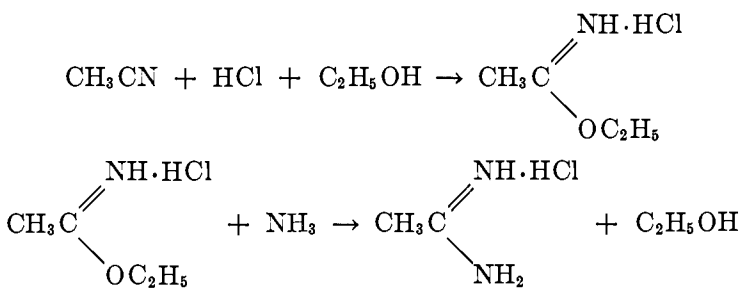


III. Preparation of Amidines

A. Unsubstituted amidines

1. From imidic esters

Pinner in 1877 (109, 129) described the synthesis of unsubstituted amidines from nitriles *via* the imidic esters. This is still the most practical and useful method of those reported in the literature. The nitrile is dissolved or suspended in an anhydrous alcohol and treated with an excess of dry hydrogen chloride, forming an imidic ester hydrochloride. This intermediate is then caused to react with ammonia dissolved in alcohol, forming the amidine hydrochloride.



The above method is very general: alcohols other than ethanol have been used (109), and hydrogen bromide may be substituted for hydrogen chloride. Mononitriles and dinitriles in both the aromatic and the aliphatic series have been employed (44, 85); Pinner (131) has even prepared the corresponding imidic ester hydrochloride from cyanogen. Both Pinner (109) and Gautier (54) have prepared formamidine hydrochloride from hydrogen cyanide by this method. It is not always necessary to isolate the imidic ester hydrochloride. After removal of most of the excess hydrogen chloride, ammonia may be passed into the mixture. Cyanohydrins of aldehydes and ketones also yield the desired products. Functional groups which do not react with the reagents or the expected products will not alter the course of the reactions; thus Pinner (127) was able to prepare α-carbethoxyacetamidine from ethyl cyanoacetate.

$$\begin{array}{l} CH_2CN \\ | \\ COOC_2H_5 \end{array} \rightarrow \begin{array}{l} NH\cdot HCl \\ \| \\ CH_2COC_2H_5 \\ | \\ COOC_2H_5 \end{array} \rightarrow \begin{array}{l} NH\cdot HCl \\ \| \\ CH_2CNH_2 \\ | \\ COOC_2H_5 \end{array}$$

Also phenylaminoacetamidine may be made by this method (153):

$$C_6H_5NHCH_2CN \rightarrow \begin{array}{l} NH\cdot HCl \\ \| \\ C_6H_5NHCH_2COC_2H_5 \end{array} \rightarrow \begin{array}{l} NH\cdot HCl \\ \| \\ C_6H_5NHCH_2CNH_2 \end{array}$$

The formation of the imidic ester hydrochloride is usually carried out with no solvent other than the stoichiometric amount of the alcohol. However, Ashley and coworkers (3) have used chloroform, benzene, nitrobenzene, dioxane, or an excess of ethanol as a diluent in the preparation of imidic esters of aromatic dinitriles of higher molecular weight.

Anhydrous hydrogen chloride has been the acid most commonly used for the preparation of imidic ester salts. Other acids may be used but are not as convenient. Acid appears to be necessary for this reaction except in the special case of trichloroacetonitrile which, according to Steinkopf (154), adds methanol without halogen acid present.

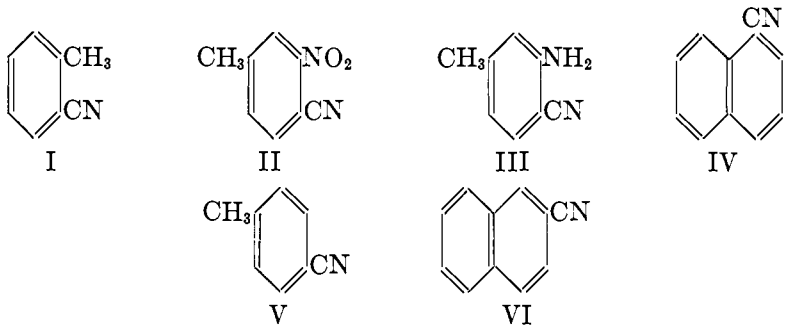
$$CCl_3CN + CH_3OH \rightarrow \begin{array}{l} NH \\ \| \\ CCl_3COCH_3 \end{array}$$

There are several limitations as to the type of unsubstituted amidines which can be prepared by Pinner's method. Acyl cyanides such as acetyl or benzoyl cyanide can not be used (109). In an attempt to prepare the imidic ester of benzoyl cyanide the only substances isolated were ethyl benzoate and decomposition products of hydrogen cyanide.

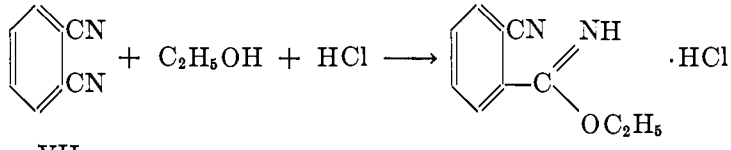
$$RCOCN + R'OH \xrightarrow{HCl} RCOOR' + HCN$$

Pinner also found that certain ortho-substituted aromatic nitriles were unreactive with ethanol and hydrogen chloride, whereas the other position isomers

did form imidic esters which could be converted to amidines. Thus *o*-tolunitrile (I), 2-nitro-4-methylbenzonitrile (II), 2-amino-4-methylbenzonitrile (III), and α-naphthonitrile (IV) were recovered unchanged after treatment with the reagents, while *p*-tolunitrile (V) and β-naphthonitrile (VI) gave the imidic esters and amidines (118).

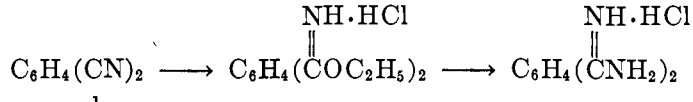


It is of interest to note that only one of the nitrile groups in *o*-phthalonitrile (VII) and in 3,4-dicyanotoluene can be converted into an imidic ester (119).



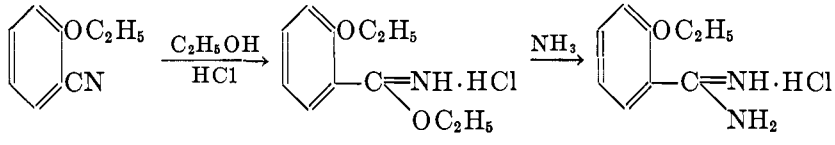
VII
o-Phthalonitrile

The other two isomeric phenylene dicyanides react to produce the expected products (132), e.g.:



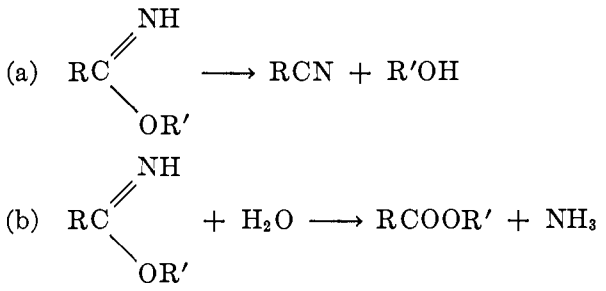
m- and *p*-
Phthalonitriles

Not all ortho groups prevent the formation of imidic esters and amidines. The exact limitations are not known, but Pinner and Dietz (128) have prepared *o*-ethoxybenzamidine (VIII) by this method.



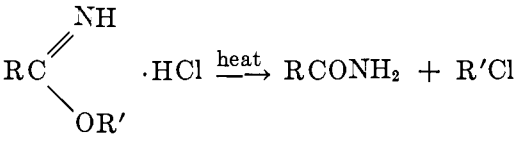
VIII
o-Ethoxybenzamidine

Other limitations of this method are due to various side reactions. Pinner (109) and Derby (39) have pointed out the instability of the imidic ester hydrochlorides. Decomposition in aqueous solution occurs as follows:

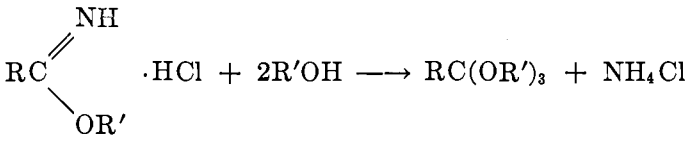


Reaction (b) is accelerated by hydrogen ions. Since the imidic esters are always obtained as hydrochlorides, the two steps of this method of preparing amidines must be carried out in anhydrous media. An exception to this general rule has recently been recorded. Nicotinamidine is best prepared by treatment of ethyl nicotinimidate with ammonium chloride dissolved in aqueous alcohol (8b).

Salts of imidic esters are difficult to keep, since traces of moisture will cause the above side reactions to take place. Spontaneous decomposition of the dry salts also occurs upon long standing; Derby (39) was able to demonstrate the formation of benzamide and ammonium chloride from ethyl benzimidate. Pinner (109) gives the following equation to represent the decomposition of the salts of imidic esters during recrystallization:

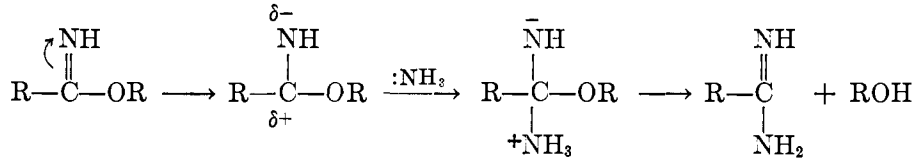


Imidic ester hydrochlorides can form ortho esters in the presence of an excess of alcohol (136).



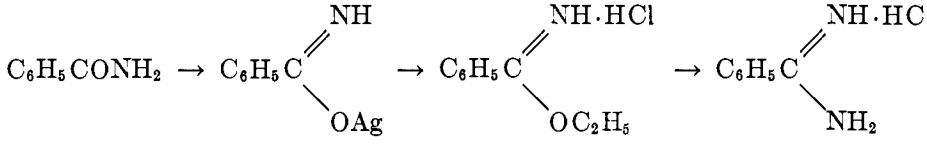
The important rôle of these side reactions is reflected by the experimental procedures used and the yields obtained. Using the method of Pinner, Derby (39) employed equimolecular amounts of nitrile and alcohol, and kept the temperature of reaction at 0°C. during the formation of the imidic ester; anhydrous ether was added to the reaction mixture to facilitate the isolation of the product. However, Ashley and coworkers (3) found no evidence for the existence of unstable hydrochlorides in their work, in which they used aromatic nitriles of higher molecular weight. Thus, while more caution must be taken in the preparation of low-molecular-weight or aliphatic imidic esters, such as ethyl acetimidate, the use of aromatic nitriles allows greater flexibility in experimental conditions.

No definite mechanism for the formation of the amidine from the imidic ester has been established. Knorr (76) suggested that the reaction involved an ammonium ion. However, benzamidine may be formed by the action of alcoholic ammonia on the free imidic ester (3, 15). Perhaps the reaction mechanism is similar to that suggested for the hydrolysis of esters.



Representative preparatory directions using the method of Pinner may be found in *Organic Syntheses* (101), in *Die Methoden der organischen Chemie* by Houben (63), and in *Die Imidoäther und ihre Derivate* by Pinner (109).

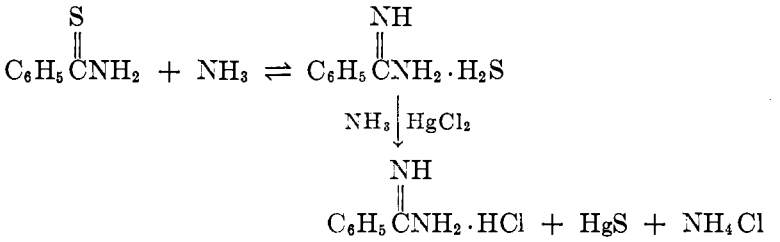
Tafel and Enoch (157) have prepared ethyl benzimidate hydrochloride by a method different from that used by Pinner. Treatment of benzamide with silver nitrate and sodium hydroxide in aqueous solution produced a compound which turned white after standing. This white compound, silver benzamide, was caused to react with ethyl iodide, followed by treatment with anhydrous ether and hydrogen chloride. Ethyl benzimidate hydrochloride was produced, and this compound was converted into the amidine by means of ammonia; both products were identical with those obtained by Pinner's method. These workers then used other aromatic amides to show that the method was general.



Mention should be made of the fact that the addition compounds of nitriles with hydrogen chloride do not produce amidines when treated with ammonia but regenerate the nitrile (152). This observation has led to the suggestion that they are salt-like complexes of the nitrile with hydrogen chloride and not true imidyl chlorides.

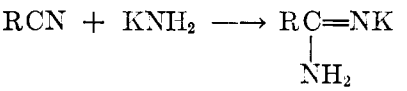
2. From thioamides

Bernthsen (11, 12) was the first to report the use of thioamides in the preparation of amidines. An unsubstituted aromatic or aliphatic thioamide is caused to react with concentrated ammonium hydroxide, a reaction, which sets up an equilibrium between the thioamide and amidine hydrosulfide. The addition of mercuric chloride assists in driving the reaction to completion, owing to the formation of insoluble mercuric sulfide. It is also possible that the ammonia and mercuric chloride form aminomercuric chloride (11), which then reacts with the amidine hydrosulfide.



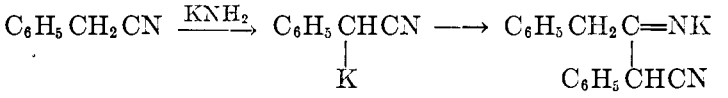
3. Amination of nitriles with alkali metal amides

Both aromatic and aliphatic nitriles add alkali metal amides to produce salts of amidines (10, 32, 48, 74, 178). The reaction may be carried out in anhydrous media such as benzene, toluene, xylene, anisole, or biphenyl or by reaction in liquid ammonia (32, 48). The amides of sodium, potassium, and calcium have been used. In a considerable number of cases potassium amide appears to give better yields (32).

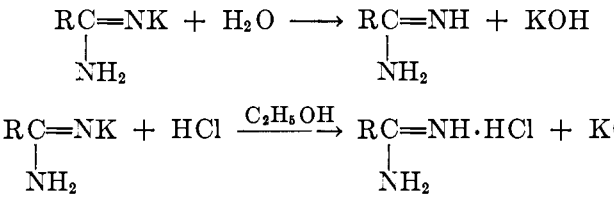


The lower aliphatic nitriles undergo considerable polymerization upon treatment with sodium amide in benzene at 60–70°C.; hence, in these cases the reaction is best carried out at a low temperature in liquid ammonia. Under the latter conditions, yields of 30 to 50 per cent of potassium acetamidine, propionamidine, *n*-butyramidine, and *n*-valeramidine may be obtained. By the action of sodium amide in benzene at 60–70°C. yields of 85–90 per cent may be obtained from branched-chain nitriles (such as α,α-diethylacetamidine) or from aromatic nitriles.

The reaction fails with nitriles containing reactive methylene groups, such as phenylacetonitrile. The latter undergoes salt formation and subsequent condensation to a dimer:

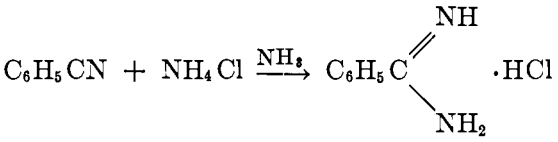


Conversion of the alkali metal salts to the amidines may be accomplished by careful hydrolysis with water (178) at a low temperature in order to avoid hydrolysis to the amide. Frequently better yields result by treatment with absolute alcoholic hydrogen chloride (32) to produce the amidine hydrochloride.



4. Use of nitriles and ammonium chloride

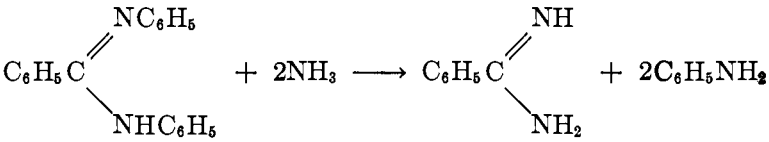
Cornell (32) has prepared benzamidine hydrochloride and aliphatic amidines in low yields by heating the corresponding nitriles in sealed tubes with ammonium chloride in liquid ammonia.



Bernthsen has also prepared unsubstituted amidines by this method (12). Cornell reports that no reaction occurs when only the nitrile and ammonia are used.

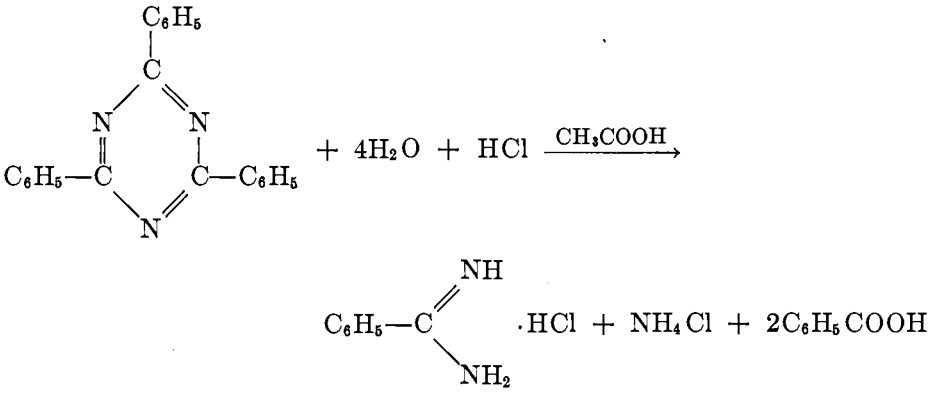
5. Ammonolysis of substituted amidines

Niemann has prepared benzamidine by treating *N*,*N'*-diphenylbenzamidine with an excess of ammonia (98).



6. From triazines

Robin (138) has obtained benzamidine hydrochloride by heating 2,4,6-triphenyltriazine with hydrochloric and acetic acids at 120°C.

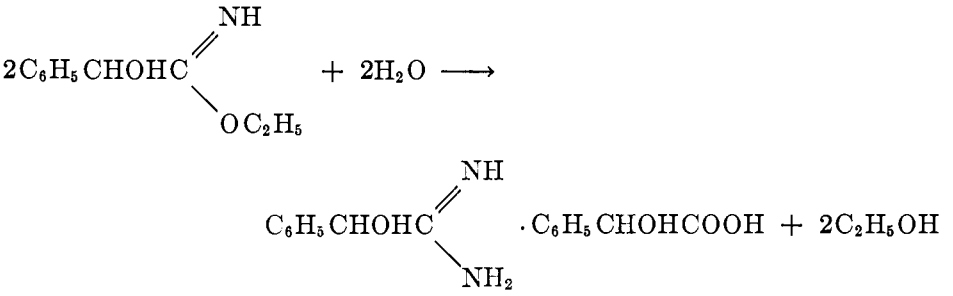


7. From amides

A variety of methods have been reported for the preparation of acetamidine salts. Strecker in 1857 (156) made the hydrochloride by passing hydrogen chloride through molten acetamide. Fichter, Stutz, and Grieshaber (49) obtained acetamidine nitrate by heating acetamide and ammonium nitrate at 170°C. in liquid ammonia for 20 hr.

8. By hydrolysis of imidic esters

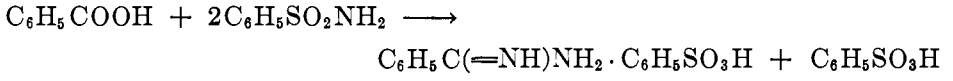
Rule (148) showed that *mandelamidine mandelate* was formed, in fair yield, by shaking ethyl mandeloimidate with water at room temperature for 5 days.



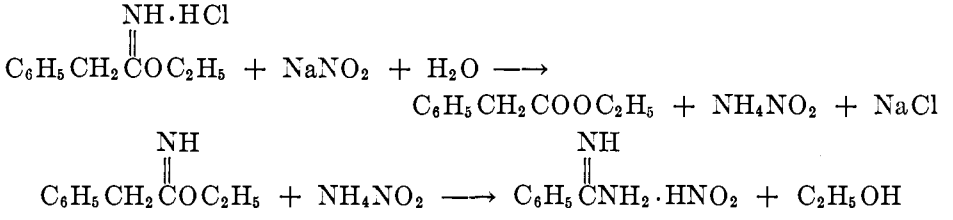
This decomposition is rather unusual, but Rule found that free imidic esters prepared from other cyanohydrins reacted with water to form analogous products.

9. Miscellaneous

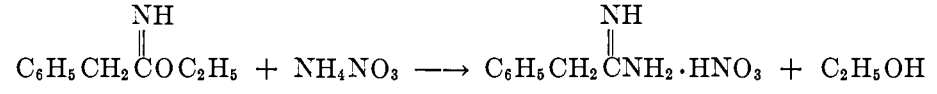
By heating benzoic acid and benzenesulfonamide at 225°C., Rouiller (140) prepared the benzenesulfonate of benzamidine; no reaction took place between benzamide and benzenesulfonamide under the same conditions.



Bernton (15) has reported the formation of the nitrite of phenylacetamidine by the action of a solution of sodium nitrite on ethyl phenylacetimidate hydrochloride. This unusual reaction probably occurs in the following stages:



Bernton also noted that ammonium nitrate converted ethyl phenylacetimidate into the nitrate of the amidine.



Acetamidine nitrate has been formed by the electrolysis of a mixture of ammonium carbonate, ethanol, and ammonia (49). By substitution of *n*-propyl alcohol or *n*-butyl alcohol for ethanol, propionamidine and *n*-butyramidine may be obtained. Fichter (49) also obtained acetamidine by the oxidation

of ethanol or acetaldehyde in ammoniacal ammonium nitrate solution with calcium permanganate or ammonium persulfate.

Amidoximes may be reduced catalytically or electrolytically to amidines (94).

The formation of unsubstituted amidines by the action of ammonia on ortho esters represents a possible method of preparation. Although this reaction is mentioned in a number of text books, no specific data on the reaction appear to be recorded in the literature.

$$RC(OC_2H_5)_3 + 2NH_3 \longrightarrow R\overset{\overset{NH}{\|}}{C}NH_2 + 3C_2H_5OH$$

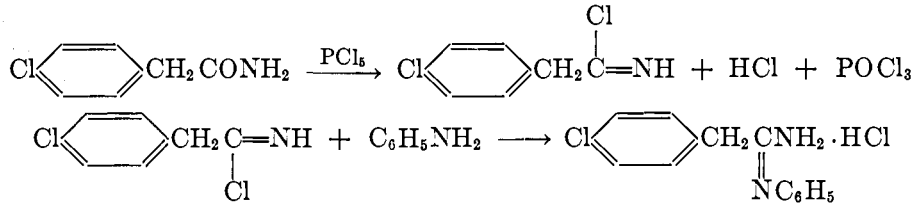
B. MONOSUBSTITUTED AMIDINES

1. From amides

The preparation of monosubstituted amidines using *N*-substituted amides is one of the more common methods. The amide is first converted to the imidyl chloride, usually by treatment with phosphorus pentachloride; the halogen-substituted compound is then caused to react with ammonia. Thus Lossen (90) was able to prepare *N*-phenylbenzamidine.

$$C_6H_5CONHC_6H_5 \xrightarrow{PCl_5} C_6H_5\underset{\underset{Cl}{|}}{C}{=}NC_6H_5 \xrightarrow{NH_3} C_6H_5\underset{\underset{NH_2}{|}}{C}{=}NC_6H_5$$

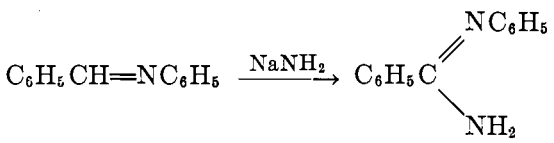
Walther and Grossmann (172) have prepared *N*-phenyl-α-(*p*-chlorophenyl)-acetamidine from *p*-chlorophenylacetamide by the following reactions:



The extension of the method to the preparation of unsubstituted amides is not satisfactory because low yields are obtained, probably because the imidyl chloride is converted to the nitrile.

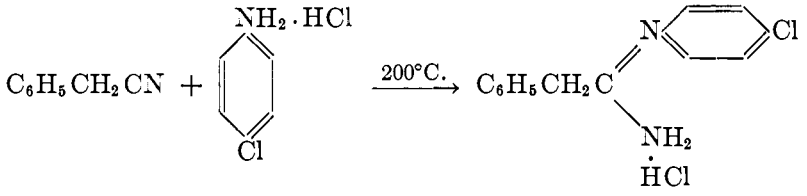
2. Addition of sodium amide to Schiff bases

Kirsanov and Ivashchenko (75) reported in 1935 a new procedure for the preparation of substituted amidines. A Schiff base is treated with sodium amide in the presence of dry toluene at 120°C. Ammonia is evolved, and the residue yields monosubstituted amidines in yields ranging from 13 to 23 per cent. Although many side products are formed, no disubstituted amidines were isolated.



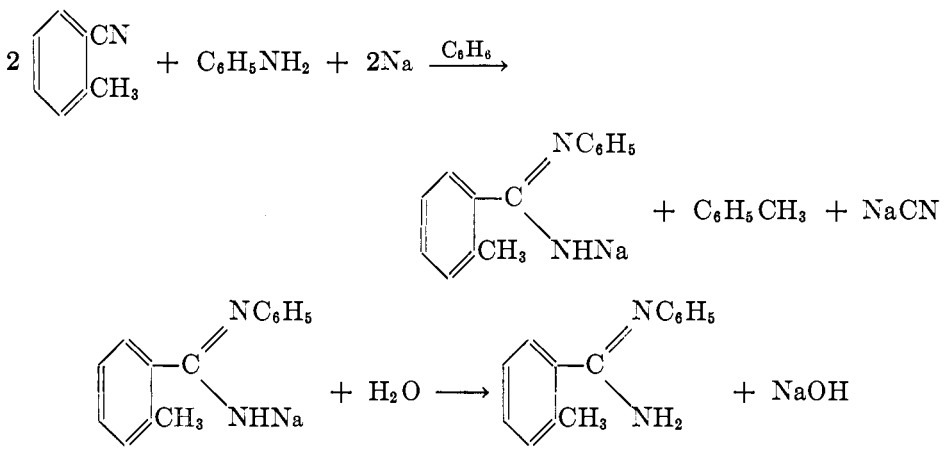
3. From nitriles

Both aliphatic and aromatic nitriles can be caused to react with either aryl or alkyl primary amine hydrochlorides under the influence of heat to form amidines (11, 12, 43, 149, 172).



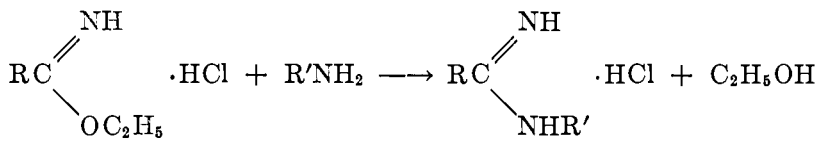
A disadvantage of this method is that disubstituted amidines may be formed. Heating acetonitrile and aniline hydrochloride at 170°C. caused the formation of *N*-phenylacetamidine, while heating to 240°C. produced *N*,*N'*-diphenylacetamidine (11).

Lottermoser (91) and others (172) have applied this method successfully by the use of the free amine and powdered sodium. The sodium salt of the amidine, which is obtained, is converted to the free base by hydrolysis with water. *N*-Substituted amidines can be prepared from *o*-tolunitrile by this method. This is of interest because it will be recalled that *o*-tolunitrile did not produce *o*-methylbenzamidine by Pinner's method.

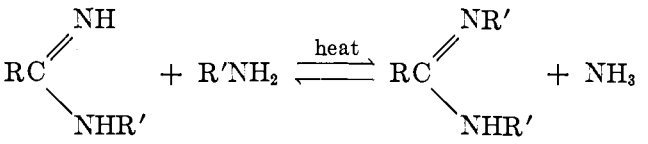


4. From imidic esters

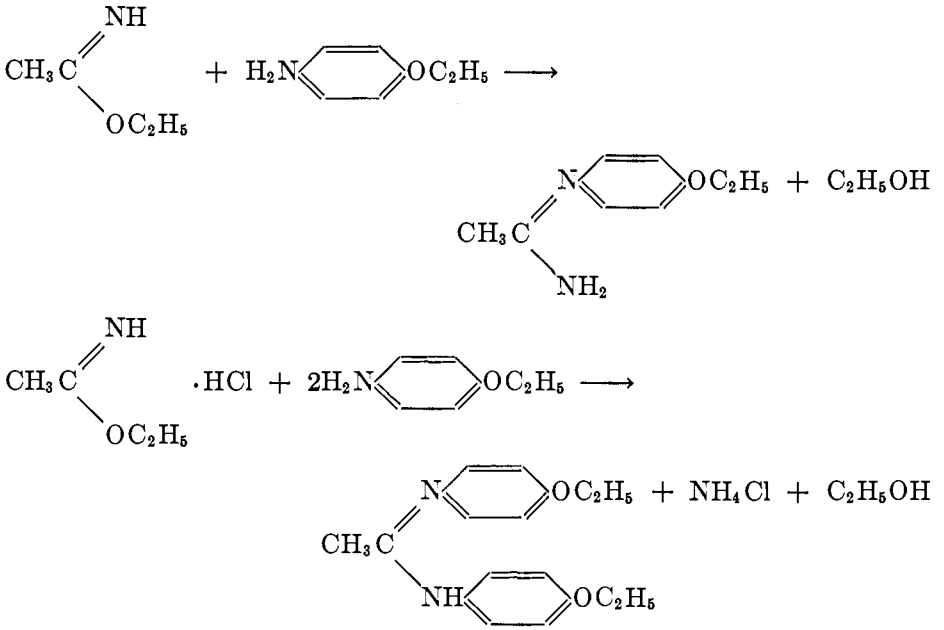
Just as unsubstituted amidines are formed by the action of ammonia on imidic esters, so may monosubstituted amidines be prepared by replacing the ammonia by primary amines (90, 109).



Pinner points out, however, that higher temperatures and longer periods of reaction cause the formation of disubstituted products, probably because of the existence of the following equilibrium:

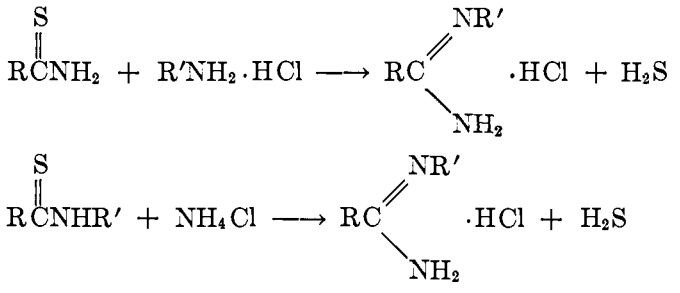


Hill and Rabinovitz (60) have used Pinner's method to prepare both mono- and di-substituted amidines.



5. From thioamides

The following equations represent the extension of Bernthsen's method of preparing unsubstituted amidines to that of monosubstituted ones (11, 12):

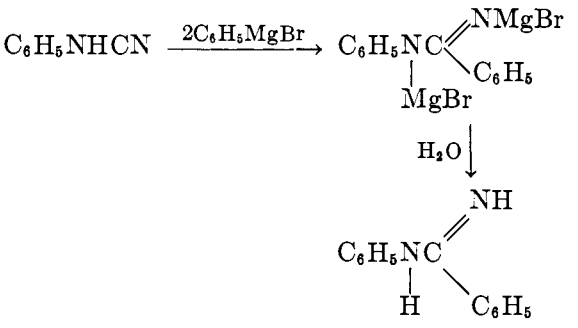


The limitations of Pinner's method should also apply to this process. *S*-Alkyl isothioamides may also be used.

6. From cyanamides

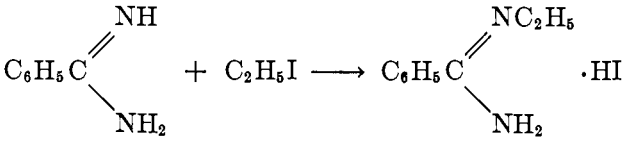
Busch and Hobein (23) have prepared several amidines by the action of the Grignard reagents on phenylcyanamide.

Phenylcyanamide was caused to react with an excess of phenylmagnesium bromide, and the addition product decomposed to yield *N*-phenylbenzamidine.



7. Alkylation of unsubstituted amidines

Pinner and Klein (130) prepared *N*-ethylbenzamidine by heating benzamidine and ethyl iodide at 100°C.

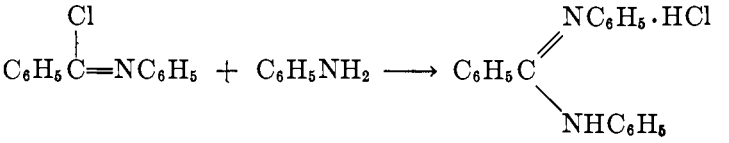


Alkylation can proceed further, forming disubstituted products (134, 135).

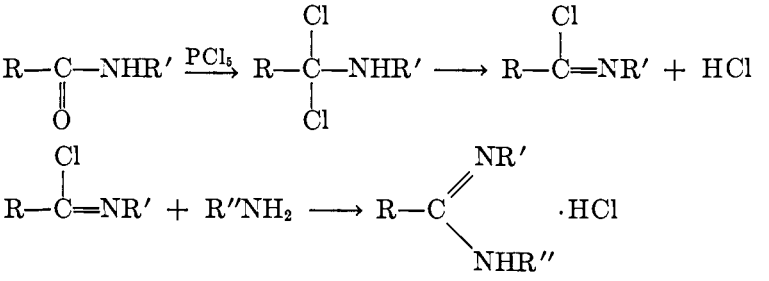
C. SYMMETRICAL DISUBSTITUTED AMIDINES

1. From amides

Gerhardt in 1858 (55) prepared *N,N'*-diphenylbenzamidine by heating *N*-phenylbenzimidyl chloride with aniline.

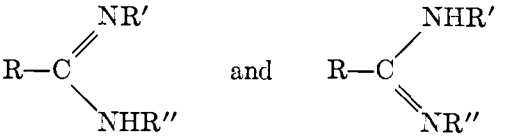


Other early workers—Wallach (166), Bamberger and Lorenzen (7), and von Pechmann (106, 107)—have extended this reaction as a general preparation of amidines.

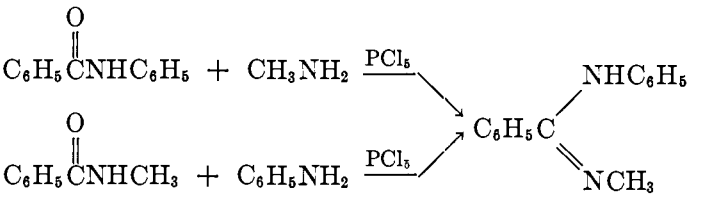


The usual method is to first form the imidyl chloride, remove the excess reagent, and then add the amine (7, 59, 106, 166). Various workers (7, 60, 151) have prepared amidines by heating the amine and amide with about ten parts by weight of phosphorus trichloride at 110–120°C. for 3 hr.; the amidine is isolated after dissolving the reaction mixture in cold water and adding alkali. Bureš and Kundera (21) used a similar procedure, substituting phosphorus oxychloride or pentachloride for the trichloride.

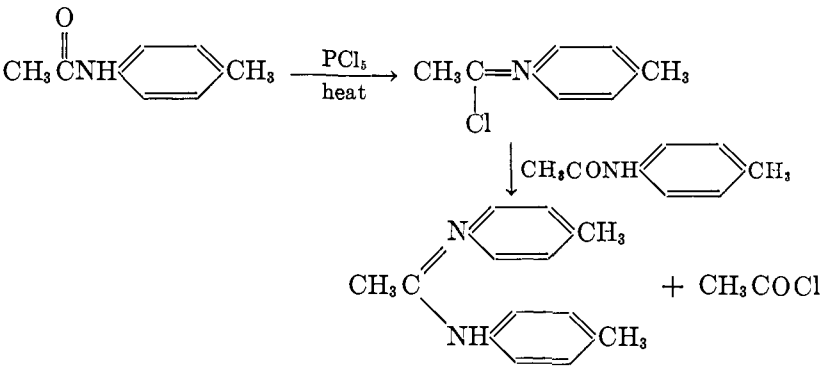
It is possible to write two different isomeric formulas for a symmetrical disubstituted amidine.



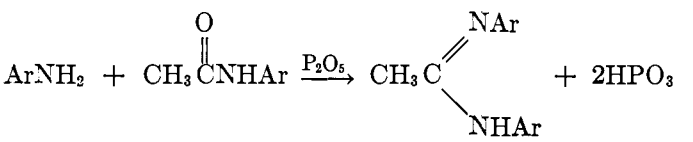
von Pechmann (105, 106, 107) in 1895 demonstrated that attempts to synthesize the two forms of such amidines produced the same compound. This fact has been confirmed by other workers (21). Thus there are usually two alternatives in the choice of amide and amine in the synthesis of a given amidine. The following equations will illustrate this point:



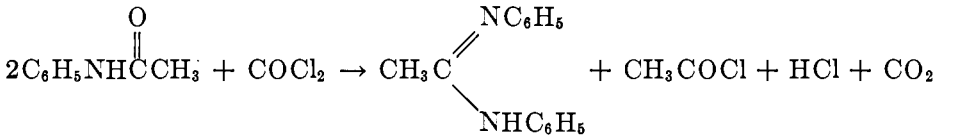
Wallach (167) prepared *N,N'*-di-*p*-tolylacetamidine by heating *p*-methylacetanilide and phosphorus pentachloride.



Amidines may be formed by heating an aryl amine and an amide in the presence of phosphorus pentoxide or other condensing agents (150).

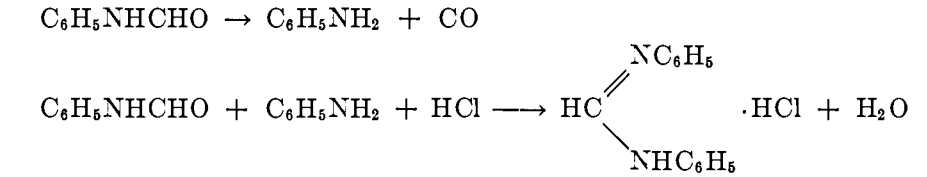


Disubstituted amidines may be prepared from acetanilide, its derivatives, homologs, or analogous compounds—with the exception of arylglycine anilides—by treatment with phosgene in the presence or absence of condensing agents (26).

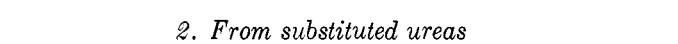


The reaction is stated to proceed smoothly and no by-products are formed.

Tobias (161) and Wallach (168) in 1882 prepared *N*,*N*′-diphenylformamidine. hydrochloride by treating formanilide with hydrogen chloride gas at 100°C. The formation is thought to take place in the following manner:

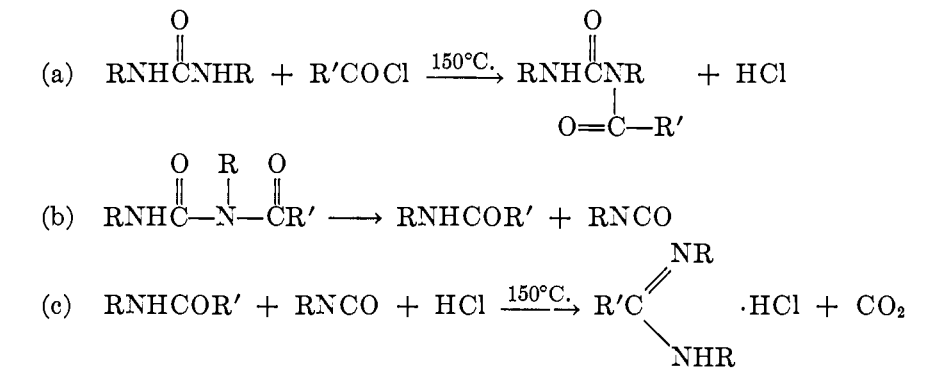


Wallach (168) extended this method to the preparation of the corresponding acetamidine by heating acetanilide with hydrogen chloride at 150°C. *N*,*N*′-Diphenylacetamidine was made by heating acetanilide with aniline hydrochloride. *N*,*N*′-Diphenylformamidine has been prepared by heating aniline and formic acid in the presence of boric acid or a borate and (or) iron (68). The first stage of the mechanism is probably the formation of formanilide, the amidine then being formed as described above.



2. From substituted ureas

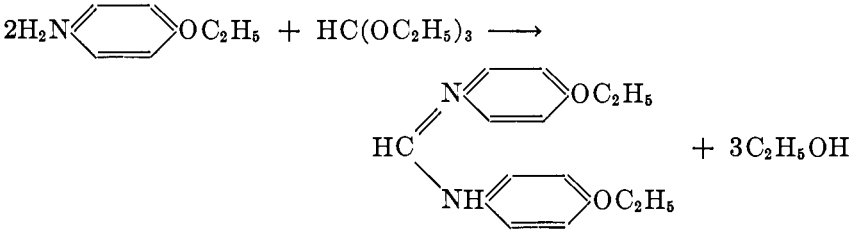
Dains (33, 38) has shown that amidines may be prepared from symmetrical diaryl and dialkyl ureas and acid chlorides. Both aromatic and aliphatic acyl halides may be used.



Kuhn had previously shown (78) that benzanilide forms *N*,*N*′-diphenylbenzamidine when heated with phenyl isocyanate.

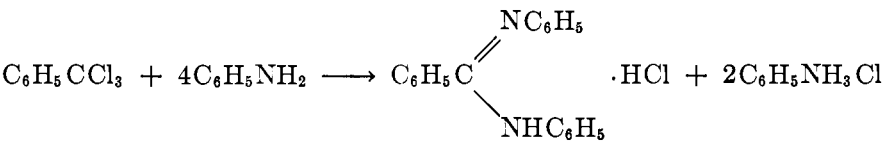
3. From orthoformic ester

Claisen (28) and others (37, 56, 171) refluxed ethyl orthoformate and aromatic amines in an alcoholic solution to form substituted formamidines. Yields as high as 77 per cent have been reported (37). The reaction between phenetidine and orthoformic ester illustrates this method:



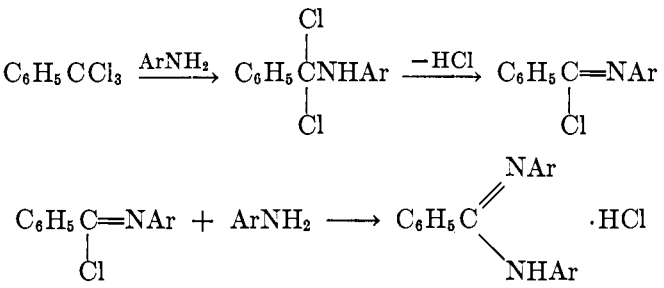
4. From benzotrichloride

In 1865 Limpricht (88) demonstrated that *N*,*N'*-diphenylbenzamidine could be produced by the action of aniline in excess upon benzotrichloride according to the following reaction:

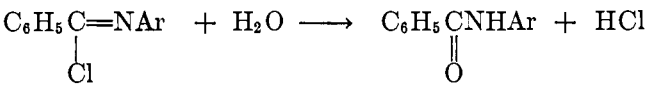


Doebner (41) confirmed this observation. Joshi, Khanolkar, and Wheeler (70) modified the procedure by using nitrobenzene as a solvent to reduce the violence of the reaction; yields up to 85 per cent were obtained. The method works well with meta- and para-substituted anilines, but satisfactory results could not be obtained with benzidine and certain ortho-substituted aromatic amines.

The following mechanism has been proposed (70):

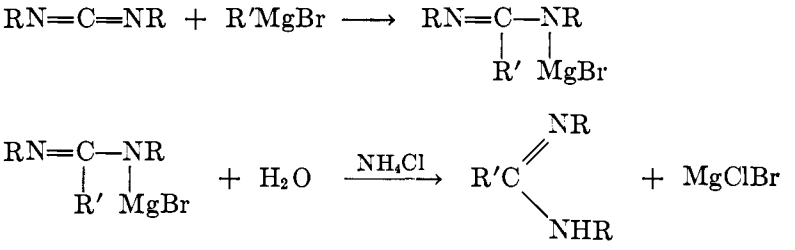


If moisture is present during the reaction, a benzanilide is formed according to the reaction:



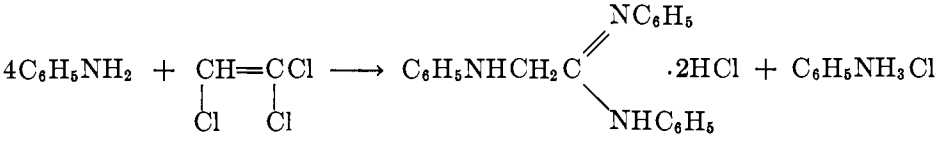
5. From dialkylcarbodiimides

Busch and Hobein (23) have devised a method of preparation in which diphenyl carbodiimide and aryl or alkyl magnesium halides are used. The following equations serve as illustration:



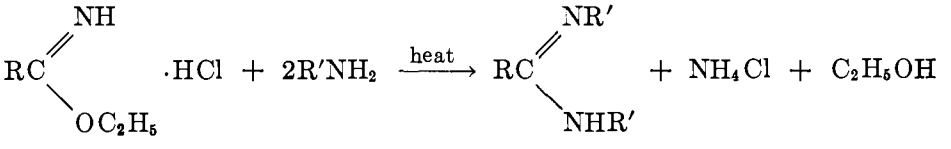
6. From trichloroethylene

Amidines have been prepared from trichloroethylene and aromatic amines (65, 141). The two reagents are boiled with 15 per cent sodium hydroxide to produce the disubstituted amidines in yields of 60–65 per cent. The method is not general, since certain amines are unreactive and since α-aminoacetamidines are produced.



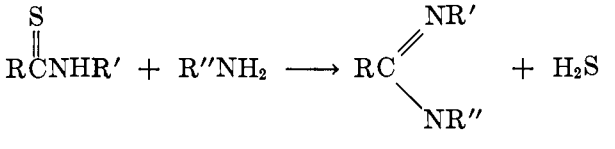
7. From imidic esters

The extension of Pinner's method for preparing amidines to the formation of symmetrical disubstituted amidines has been described (60, 92, 109, 111,172).

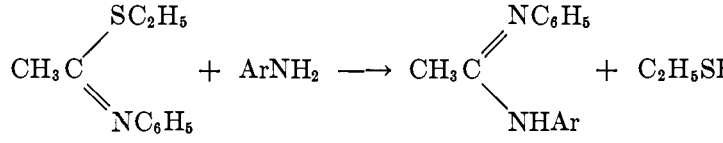


8. From thioamides

Bernthsen (12) has shown that disubstituted amidines can be prepared from *N*-alkylthioamides.

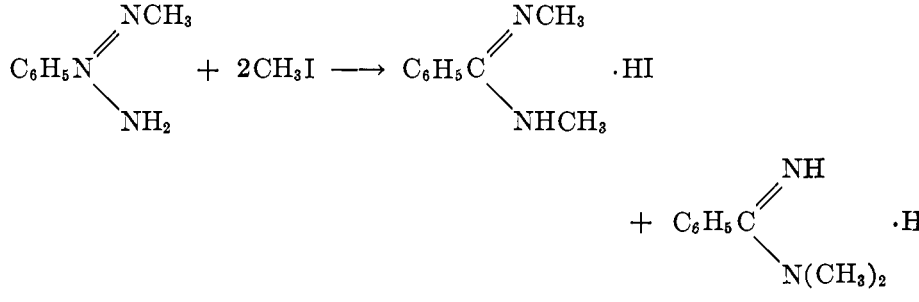


Wallach *et al.* (169, 170) have utilized *S*-alkyl isothioanilides to prepare amidines. Thus *S*-ethyl isothioacetanilide has been caused to react with various aromatic amines:



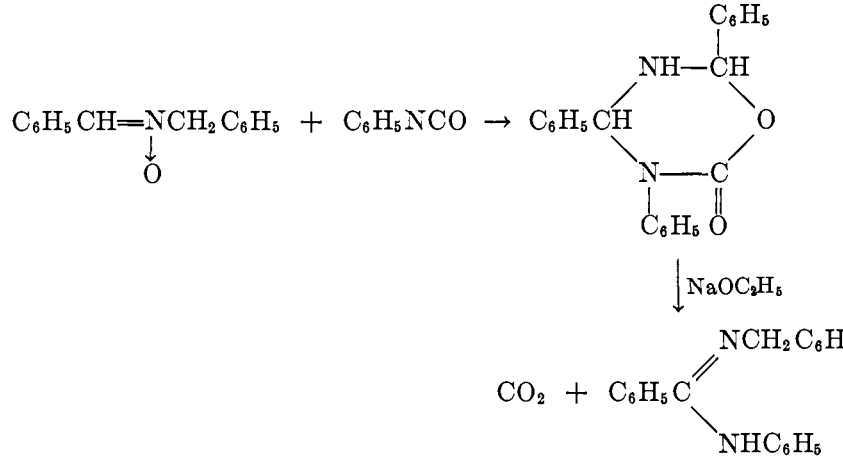
9. By alkylation

Pyman (135) has studied the alkylation of monosubstituted amidines. Symmetrical disubstituted amidines can be prepared by causing amidines to react with alkyl halides, but this method is not a general, desirable one. Both the symmetrical and the unsymmetrical dimethylbenzamidines were formed when *N*-methylbenzamidine was treated with methyl iodide:



10. From isocyanates

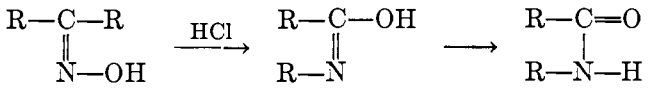
Beckmann and Fellrath (9) have prepared *N*-phenyl-*N'*-benzylbenzamidine from phenyl isocyanate and *N*-benzylbenzaldoxime according to the following reactions:



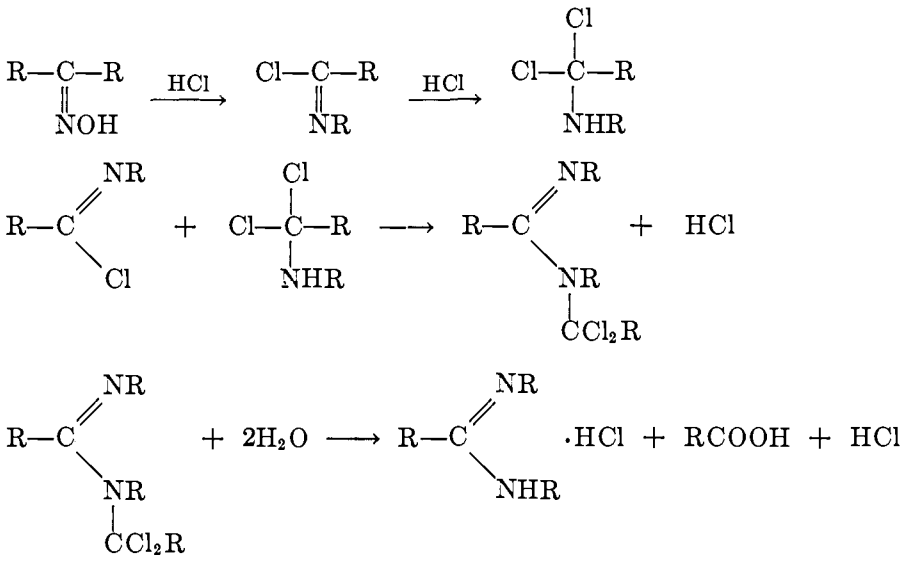
11. By the Beckmann rearrangement

Stephen and Bleloch (155) have found that amidines are produced during the Beckmann transformation of ketoximes when thionyl chloride, acetyl chloride, hydrogen chloride, or phosphorus pentachloride is used as the reagent. Yields as high as 20 per cent have been obtained, although the amide predominates in all cases.

The normal Beckmann transformation of ketoximes proceeds as follows:



Stephen and Bleloch suggest the following equations to explain the formation of symmetrical disubstituted amidines:



12. Other methods

Brunner, Matzler, and Mössmer (20) have prepared *N*, *N'*-diphenylacetamidine by heating diacetamide and aniline hydrochloride at 150°C. A similar reaction using diacetamide and *o*-nitroaniline hydrochloride was also carried out. The diacylamides can be prepared by heating the corresponding acid anhydride with potassium cyanate.

Symmetrical disubstituted amidines are formed by the action of alkyl hypochlorites on Schiff bases. Thus, *N*, *N'*-diphenylbenzamidine was made by the action of tertiary-amyl hypochlorite on benzalaniline in carbon tetrachloride solution (51).

Ott and Dittus (103) report that aminoamidine hydrochlorides can be prepared by the reaction of dichloroacetylene with primary amines but not with secondary amines. Since ammonia reacts with dichloroacetylene to give

chloroacetonitrile in good yields, the products formed by the action of primary amines are probably substituted α-aminoacetamidines.

When dry hydrogen chloride is introduced into an ether or benzene solution of hydrogen cyanide, a compound having the formula $C_2H_5N_2Cl_3$ ($2HCN \cdot 3HCl$) precipitates out (29). Dains has prepared symmetrical disubstituted formamidines [HC(=NR)NHR] by treating this compound with aromatic amines (34).

The selective oxidation of alkylidene bis-arylamines to *sym*-diarylformamidines has been studied by Wagner (165). In some cases 50 to 78 per cent yields have resulted by the use of potassium permanganate in acetone.

$$(C_6H_5NH)_2CH_2 + O(KMnO_4) \longrightarrow C_6H_5NHCH{=}NC_6H_5 + H_2O$$

Symmetrically substituted amidines are reported to be formed by the condensation of β-aminoanthraquinone with carbon tetrachloride and other aromatic hydrocarbons (6).

$$2ArNH_2 + CCl_4 + Ar'H \longrightarrow Ar'{-}\overset{\overset{NAr}{\|}}{C}{-}NHAr + 4HCl$$

D. UNSYMMETRICAL DISUBSTITUTED AMIDINES

1. From imidic esters

Pinner (109), 111, 122) and Luckenbach (92) have prepared unsymmetrical disubstituted amidines from secondary amines and imidic ester hydrochlorides.

$$RC(=NH)OC_2H_5 \cdot HCl + R'R''NH \longrightarrow RC(=NH)NR'R'' \cdot HCl + C_2H_5OH$$

The R groups may be alkyl or aryl.

2. From thioamides

Bernthsen (12) has prepared *N*, *N*-dialkylated amidines by use of the appropriate thioamides and amines. The following equations illustrate this method:

$$RC(=S)NH_2 + R'R''NH \longrightarrow RC(=NH)NR'R'' + H_2S$$

$$RC(=S)NR'R'' + NH_3 \longrightarrow RC(=NH)NR'R'' + H_2S$$

3. From nitriles

Bernthsen (12) has also prepared *N*, *N*-diphenylbenzamidine by heating benzonitrile and diphenylamine hydrochloride at 180°C. The reaction mixture was extracted with water and the free amidine precipitated by the addition of ammonium hydroxide. Yields ranged from 12 to 30 per cent; acetonitrile may also be used.

$$C_6H_5CN + (C_6H_5)_2NH\cdot HCl \longrightarrow C_6H_5\overset{\overset{NH}{\|}}{C}N(C_6H_5)_2\cdot HCl$$

4. From dialkylcyanamides

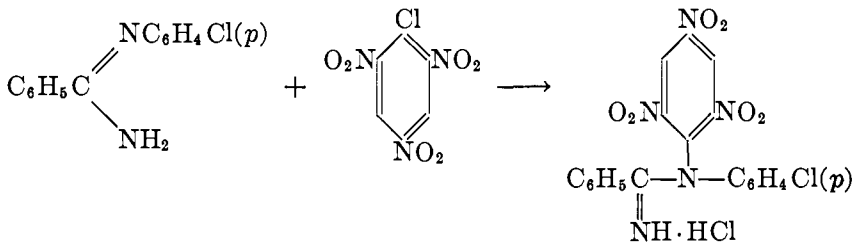
Adams and Beebe (1) have prepared amidines by hydrolyzing the addition products obtained from dibenzylcyanamide and alkyl- or aryl-magnesium bromides in yields as high as 75 per cent.

$$R_2NCN + R'MgBr \longrightarrow R_2N\overset{\overset{NMgBr}{\|}}{C}R'$$

$$R_2N\overset{\overset{NMgBr}{\|}}{C}R' + 2HCl \longrightarrow R'\overset{\overset{NH}{\|}}{C}\underset{\underset{NR_2}{|}}{} \cdot HCl + MgBrCl$$

5. By alkylation

As pointed out previously, the alkylation of *N*-methylbenzamidine with methyl iodide produces *N*,*N*-dimethylbenzamidine among other products. Activated aryl halides may also be used. For example, von Walther and Grossmann (172) have prepared *N*-*p*-chlorophenyl-*N*-2,4,6-trinitrophenylbenzamidine from picryl chloride by the following reaction:

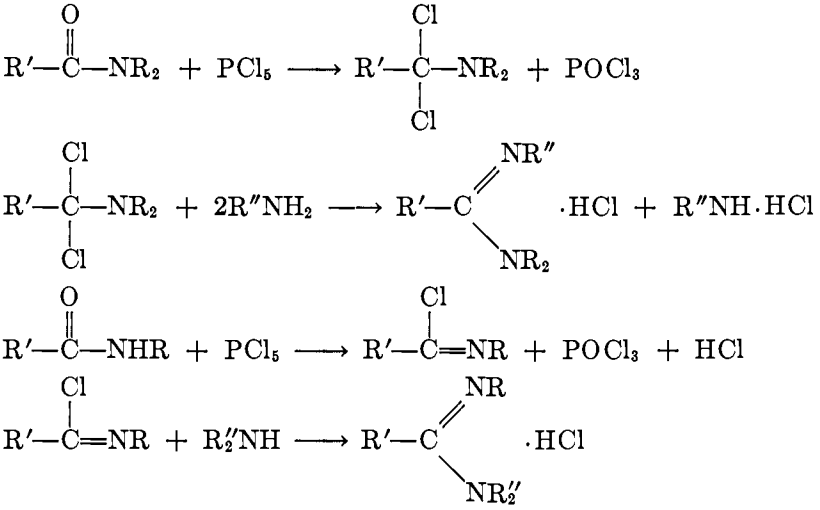


E. TRISUBSTITUTED AMIDINES

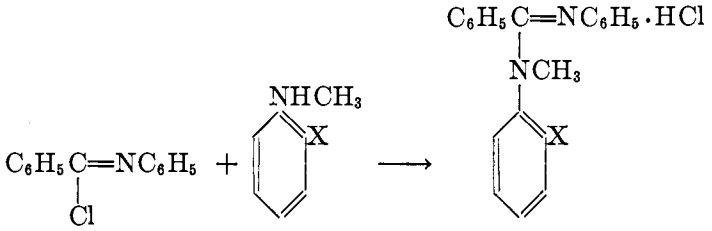
1. From amides

There are relatively few preparations for trisubstituted amidines in the literature. The most common method is by the use of disubstituted amides and primary amines or by the use of monosubstituted amides and secondary amines (9, 17, 19, 60). The amide is first treated with phosphorus trichloride or pentachloride. The chloro compound is then treated with the appropriate amine to form the desired amidine. The intermediary halogenated amide may or may not be isolated; Hill and Rabinowitz (60) obtained amidines by heating

the amide, amine, and phosphorus halide simultaneously, whereas other workers (9, 18) carried out the preparation in two steps. The following equations indicate the generality of the method:

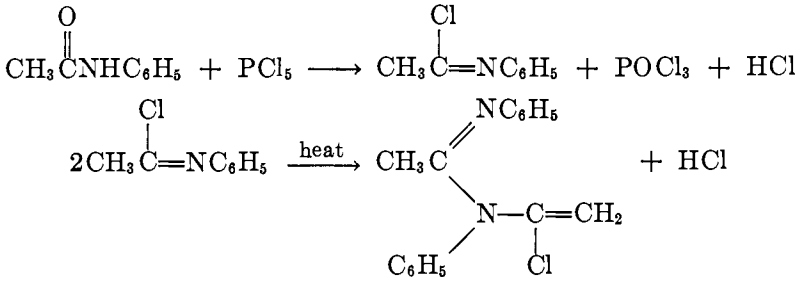


In 1932 von Braun and Weissbach studied the effect of steric hindrance in the preparation of amidines according to the following reaction (19):



When the amine was methylaniline (X=H), the yield was 36 per cent. As X increased in size, the yield decreased rapidly; when X was Cl, the yield was approximately 10 per cent.

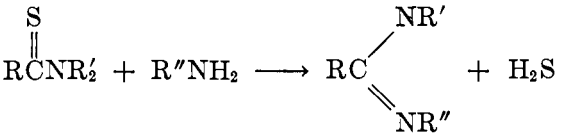
von Braun, Jostes, and Heymons found that acetanilide could be caused to react with phosphorus pentachloride to form a trisubstituted amidine in a yield of 50 per cent (18).



Wallach had previously assigned a different structure to the product (166, 167).

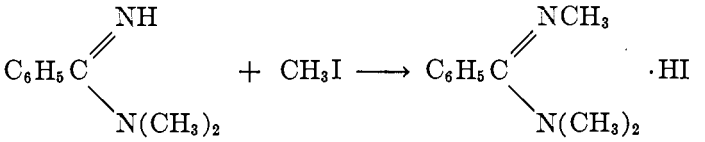
2. From thioamides

The use of thioamides in the preparation of amidines has been mentioned in the preceding sections. Thus, Bernthsen (11) was able to prepare trisubstituted amidines from disubstituted thioamides and primary amines.



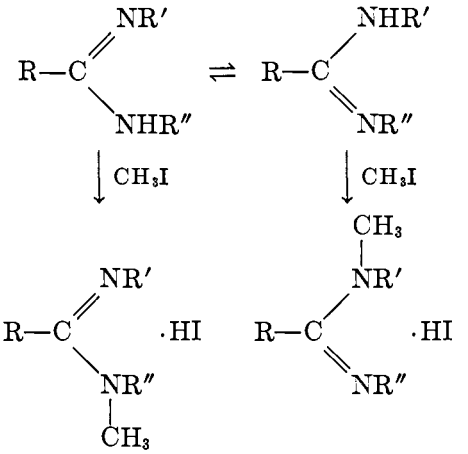
3. By alkylation

Pyman (135) and earlier workers (9, 17, 27) have demonstrated that trisubstituted amidines can be prepared by the treatment of disubstituted amidines with alkyl halides. *N*,*N*-Dimethylbenzamidine yields 64 per cent of the trimethyl compound when treated with methyl iodide.



In every case of alkylation studied, Pyman recovered some unchanged amidine; in the above example, this amounted to 9 per cent.

Alkylation of symmetrical disubstituted amidines leads to the formation of two products, owing to the tautomerism of the starting material (9, 108).



If R′ and R″ are greatly different in character, one derivative is formed in large excess. Pyman suggested that the alkyl group becomes attached to the less basic nitrogen atom.

IV. Properties and Reactions of Amidines

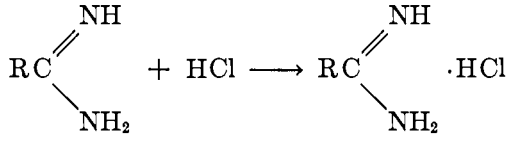
1. The basic character

Unsubstituted amidines are strong monacid bases. They form well-crystallized salts: hydrochlorides, sulfates, acetates (109); nitrates, carbonates (84);

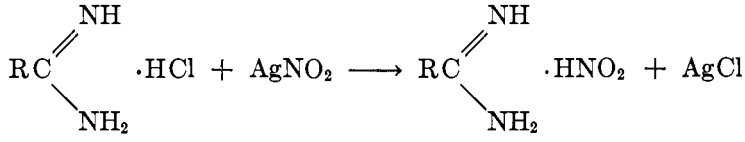
mandelates (148); picrates and chloroplatinates (172), etc. Under certain conditions even the nitrites are stable (90).

The basic strengths of the different amidines vary with substitution. Bernthsen (12) noticed that *N*,*N*-diphenylbenzamidine is strongly basic, whereas the *N*,*N'*-diphenylbenzamidine reacts neutral to litmus in alcoholic solution. The latter is a weaker base than ammonia, because Bernthsen was able to precipitate it from a hydrochloric acid solution by the addition of ammonia; *N*,*N*-diphenylacetamidine is evidently a stronger base than ammonia, because sodium hydroxide had to be used to precipitate the free base. It can also be concluded that benzamidine and acetamidine are stronger bases than ammonia, since the hydrochlorides can be obtained directly from solutions which contain an excess of ammonia (101). A search of the literature did not reveal any quantitative studies on the relative basic strengths of amidines.

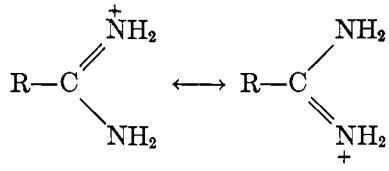
The hydrochlorides are usually obtained by the addition of hydrogen chloride gas to alcoholic or ether solutions of the bases.



As with the amines, the free bases can be recovered by the use of alkali. Lossen *et al.* (90) have prepared nitrites by treating a cold aqueous solution of the amidine hydrochloride with silver nitrite:

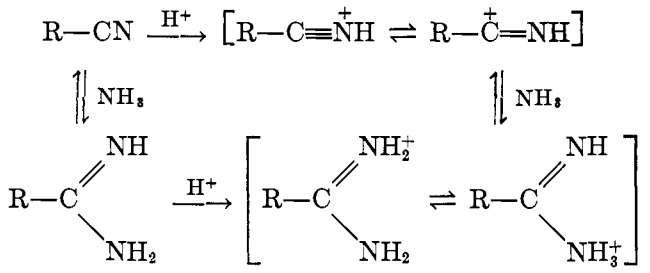


Several workers have attempted to describe the chemical structure of the amidinium cation. Sidgwick (152) indicates the structure as follows, in which either nitrogen atom could be written with the double bond.

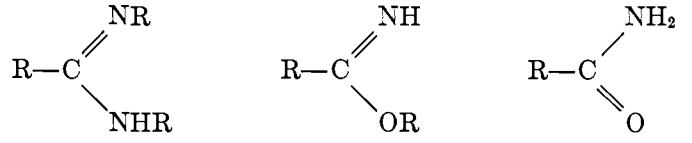


It would thus be a resonance hybrid of the two alternatives (isosteric with the nitro group and the carboxylate anion).

Amidines and nitriles have the ability to form benzimidazoles from *o*-phenylenediamine. Hölljes and Wagner (61) suggest that the reactions may proceed by a single essential reaction involving *hydrogen-ion catalysis*. The essential relationships may be summarized in the following scheme:

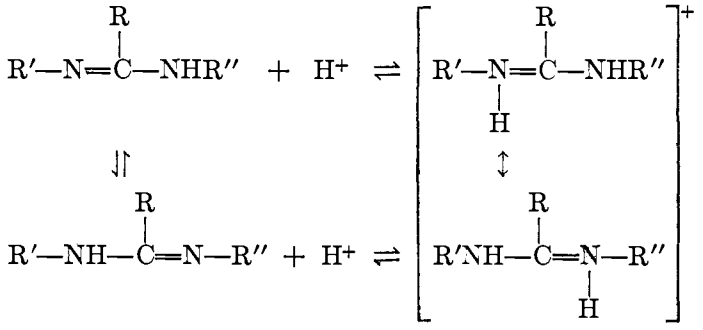


Burtles and Pyman present a third point of view (22). They suggest that the imino nitrogen of amidines is the one conferring basic properties on the molecule. Imidic esters are basic, whereas unsubstituted amides are not markedly basic.



Amidine (basic) Imidic ester (basic) Amide (not basic)

Thus it appears that the conversion of the two isomeric forms of an amidine (A and B) into salts may be represented as follows:



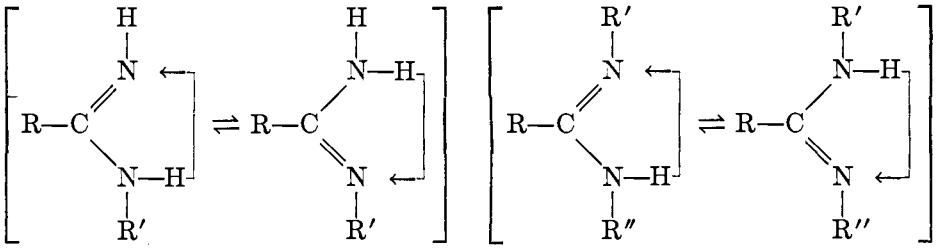
The two salts are thus identical, since the common ion is a resonance hybrid. From studies on the tautomerism of amidines, it might be concluded that resonance is likely in the salts of unsubstituted amidines and in those of the symmetrically disubstituted amidines having identical groups on the nitrogen atoms. It seems likely that one of the resonance forms postulated by Sidgwick should be partially stabilized when the two nitrogen atoms contain extremely unlike groups. In this connection mention should be made of the fact that the products obtained by the action of alkyl halides on amidines are salts and that Pyman always obtained two methylation products by the action of methyl iodide on amidines containing dissimilar groups (see page 383).

2. Physical properties

Tables of data on density and refractivities for some amidines are given by v. Auwers and Ernst (4).

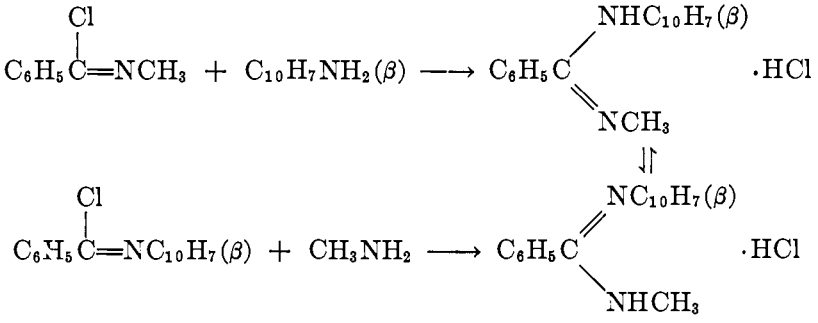
3. *Tautomerism*

A large amount of experimental evidence indicates that monosubstituted and symmetrical disubstituted amidines having different groups on the nitrogen atoms exhibit tautomerism. The mechanism of tautomerism is an intramolecular process involving proton addition and elimination.

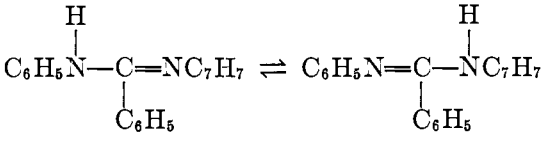


Supporting evidence for the existence of tautomerism lies in the fact that (*a*) a single amidine results from reactions designed to prepare the two isomerides, (*b*) the alkylation of an amidine yields two products, and (*c*) the hydrolysis of *N*,*N*′-substituted amidines produces a mixture of amides and amines.

Many authors have tried to synthesize the two isomers of a given amidine (21, 22, 30, 69, 93, 105, 106, 107), but a single substance was usually obtained. Thus, von Pechmann (106) did not obtain two different products by the following reactions for the preparation of the isomeric *N*-β-naphthyl-*N*′-methylbenzamidines:

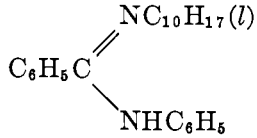


von Pechmann at one time reported the preparation of the two isomeric *N*-*p*-tolyl-*N*′-phenylbenzamidines (104), but it was later shown (93, 105) that the two products formed a mixture in tautomeric equilibrium, it being impossible to prove the location of the hydrogen atom in the triad system.

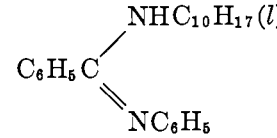


Cohen and Marshall (30) attempted to form the two tautomers (IX and X) of a disubstituted amidine by the introduction of optically active bornyl groups

into the molecule. They were unsuccessful, since the two products prepared by different methods of synthesis were identical in every respect.

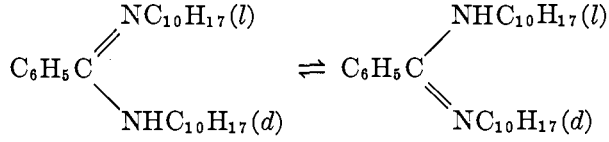


IX



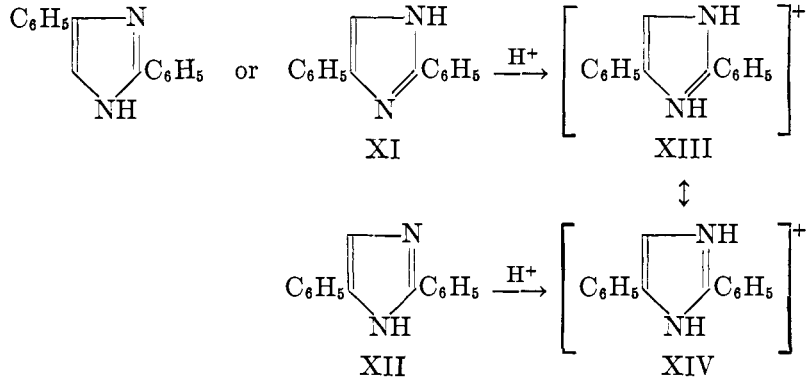
X

They also prepared *N*-*l*-bornyl-*N'*-*d*-bornylbenzamidine and demonstrated that the compound was an optically inactive meso form.



The *d*-camphorsulfonic acid salt of this amidine could not be separated into two forms by repeated recrystallization.

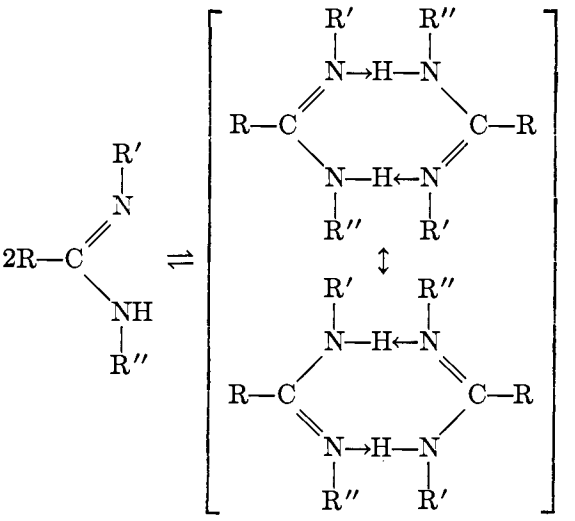
Burtles and Pyman (22) have isolated the two tautomeric forms of the cyclic amidines 2,4-diphenylimidazole (XI) and 2,5-diphenylimidazole (XII), and have demonstrated them to be different compounds by their physical characteristics. However, the isomers formed identical salts. A consideration of the proposed structures of the amidinium cation indicates that this fact is to be expected. Thus, the structures XIII and XIV may be resonance forms; or either one of the two may be a stable form; or both XIII and XIV may be unstable, each forming a single stable resonance hybrid.



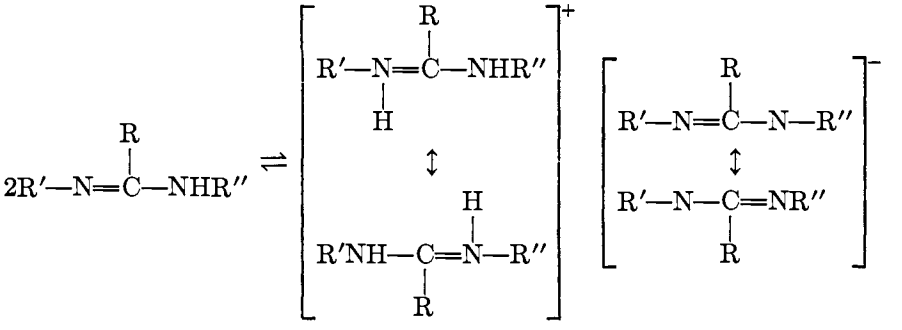
The above authors point out that the previous attempts of von Pechmann and others to synthesize the two isomeric forms of amidines have necessarily failed wherever the bases have been converted into their *salts*.

In neutral media it has been shown by Hunter and Marriott (64) that amidines containing a hydrogen on the nitrogen are associated to some extent.

This may be due to hydrogen-bonding, with resonance occurring in the dimer in a fashion similar to that observed with carboxylic acids: e.g.,

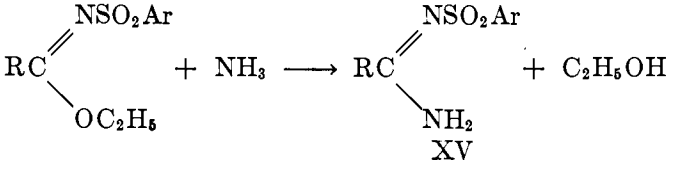


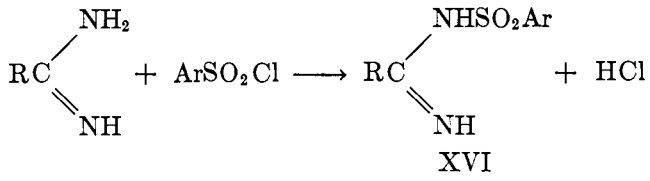
It is also possible that dimerization could involve salt formation with resonating cations and anions: e.g.,



Trisubstituted amidines are not associated.

The literature contains no authentic case of the isolation of two pure tautomeric forms of a mono- or di-substituted amidine. It seems that only a strong influence operating so as to immobilize the hydrogen atom could prevent protropy. Thus, Barber (8) was able to isolate the two forms of a substituted sulfonamidine (an amidine substituted with a highly electronegative group). Form XV could easily be converted into the stable form XVI.





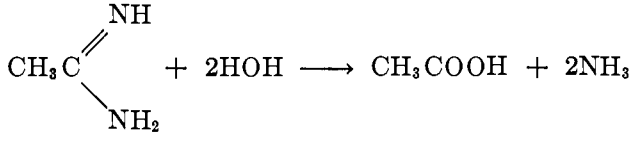
XVI

Barber based the above structures of these isomers on the hydrolytic products.

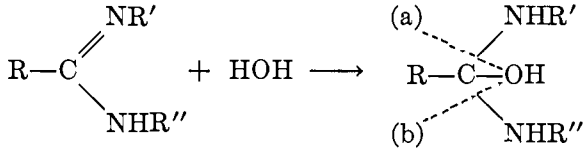
The fact that two monoalkylated products are obtained when certain amidines are heated with methyl iodide has been explained by the existence of tautomerism. Earlier workers (107) reported that only one methylated product was isolated; but Pyman (135) has demonstrated that in all cases *two* products were formed.

4. Hydrolysis

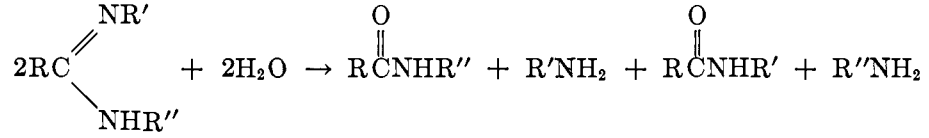
Amidines are characterized by their relative ease of hydrolysis. Those of the type $RC(=NH)NH_2$ react with water under milder conditions than do corresponding esters, nitriles, or amides. Thus, acetamidine forms acetic acid and ammonia when an aqueous solution is heated (109).

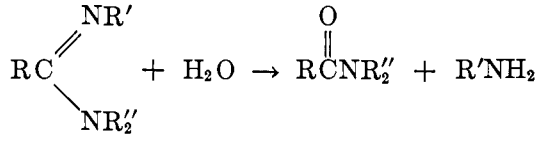


By a study of the products of hydrolysis, the structures of many amidines have been determined. Markwald (93) suggests the following reaction as the first step of hydrolysis:



Cleavage at (a) leads to the formation of $RCONHR''$ and $R'NH_2$; cleavage at (b) would form $RCONHR'$ and $R''NH_2$. In general, amidines can be hydrolyzed to amides and amines; the nature of the products can be illustrated as follows:

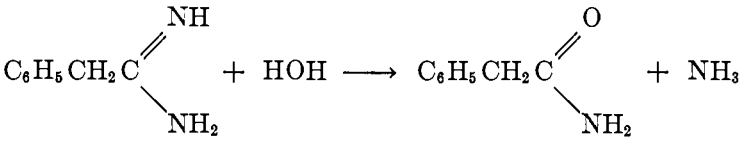




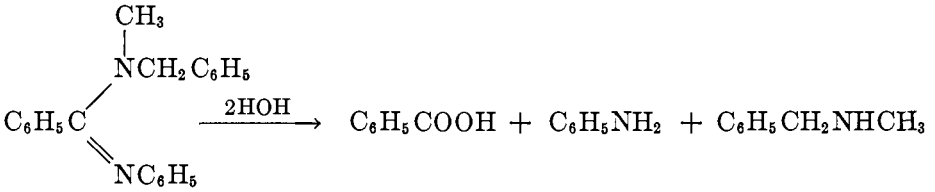
Dilute acid or alkali is usually employed as a catalyst to hasten the reaction. Alcohol (11) or other solvents are often used in the hydrolysis of high-molecular-

weight or insoluble amidines. The initial degradation forms the amide and amine; further breakdown of the amide into an acid and another amine depends upon the hydrolytic conditions. Thus, hydrolysis of *N*-phenylbenzamidine at 120°C. produced benzoic acid, aniline, benzanilide, and ammonia (91).

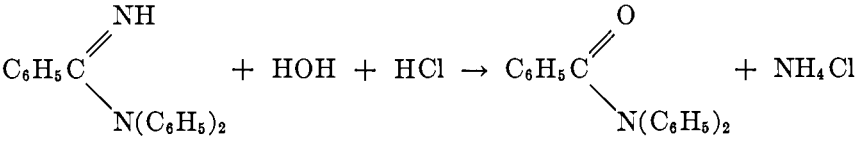
The ease of hydrolysis depends upon the molecular weight of the amidine as well as the degree of substitution on the nitrogen atoms. *α*-Phenylacetamidine forms the amide and ammonia when its aqueous solution is warmed.



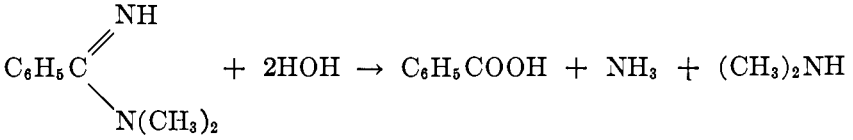
Beckmann and Fellrath (9) found it necessary to use concentrated hydrochloric acid at 200°C. for a period of 4 hr. to effect the following change:



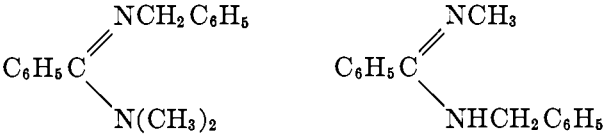
Bernthsen (12) hydrolyzed *N*,*N*-diphenylbenzamidine by using concentrated hydrochloric acid at 180°C. for several hours.



Pyman was able to hydrolyze *N*,*N*-dimethylbenzamidine by distillation with a 20 per cent solution of sodium hydroxide (135).



However, the following two amidines were stable to this treatment:



Wagner reports that steam distillation in absence of acid or alkali does not decompose symmetrical diarylformamidines appreciably, but that they are decomposed upon basic distillation (164). *N'*-Phenyl-*N*-methyl-*N*-benzyl-

benzamidine was recovered unchanged after heating to 150°C. with concentrated hydrochloric acid; it was necessary to maintain a temperature of 200°C. for 3 hr. to effect hydrolysis (9).

5. Alkylation

The alkylation of amidines in which one of the nitrogen atoms is attached to an aryl group and the other to a hydrogen or alkyl, yields as main products compounds which are alkylated on the arylamine nitrogen (27, 30, 134, 135, 177). Smaller quantities of the isomeric derivatives are also obtained.

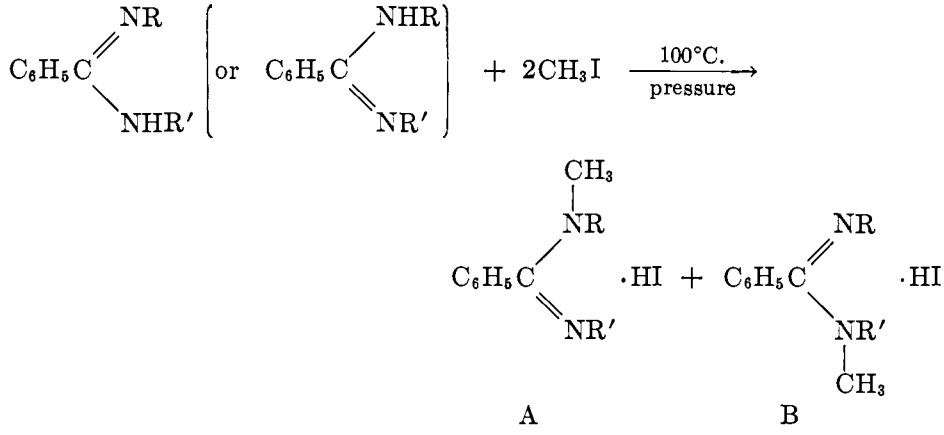
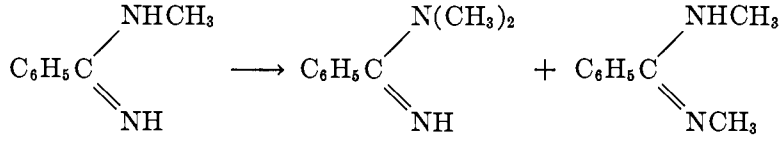


TABLE 1

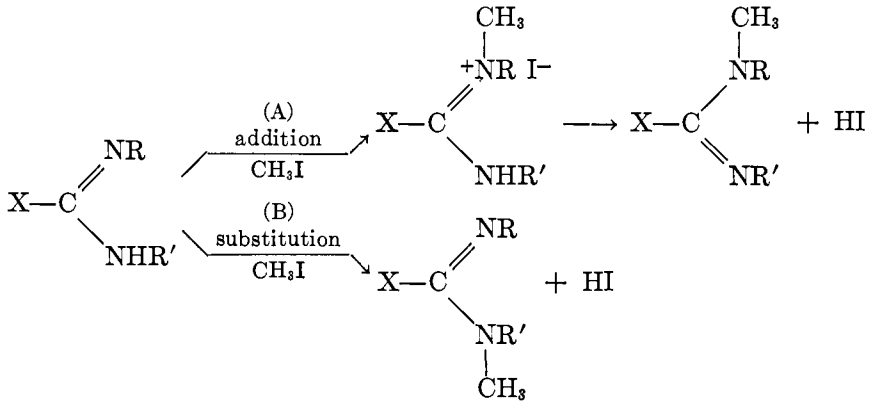
R	R′	RATIO OF A AND B FORMED (A:B)
C_6H_5	CH_3	15:1
C_6H_5	H	150:1
C_6H_5	$C_6H_5CH_2$	35:1

Pyman has illustrated these facts with the experimental evidence presented in table 1 (27, 134, 135). However, both *N*-phenyl-*N'*-*p*-nitrophenylbenzamidine and *N*-methylbenzamidine yield about equal amounts of alkylation on each nitrogen (27, 135).



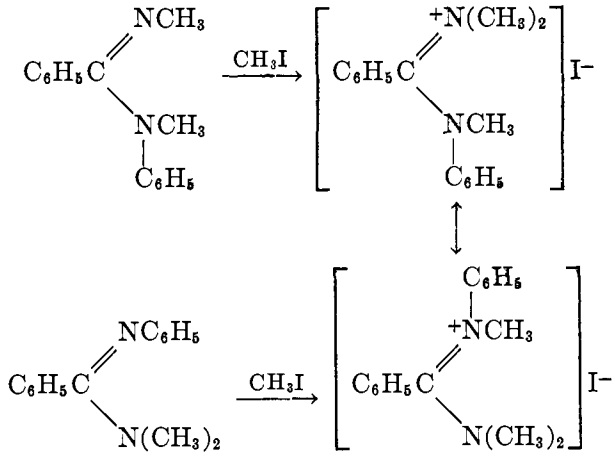
Pyman has considered the mechanism of the alkylation of amidines in an attempt to determine the position of the carbon-nitrogen double bond. The formation of two products could be due to the reaction of the amidine in two isomeric forms (RN=CX—NHR′ and RNH—CX=NR′), or to the reaction

of a single form which becomes methylated in two different ways—by direct addition to the tertiary nitrogen and by substitution of the imino group.



Wheeler (174), Young and Crookes (177), and Burtles and Pyman (22, 135) favor mechanism A, while von Pechmann (107), Cohen and Marshall (30), and Lander (86) favor B.

Pyman's choice of mechanism A was based on the results of experiments with open-chain amidines which did not contain a mobile hydrogen atom (135). Both *N*,*N*′-dimethyl-*N*-phenylbenzamidine and *N*,*N*-dimethyl-*N*′-phenylbenzamidine gave the same quaternary ammonium salt upon treatment with methyl iodide. These results are best explained by use of mechanism A.



The results illustrated in table 1 harmonize with the assumption that the relative yields depend on the polar characteristics of the groups R and R′. Thus, the phenyl group has a greater tendency to attract electrons and should therefore tend to stabilize the double bond at the phenylamine nitrogen atom; alkylation by the addition mechanism would then produce those derivatives actually obtained. Another tendency appears to be the effect of groups such as phenyl and carboxyl

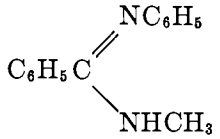
on the position of the double bond; examples are the well-known isomeric changes of β,γ- to α,β-unsaturated acids and of 1-phenyl-2-propene to 1-phenyl-1-propene.

An examination of table 1 shows that the relative basicities of the two amines RNH_2 and $R'NH_2$ are of secondary importance. Thus, the phenylamine nitrogen was alkylated to a greater extent than were the amine, benzylamine, and methylamine nitrogen atoms because of the position of the double bond. However, a study of the amounts of the secondary products in each case indicates that $C_6H_5C(=NC_6H_5)NR'CH_3$ is produced in greater proportion the stronger the basic strength of R'.

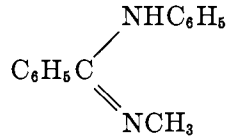
As a result of these studies, Pyman (135) concluded that:

". . . the interaction of open-chain amidines with alkyl salts leads to the attachment of the alkyl group to the nitrogen atom, which is doubly linked to carbon, and leads to the conclusion that the formation of two isomeric alkyl derivatives by the action of methyl iodide upon open-chain amidines is due to the reaction of the amidine in two isomeric forms."

If Pyman's conclusions are correct, *N*-methyl-*N'*-phenylbenzamidine reacts preferably in the form A rather than B.



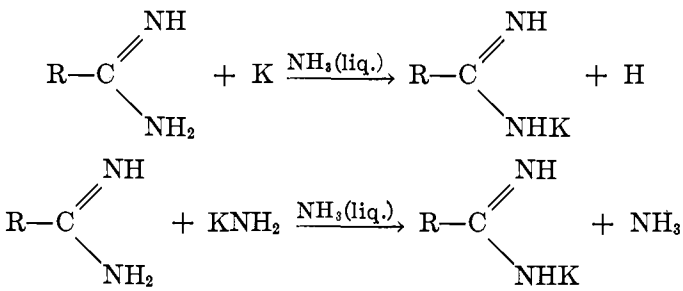
A



B

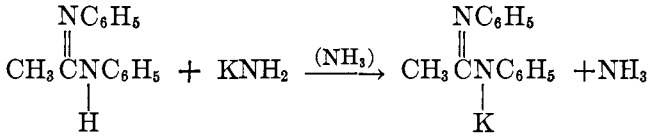
6. Amidines as carbazylic acids

Franklin (50) and Cornell (32) refer to amidines as carbazylic acids because they are, in the nitrogen system of compounds, analogous to carboxylic acids. Thus acetamidine is termed "ammonoacetic acid", and the various substituted amidines are considered as carbazylic acid esters. In a water solution amidines are far too weak to show acid properties, but in liquid ammonia these properties are clearly evident. Thus in the presence of liquid ammonia amidines react with the alkali metals and their amides to form metallic derivatives (10, 32, 50).

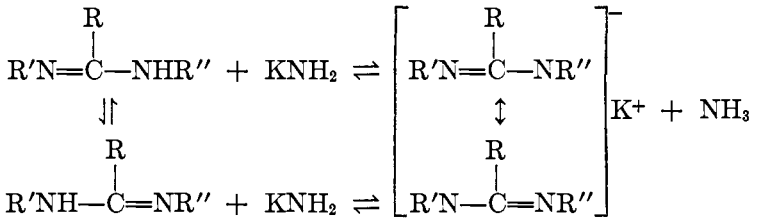


It is of interest to note that only one of the hydrogen atoms can be replaced by an alkali metal. Other metallic salts, such as the copper and silver salts, are usually formed from the potassium or sodium derivatives (32).

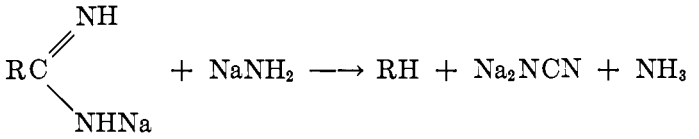
Substituted amidines react in a similar manner.



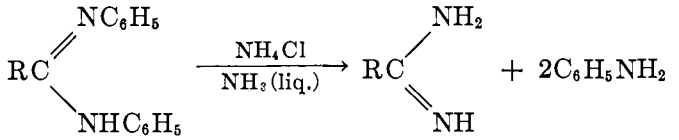
When dissimilar groups are attached to the nitrogen atoms it seems probable that the loss of a proton from the isomeric amidines results in resonating amidine *anions*.



The reaction of the metallic salts with water has been discussed in a previous section. Certain of the methods of preparing amidines also support the analogy of carbazylic acids to the carboxylic acids. A better analogy is found in the pyrogenetic decomposition of the carbazylic acid salts; thus, sodium salts of carboxylic acids may be fused with soda lime to produce hydrocarbons, and the alkali derivatives of amidines can be made to react as follows:



Substituted amidines are ammonolyzed by acid catalyst in the presence of liquid ammonia (98).

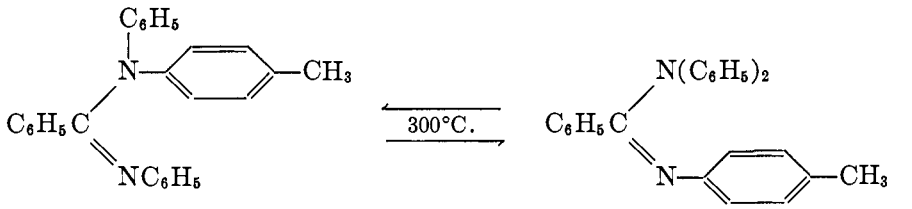


Wagner (164) has extended the analogy between amidines and carboxylic acids in a study of the closure of imidazole, pyrimidine, and oxazole rings.

7. *Effect of heat*

(*a*) *Rearrangement:* Chapman (24) discovered that amidines, when strongly heated below the decomposition point, can undergo a dynamic isomerism which involves mobile hydrocarbon radicals. *N*-Diphenyl-*N'*-*p*-tolylbenzamidine and *N*,*N'*-diphenyl-*N*-*p*-tolylbenzamidine decompose very slowly at 350°C. When the former is heated to 300°C., little change occurs; but when it is heated to 340°C. an equilibrium mixture of the two isomers is formed. An equilibrium was

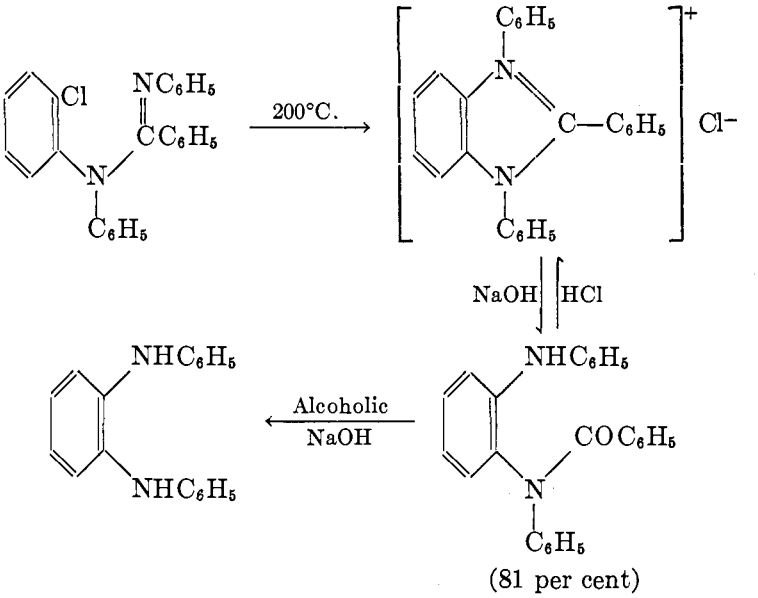
indicated because similar treatment of the latter compound produced the same mixture. According to Chapman the following equilibrium exists:



(60–65 per cent) (35–40 per cent)

This change requires much more drastic conditions than does the migration of the proton in the case of RC(=NR′)NHR″. The above proportions hold only if the groups are all similar, i.e., probability is the chief factor involved. The rearrangement was shown to be *intramolecular*, and the nature of the migrating group was found to exert very little influence on the equilibrium.

(*b*) *Ring closure:* In the course of the work on the rearrangement of amidines, Chapman and Perrott (25) discovered an interesting ring-closure reaction. Thus *N*,*N*′-diphenyl-*N*-*o*-chlorophenylbenzamidine is transformed into 1,2,3-triphenylbenzimidazolium chloride upon heating to 200°C.

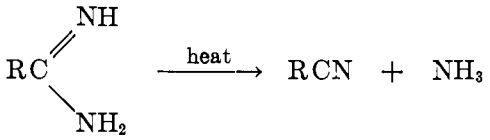


(81 per cent)

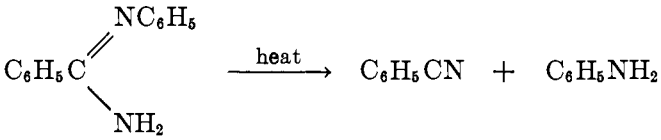
The structure of the benzimidazolium chloride was proven by its synthesis from the monobenzoyl derivative of *N*,*N*′-diphenyl-*o*-phenylenediamine. Likewise, treatment of the benzimidazolium salt with alkali produced the benzoyl derivative of the substituted *o*-phenylenediamine. Since stronger hydrolysis with alcoholic sodium hydroxide yielded *N*,*N*′-diphenyl-*o*-phenylenediamine, the authors deem it likely that these reactions will furnish a convenient method

for the preparation of substituted disecondary *o*-phenylenediamines of known constitution.

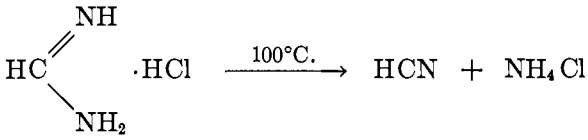
(*c*) *Pyrolysis:* Unsubstituted amidines decompose when strongly heated to form ammonia and the corresponding nitrile; under the conditions of pyrolysis, the resulting nitrile often polymerized to yield additional products (109).



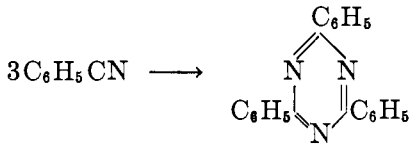
Substituted amidines decompose to produce similar products; thus, the destructive sublimation of *N*-phenylbenzamidine causes the formation of benzonitrile and aniline (11).



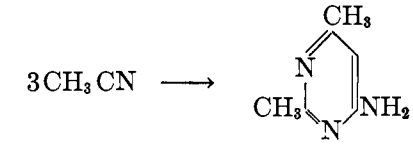
Formamidine hydrochloride decomposes at the relatively low temperature of 100°C., with the formation of hydrogen cyanide and ammonium chloride (54).



One of the secondary decomposition products that can be obtained from benzamidine is cyaphenine (2,4,6-triphenyl-1,3,5-triazine) (50), which is formed by trimerization of benzonitrile:



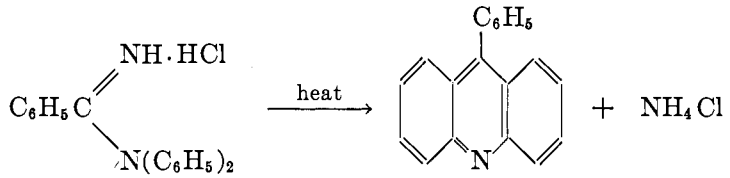
If an aliphatic nitrile is produced by pyrolysis of the amidine, a cyanalkine may be obtained by trimerization: e.g.,



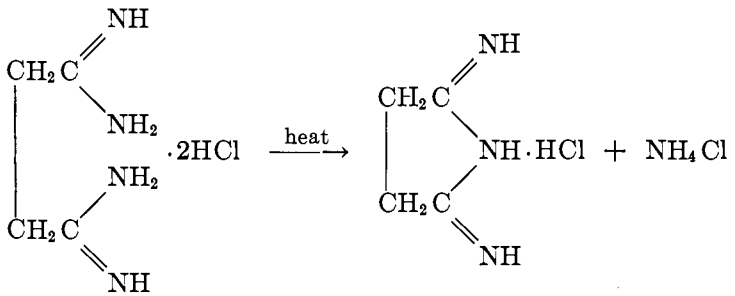
Pinner found (109) that, in the presence of acetic anhydride, amidines could be caused to decompose into the dialkylaminopyrimidines.

Other products may also be formed from the pyrolysis of amidines. Thus

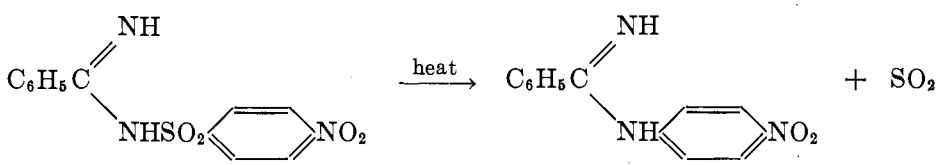
the expected breakdown products of *N*,*N*-diphenylbenzamidine are diphenylamine and benzonitrile. Bernthsen was able to isolate, besides these, a small yield of 10-phenylacridine by heating the hydrochloride at 240–250°C. for 6 hr. (12, 13).



Pinner reported (109, 110) that succinamidine dihydrochloride was converted to the imidine hydrochloride during an attempt at recrystallization from water.



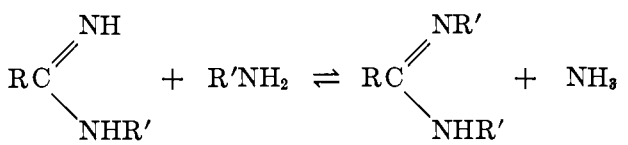
In 1943 Barber (8) reported that a sulfonyl derivative of an amidine decomposed upon heating as follows:



Barber proposes the term *desulfoxylation* for the above type of decomposition and states that the reaction proceeds smoothly.

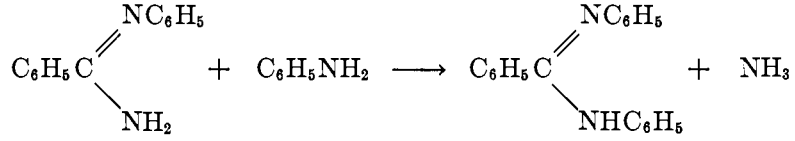
8. Ammonolysis with ammonia and amines

The existence of the following type of equilibrium at higher temperatures has been mentioned previously (109):

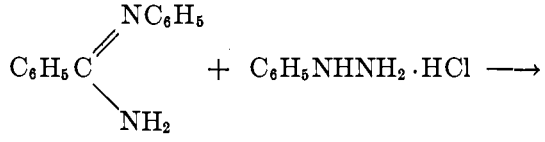


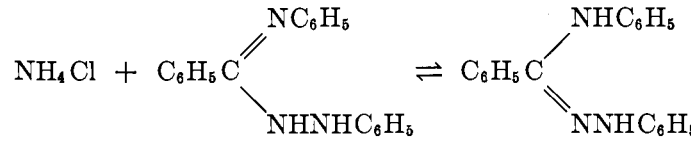
Thus by employing an excess of ammonia, Niemann (98) was able to prepare unsubstituted from substituted amidines.

Bernthsen (11) was able to convert *N*-phenylbenzamidine to *N*,*N'*-diphenylbenzamidine by heating with an excess of aniline at 250°C.

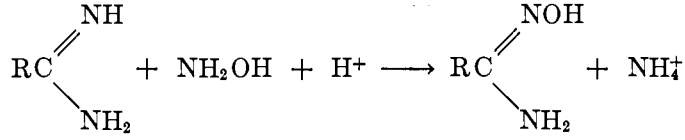


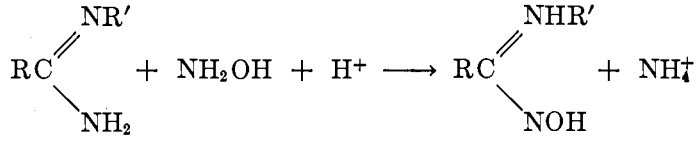
Other derivatives of ammonia have been employed to effect the same type of reaction. Monoaryl-substituted benzamidines have been treated with phenylhydrazine hydrochloride to yield similar products (106, 172); e.g.,



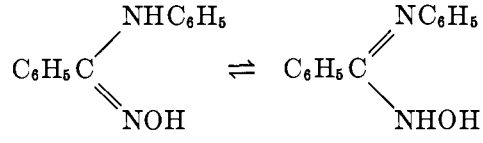


Hydroxylamine reacts with amidines in the presence of acid to form amidoximes (91, 97, 109, 172).





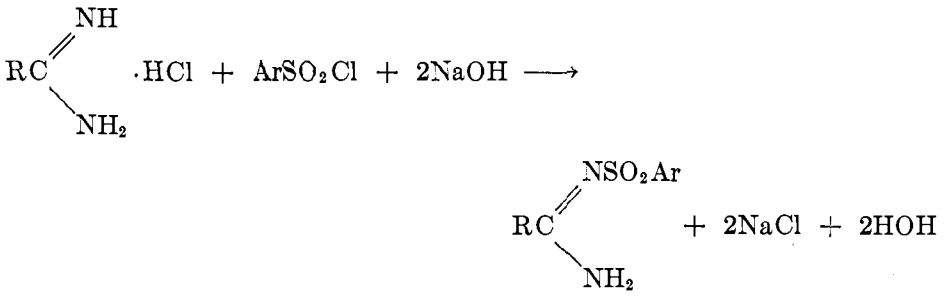
H. Muller (97) has pointed out that amidoximes can be represented by two tautomeric structures, since they are soluble in both acid and alkali.



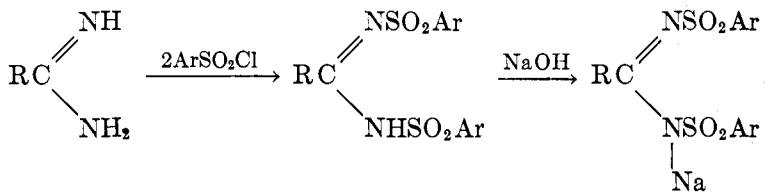
9. Action of acid chlorides

Amidines can be caused to react with compounds containing active halogen atoms, with the elimination of halogen acid. Probably one of the better reagents to use for the preparation of derivatives of amidines is an arylsulfonyl chloride.

The amidine is treated, as in the Hinsberg reaction, with the acid chloride at or below room temperature in a neutral or alkaline medium (8, 72, 84, 99).

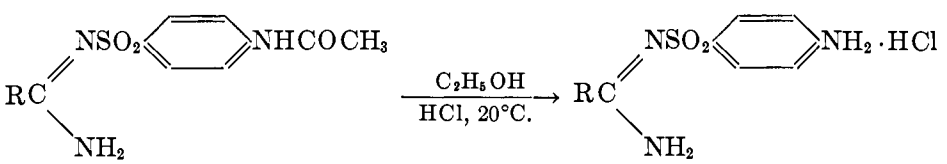


Carrying out the reaction in acetone, Kwartler and Lucas (84) were able to obtain yields of 51–59 per cent when R was alkyl or aryl. Both *mono-* and *bis*-sulfonamidines may be formed, the proportion varying with the amount of the sulfonyl chloride used in excess and with the temperature (99). The two types of products can be separated easily, since only the latter are soluble in alkali.

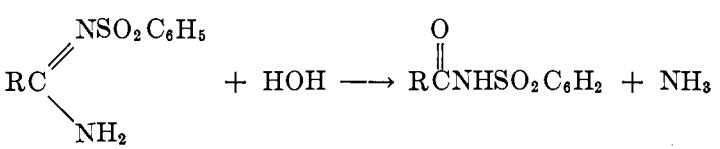


Barber and Newberry (8) found that the use of sodium hydroxide gave excellent yields, an acetone solution or suspension being employed; the use of pyridine resulted in poorer yields, probably because the unsubstituted amidines were stronger bases than pyridine.

Since many amidines are easily hydrolyzed, the reaction must be carried out at or below room temperature. The sulfonamidines are not hydrolyzed as easily; thus mild hydrolytic conditions will produce the following change (8, 84):



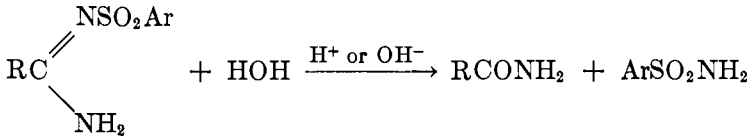
But under more drastic treatment, they will react as follows (8):



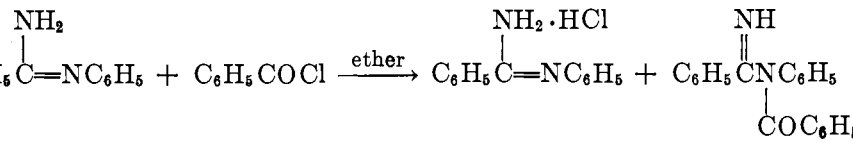
It has been mentioned previously that tautomerism is possible in the sulfonamidine series. Thus Barber (8) was able to isolate the two isomeric forms XVII and XVIII.

XVII XVIII

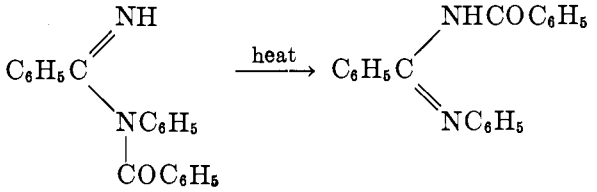
From a study of the products of hydrolysis, XVIII appeared to be the more stable form. However, Northey, Pierce, and Kertesz (99) concluded that the sulfonamidines could be represented better by XVII, since their compounds did not form alkali salts and because of the nature of the products obtained from hydrolytic cleavage.



Several workers have reported the preparation of acyl derivatives of monosubstituted amidines (90, 172, 176, 100). Substituted benzamidines and acetamidines have been used; aromatic and aliphatic acid chlorides were employed as the acetylating agents. Wheeler, Johnson, and McFarland (176) report the formation of *N*-phenyl-*N*-benzoylbenzamidine.

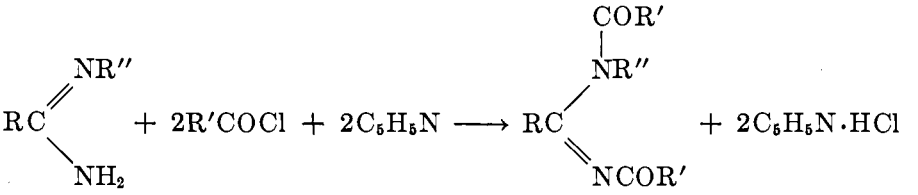


The latter underwent a molecular rearrangement upon standing or upon recrystallization from hot alcohol to form the more stable substance, *N*-phenyl-*N'*-benzoylbenzamidine.

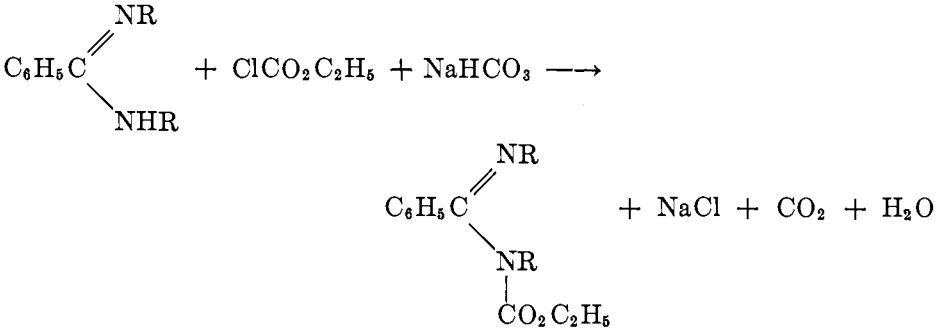


Hydrolysis of the former substance produced benzamide and benzanilide, whereas similar treatment of the latter produced *N*-benzoylbenzamide. No conclusions could be drawn from the results, since treatment of *N*-phenylbenzamidine with acetyl chloride produced *N*-phenyl-*N'*-acetylbenzamidine and the more stable *N*-phenyl-*N*-acetylbenzamidine.

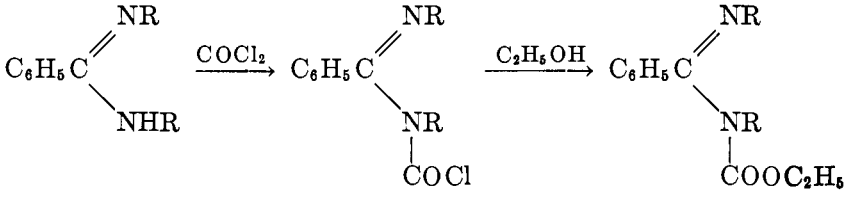
Walther and Grossmann (172) and the above authors (176) observed that diacyl derivatives are obtained when the reaction is carried out in the presence of pyridine.



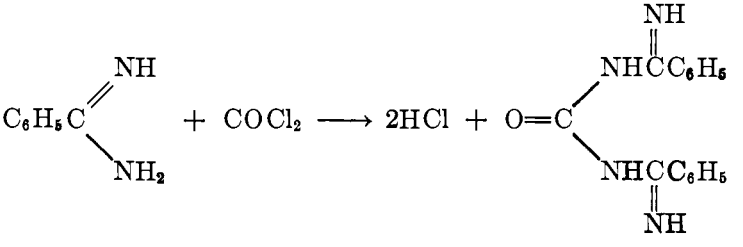
Pinner (109, 120) has reported that benzamidine and ethyl chloroformate react to form *N*-carbethoxybenzamidine. Joshi, Khanolkar, and Wheeler (70) used symmetrical disubstituted amidines and reported that the reaction proceeds smoothly when carried out in the presence of sodium bicarbonate at 20°C.



The same carbethoxy derivative was obtained by the following sequence of reactions:

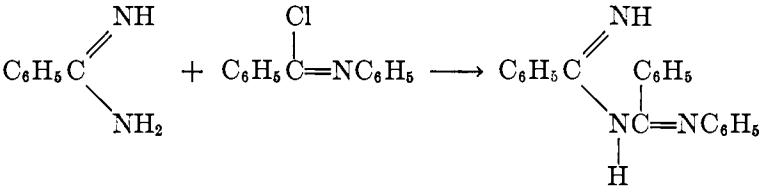


On the other hand, the reaction of benzamidine with phosgene proceeds in accordance with the following equation (109, 120):



The product, however, can be decomposed readily by heat to form a triazine derivative.

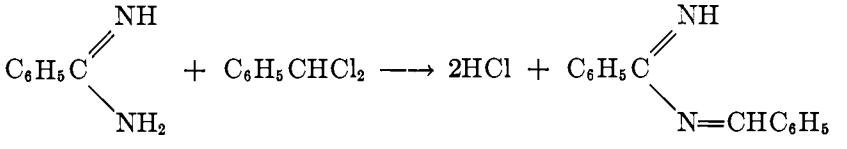
An interesting reaction is that between benzamidine and *N*-phenylbenzimidyl chloride (87).

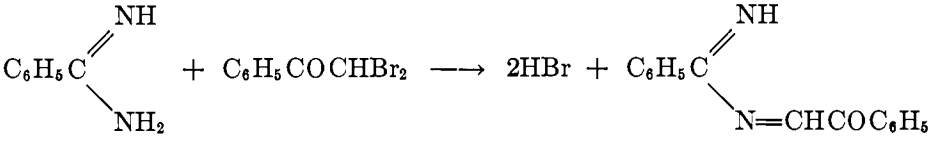


10. Reactions with other active halogen compounds

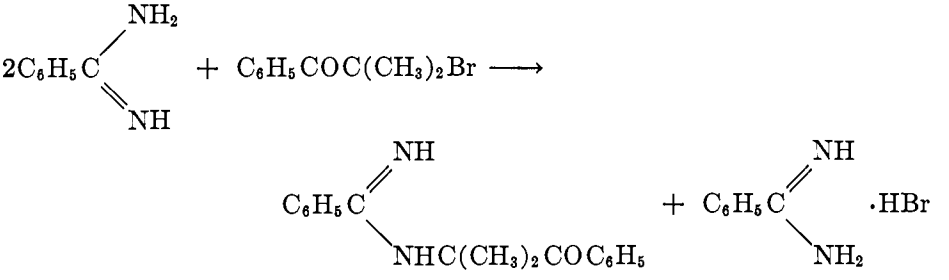
The reaction of picryl chloride and amidines (172) has been discussed in the section on the preparation of unsymmetrical disubstituted amidines.

Both benzal chloride and α,α-dibromoacetophenone react with benzamidine in a like manner (80, 81).

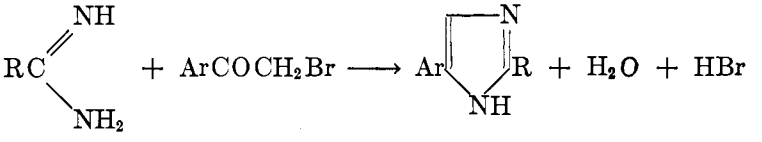




When α-bromo-α,α-dimethylacetophenone is allowed to react with benzamidine in a chloroform solution a substituted amidine is produced (80).



However, when alpha hydrogen atoms are present, a further reaction takes place in the formation of a substituted imidazole (80).

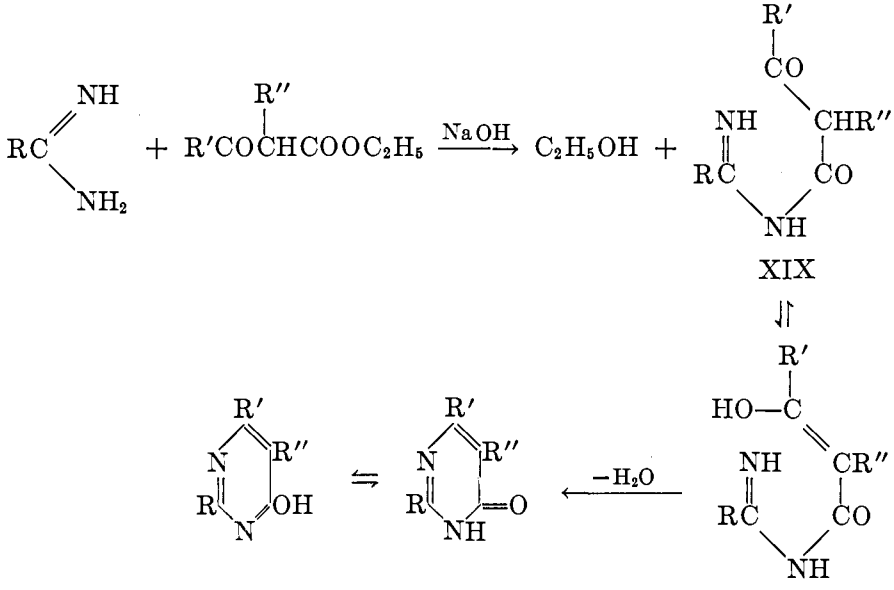


11. The formation of substituted pyrimidines

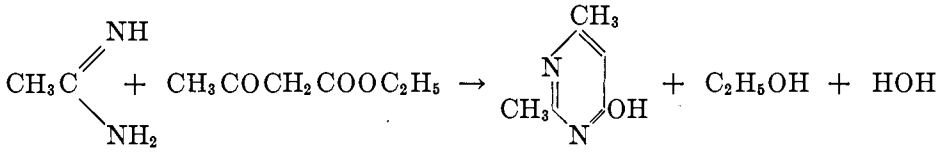
Perhaps the most important use of amidines in the field of synthetic chemistry is the synthesis of substituted pyrimidines. Unsubstituted amidines can be made to react with β-ketonic esters, α-formyl esters, other compounds containing β-dicarbonyl groupings, malonic esters, α-cyanonitriles, cyanoacetic esters, α,β-unsaturated carbonyl groups, and ethoxymethylene derivatives of the aforementioned classes to form pyrimidines. Thus many pyrimidines have been prepared which contain the following groups as substituents in the ring: hydroxyl, alkyl, aryl, cyano, amino, nitro, phenylazo, bromo, chloro, acetyl, carbethoxy, and carbethoxymethyl. In one case a benzopyrimidine was prepared, and several substituted dihydropyrimidines have been reported in the literature.

The reactions are usually carried out by allowing the reactants to stand at room temperature in the presence of an alkali hydroxide, potassium carbonate, or sodium ethoxide and ethanol. When compounds containing an α,β-unsaturated carbonyl group are used, the mixture is often heated to effect the reaction.

(*a*) *From β-ketonic esters:* According to Pinner (109, 114) the reaction between a β-ketonic ester and an amidine takes place as follows:



The intermediate (XIX) is often isolated as a by-product. Thus 2,6-dimethyl-4-hydroxypyrimidine can be prepared by the reaction of acetamidine and ethyl acetoacetate.



Pinner (109) has stated that formamidine will not form a pyrimidine under the same conditions; otherwise R may be either alkyl or aryl.

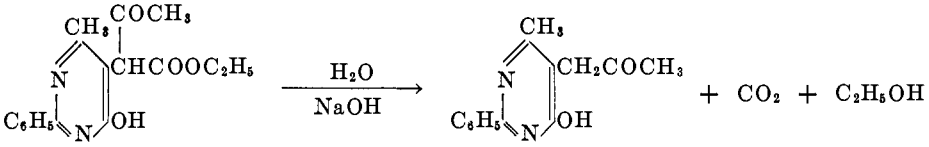
The wide applicability of this method can be seen by an inspection of table 2.

Pinner (123) attempted to carry out the same type of reaction with ethyl salicylate, because of its similarity to acetoacetic ester, but the product isolated

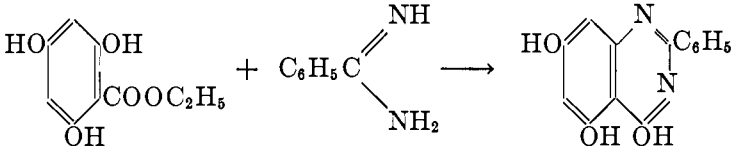
TABLE 2

R′	R″	REFERENCES
$-CH_3$	$-H$	(52, 109, 114)
$-COOC_2H_5$	$-H$	(116)
$-H$	$-H$	(53)
$-CH_2COOC_2H_5$	$-H$	(127)
$-CH_3$	$-CH_2COOC_2H_5$	(117)
$-CH_3$	*$-CHCOOC_2H_5$ | $COCH_3$	(117)
$-CH_3$	*$-COOC_2H_5$	(109, 117, 118)

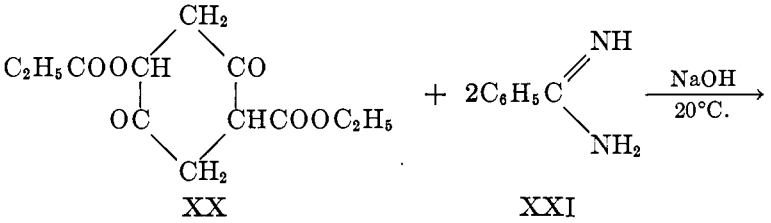
* The pyrimidines isolated in these cases did not contain the expected carbethoxy group; this is not surprising, since it is known that β-ketonic esters are easily cleaved by alkali, e.g.:



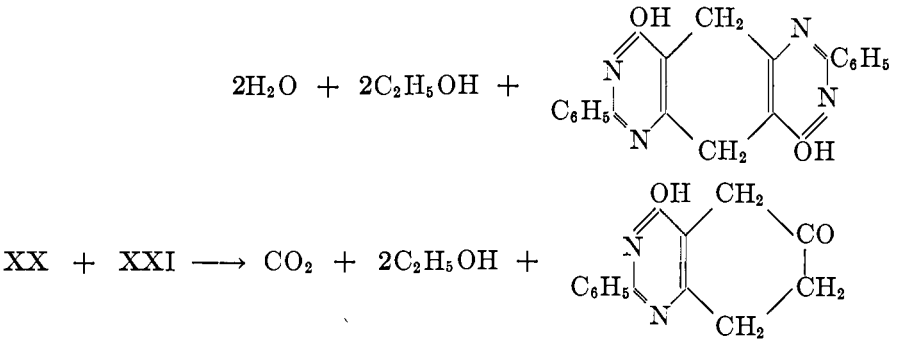
was not a pyrimidine. However, with carbethoxyphloroglucinol, a substituted benzopyrimidine was obtained.



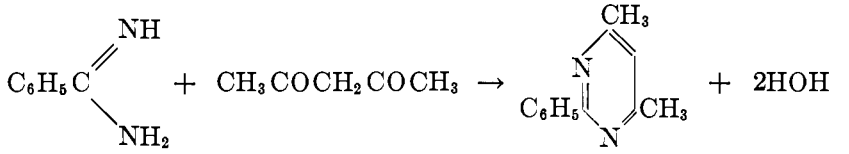
An interesting extension of the reaction is that employing a cyclic β-ketonic ester, 2,5-dicarbethoxy-1,4-cyclohexadione. Two products are obtained according to the following reactions (117):



XX XXI

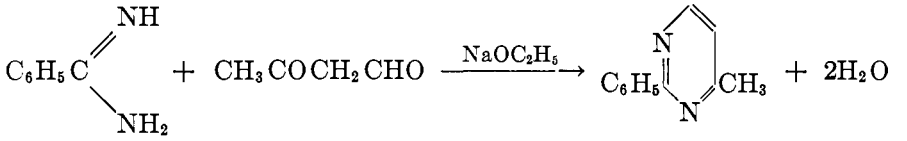


(*b*) *From β-dicarbonyl groupings:* Pinner (126) and others (52) have prepared 2-phenyl-4,6-dimethylpyrimidine by the action of benzamidine on acetylacetone in the presence of bases.

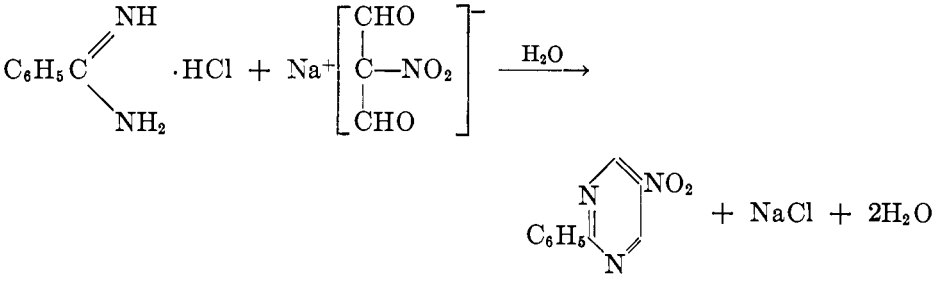


4,6-Dimethylpyrimidine is the end product when formamidine hydrochloride is used (52).

Pinner caused benzamidine to condense with the sodio derivative of formylacetone, prepared by treating acetone and ethyl formate with sodium ethoxide, to form a disubstituted pyrimidine.

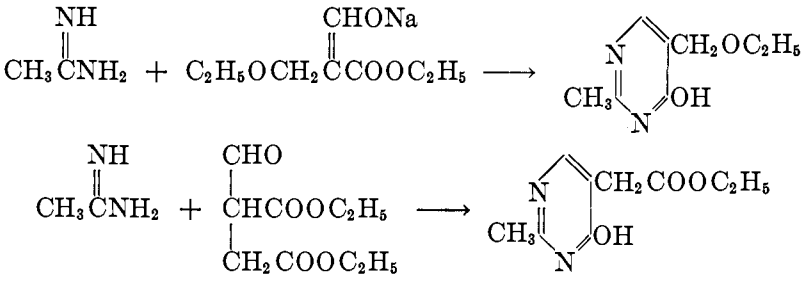


Hale and Brill prepared 2-phenyl-5-nitropyrimidine in a similar manner (57).

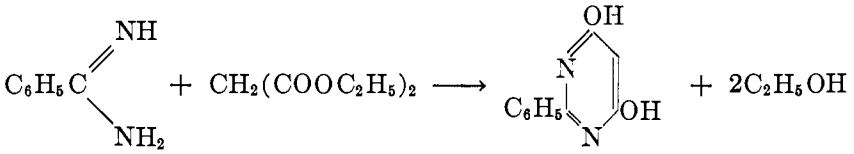


The first step in one of many syntheses of thiamin involves the condensation of acetamidine with the sodium derivative of ethyl α-formyl-β-ethoxypropionate to produce 2-methyl-4-hydroxy-5-ethoxymethylpyrimidine (137). Another

variation uses the condensation of the amidine with ethyl formylsuccinate (2, 66).

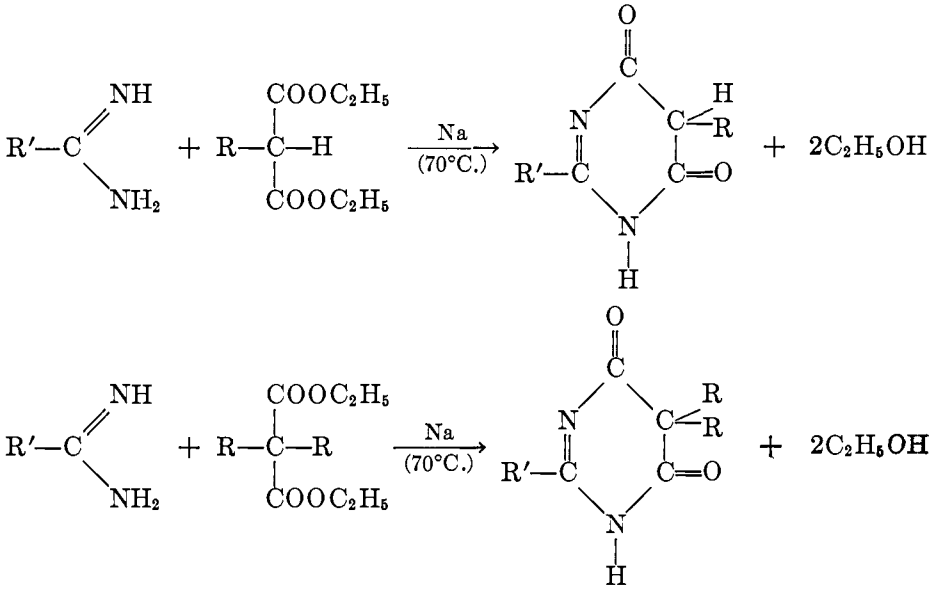


(*c*) *From malonic esters:* Pinner (113, 133) obtained a 50 per cent yield of 2-phenyl-4,6-dihydroxypyrimidine by working up a mixture of benzamidine, diethyl malonate, and sodium ethoxide which had been kept at room temperature for 2 days. When potassium hydroxide was used as the condensing agent, the yield was lowered to 10 per cent.

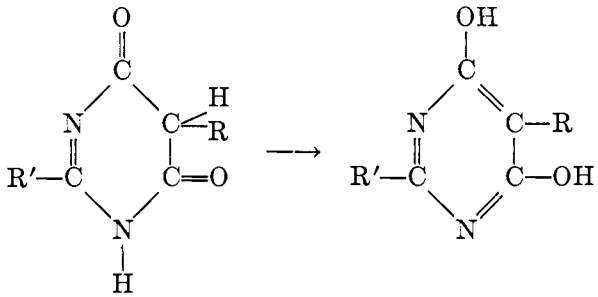


Kenner *et al.* (82) have shown that formamidine and other aryl and aliphatic amidines react in a similar fashion. Ruhemann (143) has used diethyl chloro- and bromo-malonates to form the 5-chloro- and 5-bromo-pyrimidines.

Dox and Yoder (42) have proposed this reaction as a test for the detection of monoalkylated malonic esters in the presence of dialkylated derivatives.

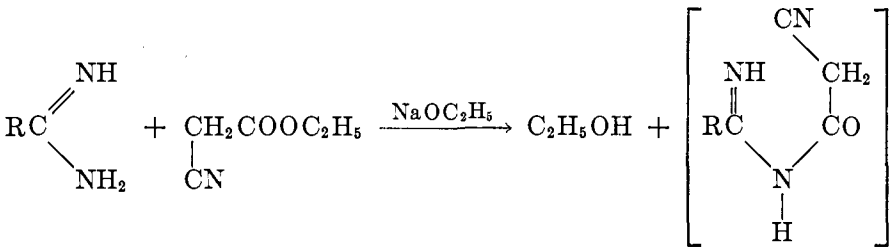


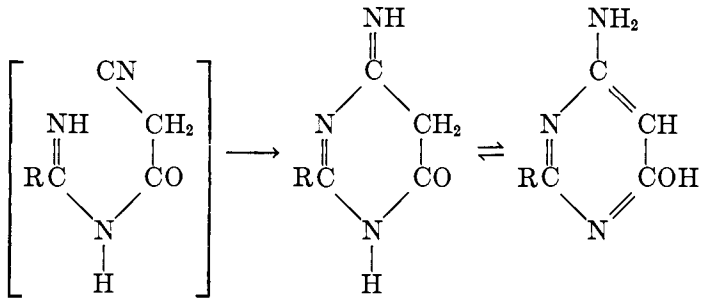
The substituted pyrimidones derived from the dialkylated malonic esters are colorless and soluble in neutral solvents; those derived from the monoalkylated derivatives are yellow-orange and insoluble. The authors suggest that the color is due to the enolic structure which is possible only in those compounds derived from the monoalkylated malonic esters.



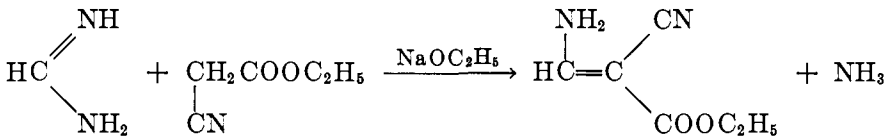
(colored)

(*d*) *From cyano esters:* In 1904 Traube and Herrmann (162) demonstrated that both acetamidine and benzamidine react with ethyl cyanoacetate in the presence of sodium ethoxide to form substituted aminopyrimidines.

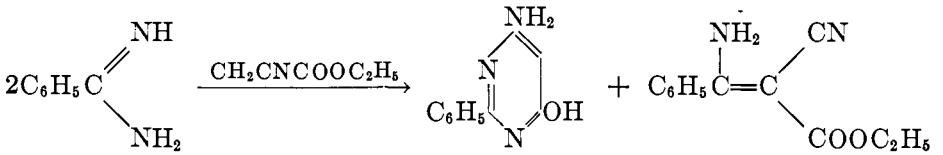




Further studies on this reaction showed that formamidine hydrochloride does not react to produce a cyclic compound, but instead gives good yields of the following product (71).

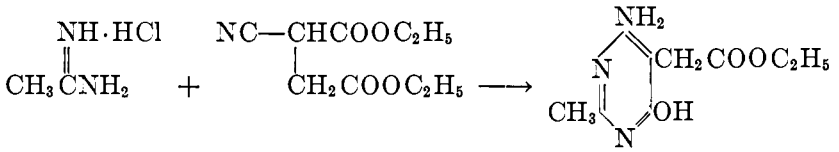


In the absence of sodium ethoxide, benzamidine will react to form two products.

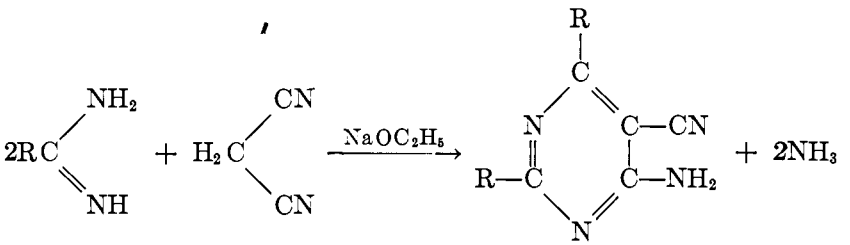


But in the presence of sodium ethoxide, the pyrimidine is the main product.

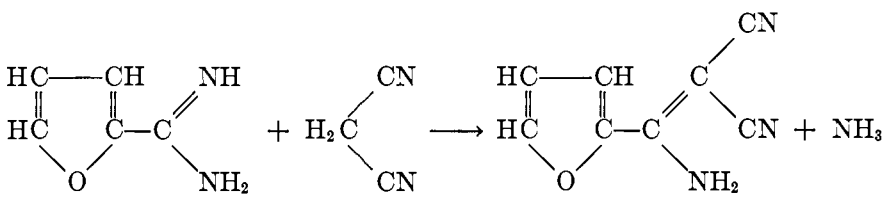
Ethyl cyanosuccinate condenses with acetamidine hydrochloride to produce the ethyl ester of 2-methyl-4-amino-6-hydroxypyrimidine-5-acetic acid (67), which is a possible intermediate in a synthesis of thiamin. A related condensation is the combination of acetamidine with ethyl α-cyano-β-ethoxypropionate to produce 2-methyl-4-amino-5-carbethoxypyrimidine (73).



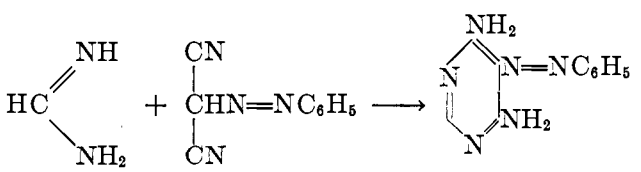
(*e*) *From malononitrile*: Amidines also react with malononitrile in the presence of sodium ethoxide to form pyrimidines (5, 71).



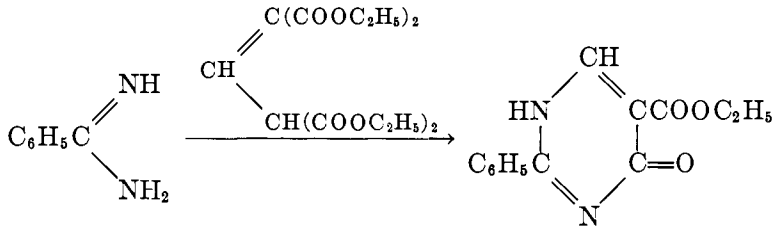
In the case when formamidine was used, the yield was 45 per cent. Both aromatic and aliphatic amidines yield the pyrimidine; however when furamidine was used, the following reaction took place:



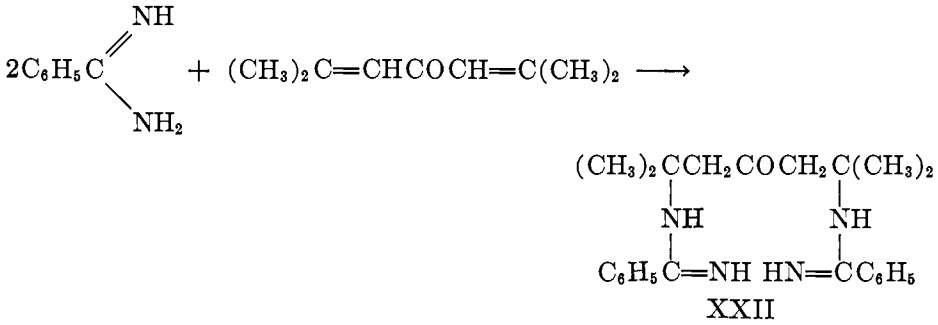
α-Phenylazomalononitrile has also been used to form a substituted pyrimidine.



(f) From unsaturated carbonyl compounds: In 1897 Ruhemann (142) reported the preparation of a phenylcarbethoxypyrimidine from benzamidine and diethyl 1,3-dicarbethoxyglutaconate by heating the two at 100°C. in the presence of sodium and ethyl alcohol.

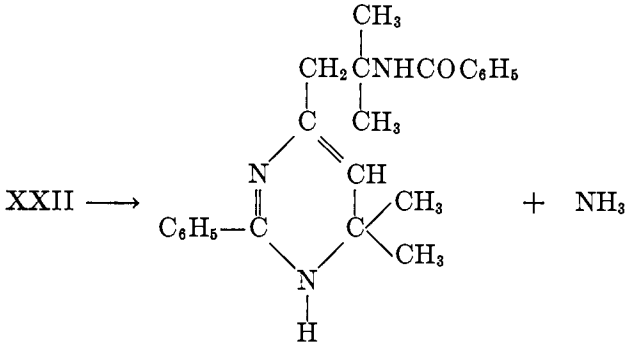


Traube and Schwarz (163) have attempted to carry out the above type of reaction using unsaturated ketones and aldehydes such as benzalacetone, acrolein, and cinnamaldehyde. Although these compounds reacted vigorously, no crystalline products could be isolated. When mesityl oxide and phorone were used, analytically pure products could be isolated.



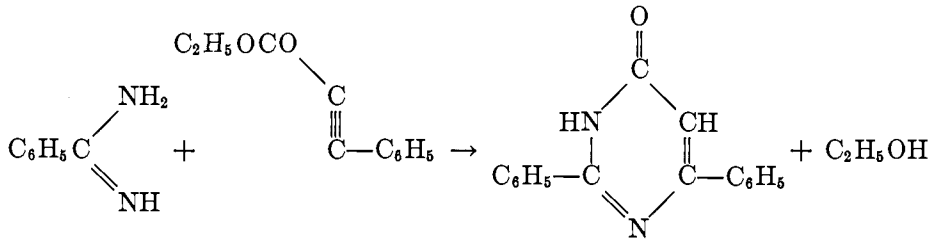
XXII

Further heating of the triacetone dibenzamidine produced a substituted dihydropyrimidine.

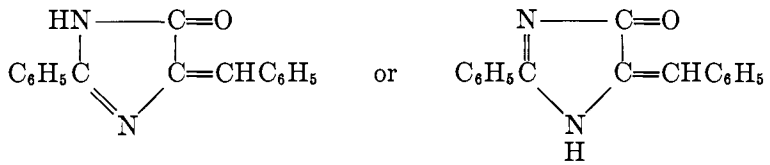


A similar equation can be written for the reaction between benzamidine and mesityl oxide; the product formed is substituted in the 6-position by a methyl group.

By allowing benzamidine and ethyl phenylpropiolate to react in the presence of sodium ethoxide at 100°C., a diphenylpyrimidine is formed (147).



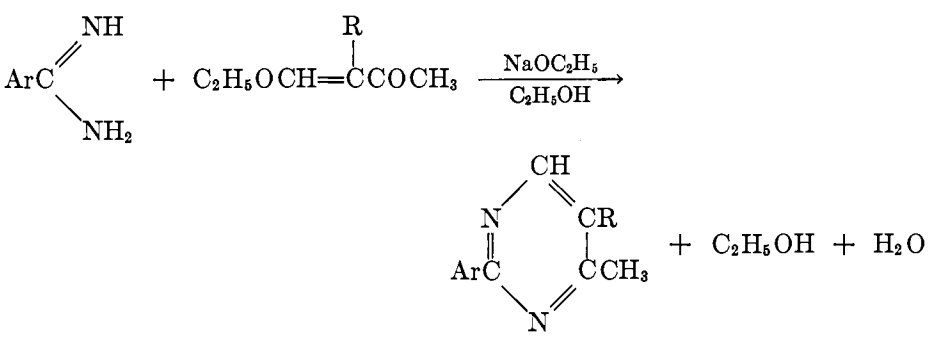
If the reaction is carried out at 20°C., a compound containing a five-membered ring is formed. According to Ruhemann and Cunnington, the compound has one of the following structures (146):



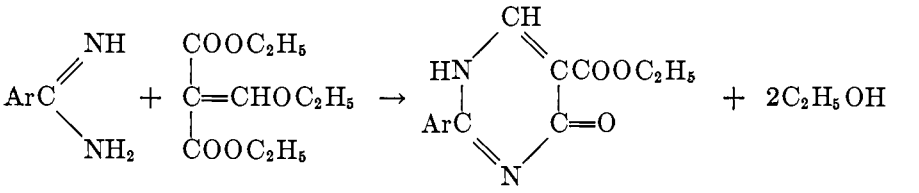
Ruhemann has studied the reaction of various compounds containing α,β-unsaturated carbonyl groupings (143, 144, 145) with benzamidine; in each case a substituted pyrimidine was formed: diethyl benzalmalonate, ethyl benzalacetoacetate, benzylideneacetylacetone, etc. were used.

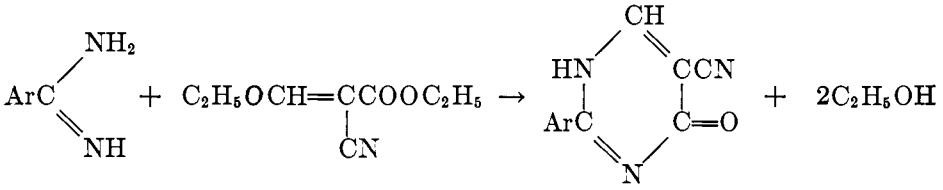
Various mechanisms have been proposed for the formation of the cyclic compounds from the reaction of an amidine with an unsaturated carbonyl compound, but none of them have been proven. It is interesting to observe that the formation of the pyrimidine derivatives mentioned in these references could be explained by a mechanism involving a 1,4-addition, commonly associated with compounds containing an α,β-unsaturated carbonyl group.

Mittler *et al.* (96) have studied the condensation of amidines with ethoxymethylene derivatives of β-ketonic esters, β-diketones, and cyanoacetic ester and found that substituted pyrimidines were produced. The following equations represent the extent of the work:

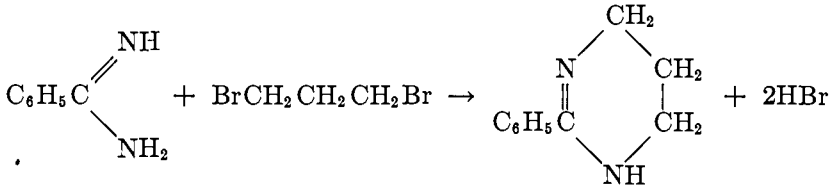


R = $-COCH_3$ or $-CO_2C_2H_5$



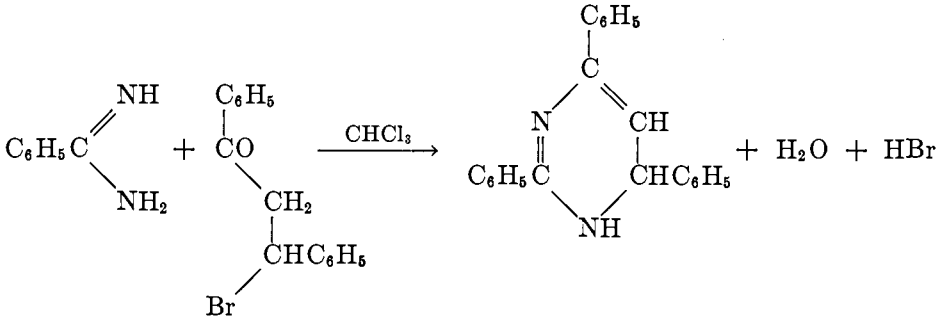


(*g*) *Miscellaneous:* Pinner obtained 2-phenyl-3,4,5,6-tetrahydropyrimidine by the alkylation of benzamidine with trimethylene bromide (126).

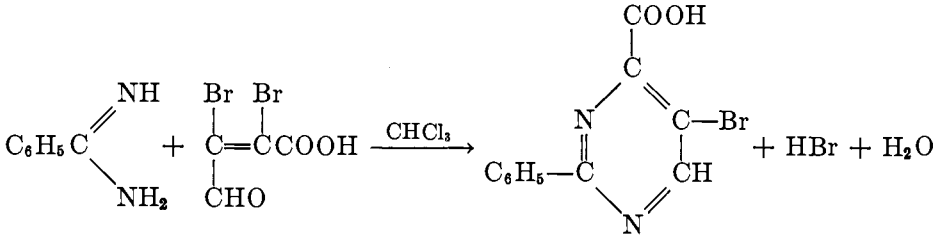


Pinner also reported the formation of 2,4-dimethyl-6-acetylaminopyrimidine by the thermal decomposition of acetamidine in the presence of sodium acetate and acetic anhydride (115).

Kunckell and Sarfert (83) utilized a β-bromoketone in synthesizing a dihydropyrimidine.

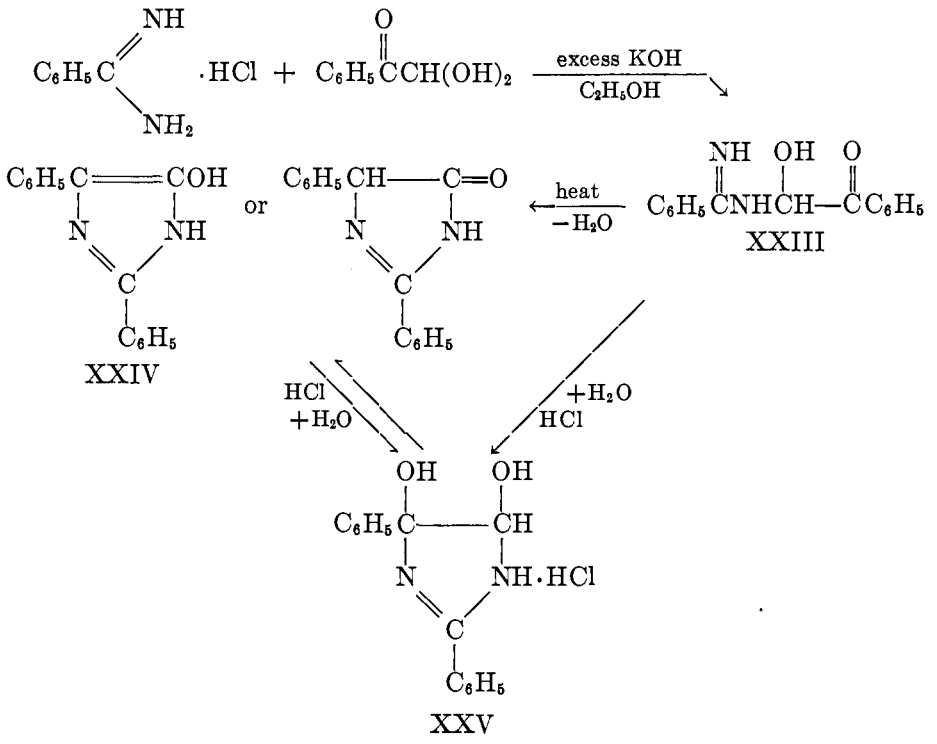


Kunckell and Zumbusch (82) reported the following reaction:



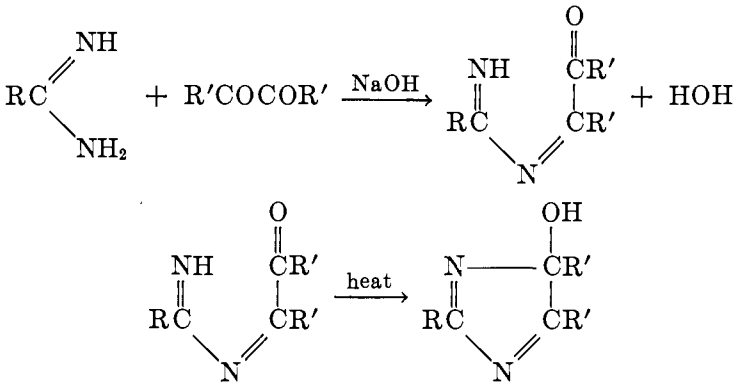
12. Formation of imidazoles and imidazolones

Kunckell has obtained an imidazole by treating an amidine with α-bromoacetophenone (80), and Ruhemann and Cunnington (146) demonstrated the formation of benzalimidazolone from the action of ethyl phenylpropiolate on benzamidine. Ekeley has studied the reaction between 1,2-dicarbonyl compounds and amidines (45, 46, 47, 173). Thus, when benzamidine hydrochloride and phenylglyoxal hydrate are caused to react in the cold and in the presence of an excess of base (potassium hydroxide), an addition product (XXIII) is formed (173). When the basic solution of this addition compound is heated, a cyclization occurs with the formation of an imidazolone (XXIV). When either compound XXIII or compound XXIV is treated with an excess of hydrochloric acid, a third compound (XXV) is formed which is very unstable in the absence of acids. These relationships are indicated by the following equations:

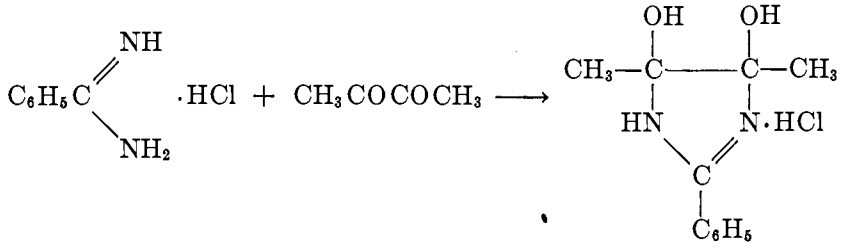


J. O. Cole (31) obtained 70 per cent yields of compound XXIV when aliphatic amidines were used. Cole also reports that a very complex mixture of compounds is obtained when only enough base is used to neutralize the hydrochloride.

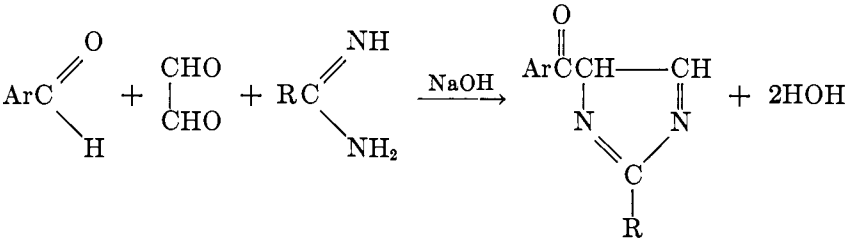
From experiments with aliphatic and aromatic 1,2-diketones Pinner (109) concluded that the following reactions were general for these types of compounds:



Diels and Schleich (40) concluded that the following reaction between benzamidine hydrochloride and diacetyl probably takes place:

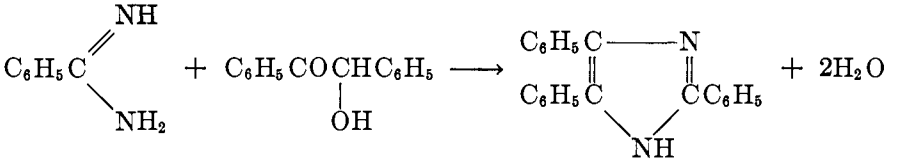


Ekeley, Ronzio, and Elliott (45, 46, 47) observed that a definite reaction takes place when a mixture of an aromatic aldehyde, glyoxal, and an amidine are treated with an excess of base.



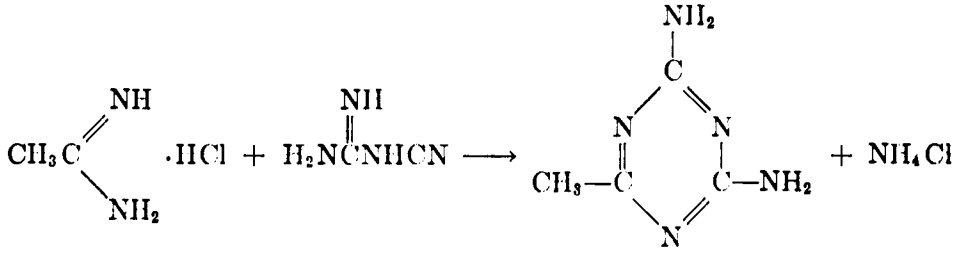
In 1901 Kunckell and Bauer (81) reported that phenylglyoxal forms a condensation product with benzamidine. This product melted at nearly the same temperature as cyaphenine and may possibly be the latter (173).

Kulisch (79) has prepared 2,4,5-triphenylimidazole (*"Lophin"*) by heating benzamidine hydrochloride and benzoin in the presence of ethanol and an excess of sodium hydroxide.



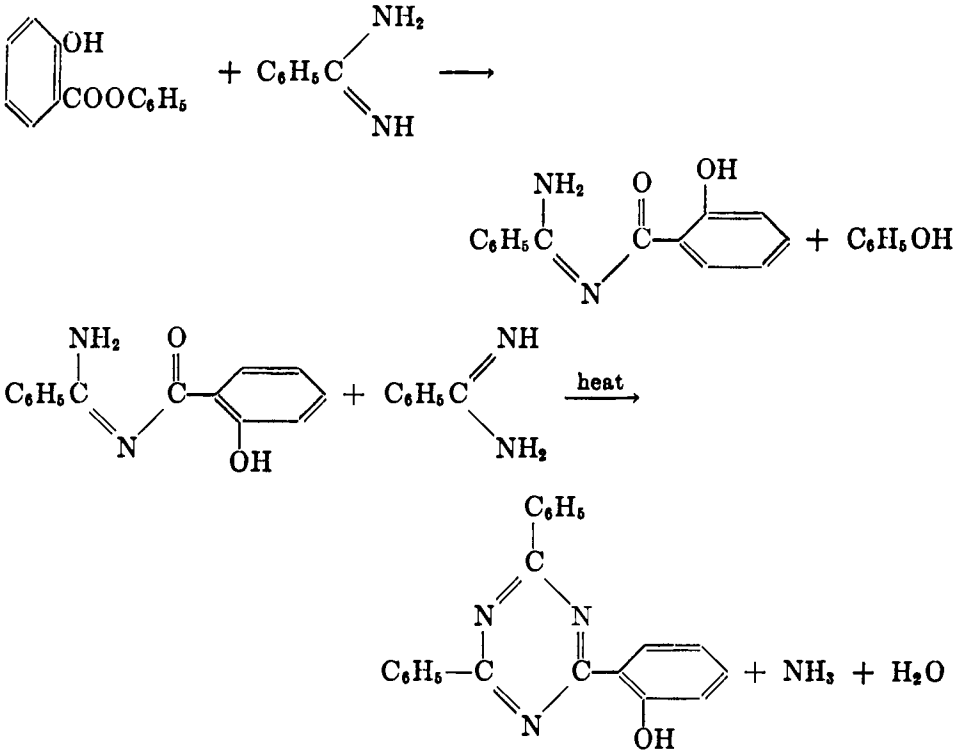
13. Formation of triazines

2-Methyl-4,6-diamino-1,3,5-triazine has been prepared in a 65 per cent yield by heating a mixture of acetamidine hydrochloride and cyanoguanidine at 230°C. (102).



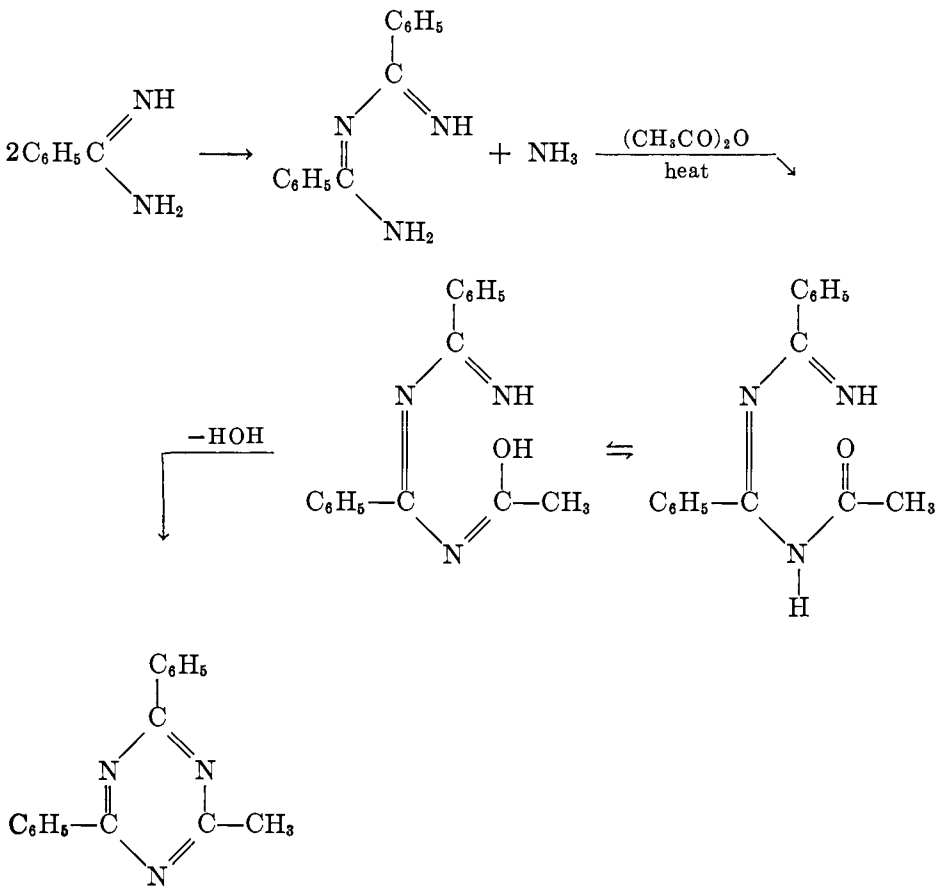
The corresponding phenyl-substituted compound is obtained by employing benzamidine hydrochloride. Closely related to the above reactions is the formation of a substituted triazine when diphenylformamidine is heated with phenylbiguanide (164).

Titherley and Hughes (160) obtained 2,4-diphenyl-6-*o*-hydroxyphenyl-1,3,5-triazine by heating with benzamidine the condensation product obtained by the action of this same amidine on phenyl salicylate.

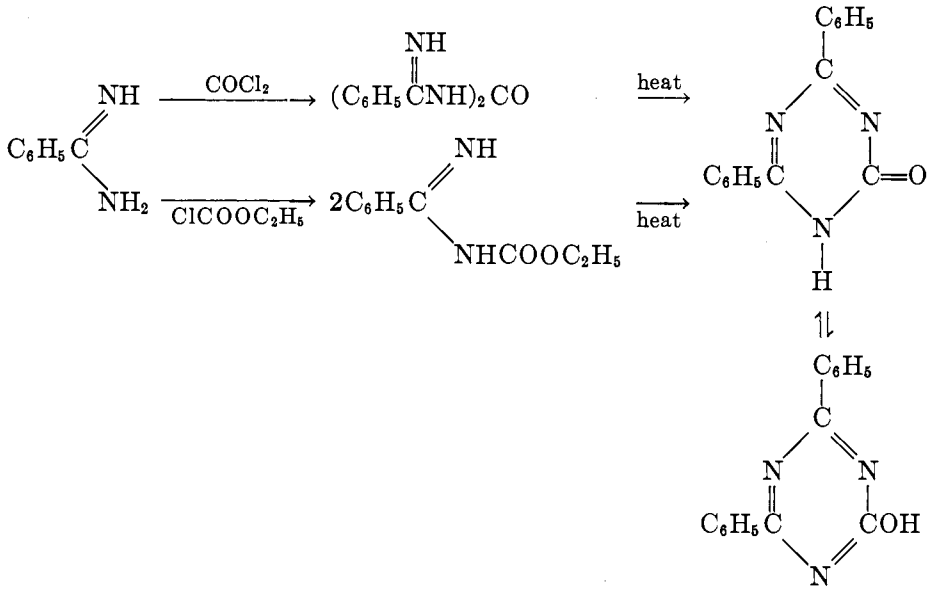


Pinner had previously reported the isolation of this triazine from the many products obtained from the reaction between benzamidine and the ethyl ester of salicylic acid (124). Carbethoxyphloroglucinol, however, reacts to form a benzopyrimidine (123).

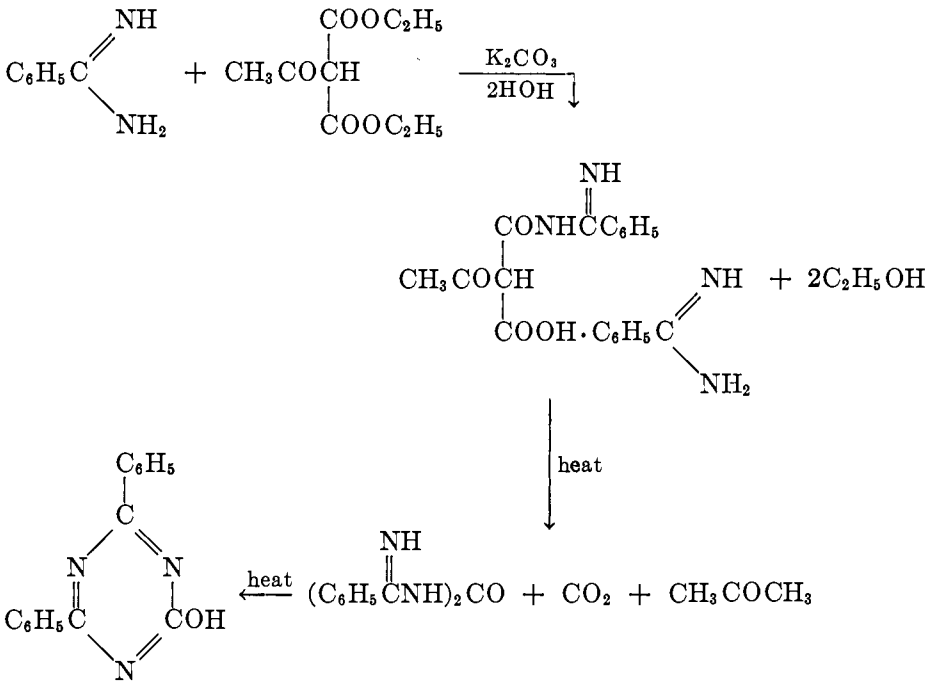
Pinner also found that the treatment of benzamidine with acetic anhydride produces 2-methyl-4,6-diphenyl-1,3,5-triazine (125, 130). The following mechanism for this transformation was suggested (109):



Pinner obtained a triazine by the action of phosgene or ethyl chloroformate on benzamidine (120). As pointed out previously, these reagents react with benzamidine to form non-cyclic intermediates first which can be isolated. The triazines can then be formed by heating the intermediates.



The same triazine is formed when the compound obtained from the reaction of diethyl acetylmalonate and benzamidine in the presence of potassium carbonate is heated to 200°C. (118).

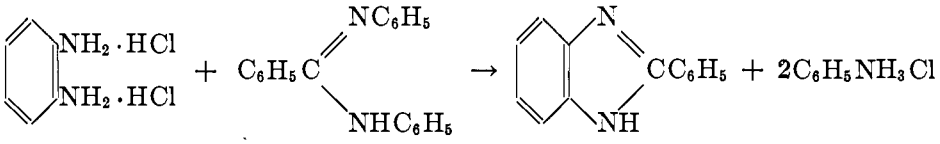


The formation of the triazine in this case seems unusual, since β-ketonic esters usually react with amidines to form pyrimidines. By using sodium hydroxide instead of the potassium carbonate, Pinner did obtain the expected pyrimidine (109, 117, 118).

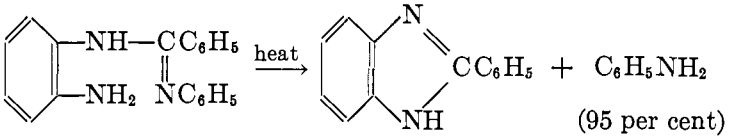
14. Formation of miscellaneous heterocycles from amidines

Benzimidazoles may be prepared by fusing amidines, acids, esters or nitriles with *o*-phenylenediamine. According to Wagner (61, 164) the yield is seldom improved by the use of amidines.

Hölljes and Wagner (61) obtained 2-phenylbenzimidazole by heating *o*-phenylenediamine hydrochloride and an excess of *N*,*N*′-diphenylbenzamidine at 200°C.

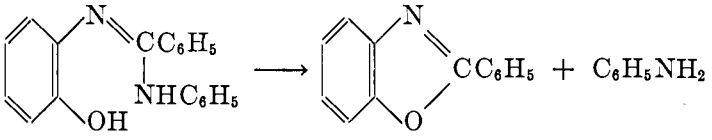


No reaction took place when the free base was used; Wagner (164) obtained a yield of 64 per cent of the 2-methyl derivative when the corresponding acetamidine was used. *N*-Phenyl-*N*′-*o*-aminophenylbenzamidine or its hydrochloride yields 2-phenylbenzimidazole upon heating to 200°C. (61).

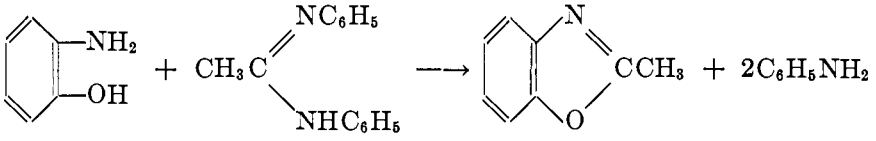


Benzimidazole itself may be prepared in 81 per cent yield by heating diarylformamidines with *o*-phenylenediamine (164).

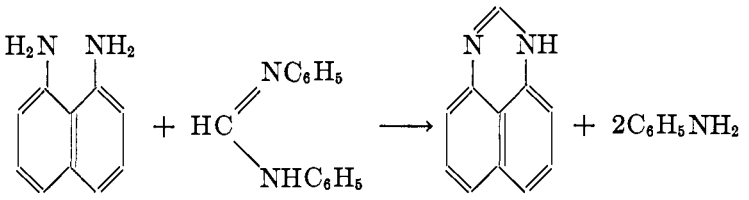
Hölljes and Wagner also prepared 2-phenylbenzoxazole in 94 per cent yield by heating *N*-phenyl-*N*′-*o*-hydroxyphenylbenzamidine at 100°C.



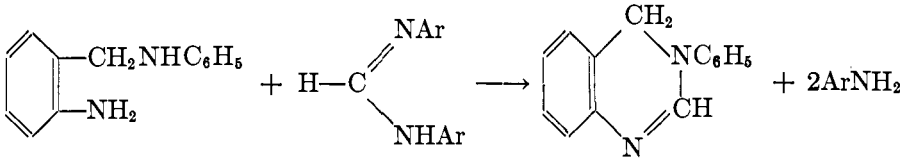
The reactions between *o*-aminophenol and *N*,*N*′-diphenylacetamidine likewise produced the 2-methyloxazole (164).



Wagner (164) prepared perimidine in 81 per cent yield by heating 1,8-diaminonaphthalene and *N*,*N*′-diphenylformamidine.

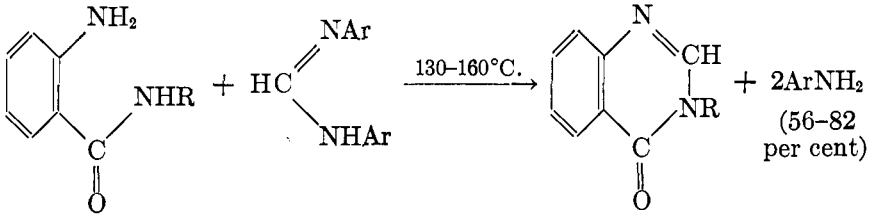


When *o*-aminobenzylphenylamine was heated with diarylformamidines, a dihydroquinazoline was formed in fair yields.



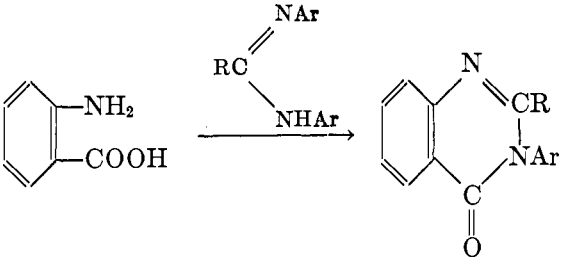
This method was not successful when acetamidine was employed.

Various modifications of the Niementowski reaction employing the use of amidines in the synthesis of 4-keto-3,4-dihydroquinazolines have been reported (95, 164).

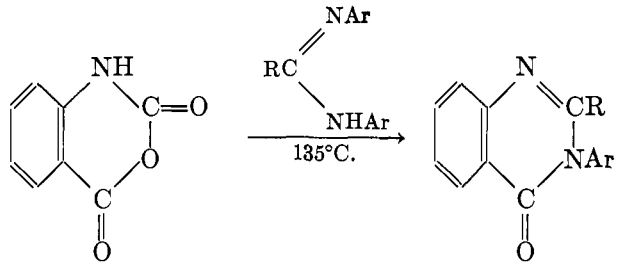


(R = H, Ar)

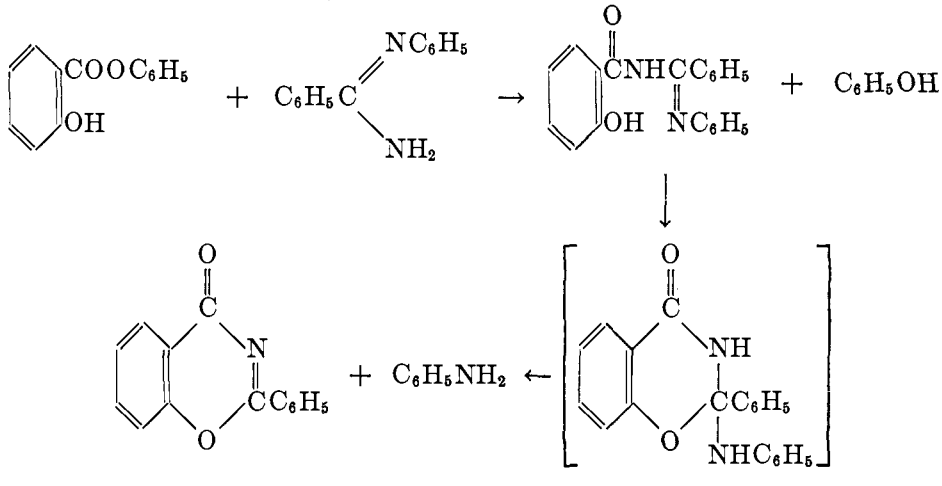
No reaction product could be isolated when acetamidine was employed. Anthranilic acid or its methyl ester may also be used (95).



R may be H or CH_3. Yields as high as 90 per cent were obtained when isatoic anhydride was substituted for the anthranilic acid.

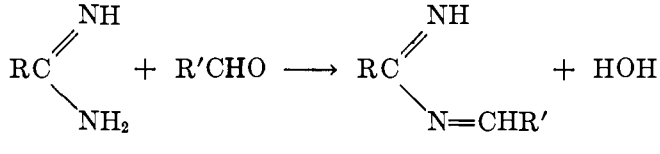


Titherley and Hughes (158, 159) have isolated benzoxazones from the reaction mixture obtained by heating *N*-phenylbenzamidine and substituted salicylic esters. The following equations indicate the proposed mechanism for the production of 2-phenyl-1,3-benzoxazine-4-one:

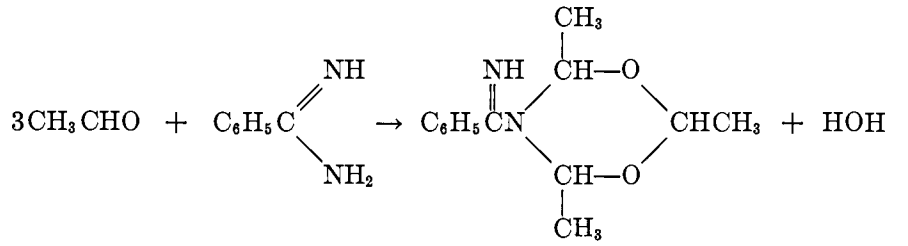


15. Reaction of amidines with aldehydes

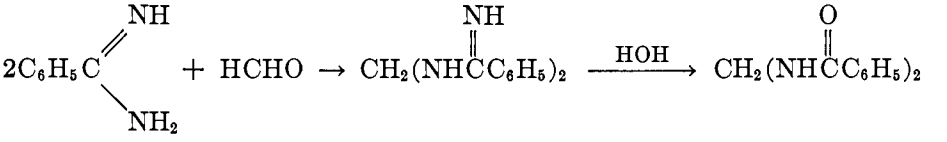
Pinner (109, 115, 121) and Kunckell and Bauer (81) have shown that the following reaction of amidines is general:



Thus, by refluxing a chloroform solution of benzamidine and an excess of benzaldehyde, *N*-benzalbenzamidine is formed (81). However, Pinner (121) observed the formation of many side products in this reaction. Freshly distilled acetaldehyde reacts in the following manner:

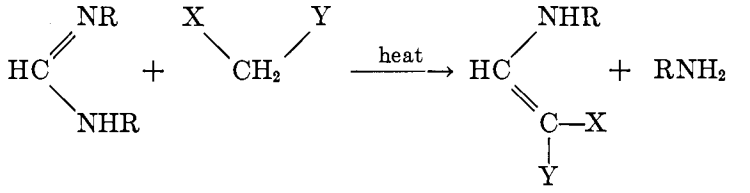


When the product of the reaction between benzamidine and formaldehyde is treated with hot water, bis(benzoylamino)methane is produced.



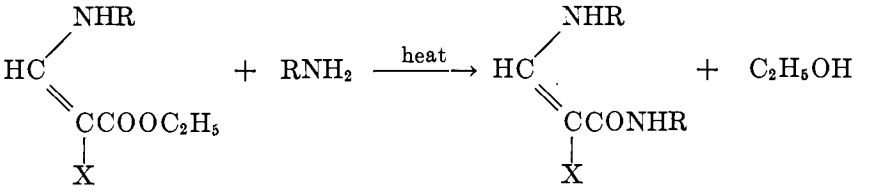
16. Reaction of formamidines with active methylene compounds

F. B. Dains has published ten papers on the reaction of symmetrical disubstituted formamidines with compounds containing active methylene groups (34, 35, 36, 37). The conclusions drawn from his work can be represented by the following equation:



R may be alkyl or aryl, and X and Y are radicals which activate the methylene group. Those compounds which contain this type of methylene group include ethyl acetoacetate, acetylacetone, diethyl malonate, acetoacetanilide, and ethyl cyanoacetate.

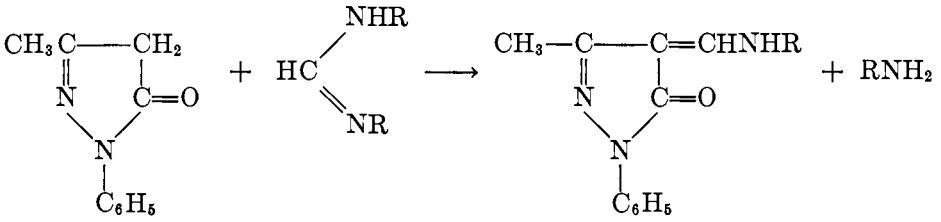
When X or Y is a carbethoxy radical, a further reaction takes place.



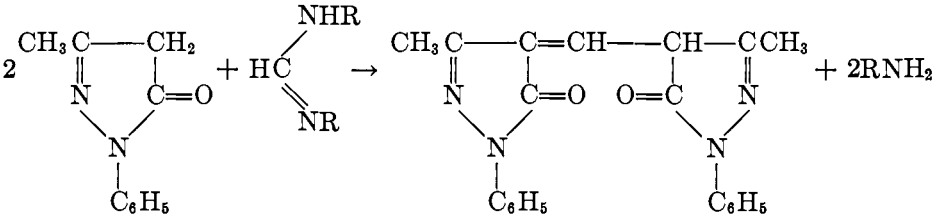
Thus with diethyl malonate, the amide is formed in yields as high as 80 per cent; however, the reaction with ethyl cyanoacetate does not produce the amide. Benzyl cyanide and benzyl phenyl ketone react with difficulty (34).

The reaction between the substituted formamidines and active methylene compound is carried out by heating the two at 125–200°C. for several hours.

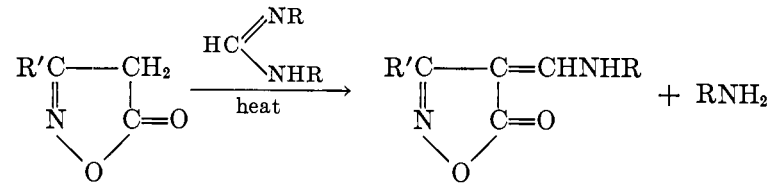
Cyclic compounds containing an active methylene group can be used as well. The reactions of a number of 1,3-disubstituted pyrazolones have been studied. Thus, 1-phenyl-3-methyl-5-pyrazolone reacts as follows:

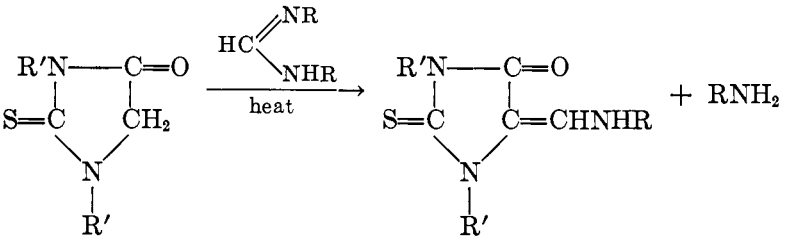


The products, alkylaminomethenyl derivatives, are all colored. When the pyrazolone is used in excess the following reaction takes place:

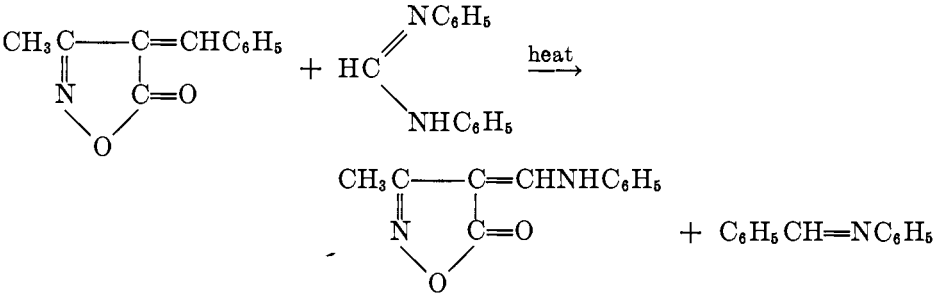


Isoxazolines and thioimidazolones react with these formamidines in the usual manner.

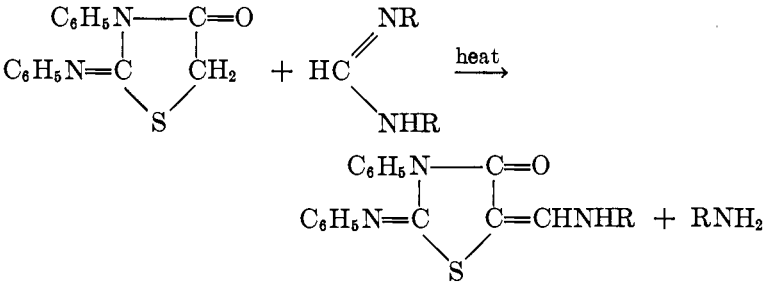




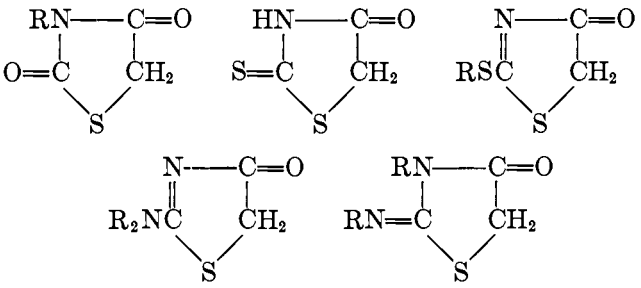
An interesting reaction takes place when 3-methyl-4-benzal-5-isoxazolone is treated with *N*,*N*′-diphenylformamidine.



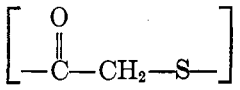
Dains has extended the work to show that all 4-thiazolidones react in the same manner with substituted formamidines.



The other types of thiazolones studied had the following general structures:



The reactivity of these compounds to disubstituted formamidines illustrates that the methylene group in the structure

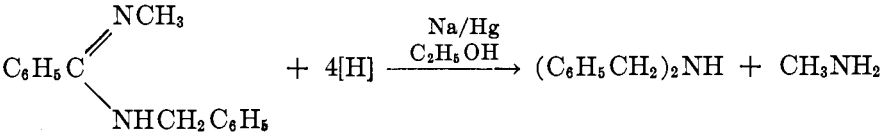


is active.

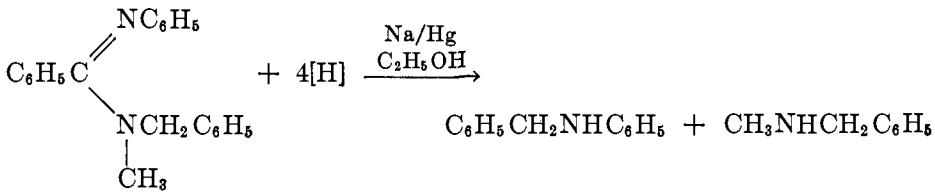
17. Reduction of amidines

The degradative reduction of amidines has been used to determine structures when hydrolysis failed or was difficult (9, 135). The procedure most commonly used for the reduction is to dissolve the amidine in absolute ethanol and to heat the solution over a water bath for several hours with sodium amalgam and acetic acid (9, 74, 135).

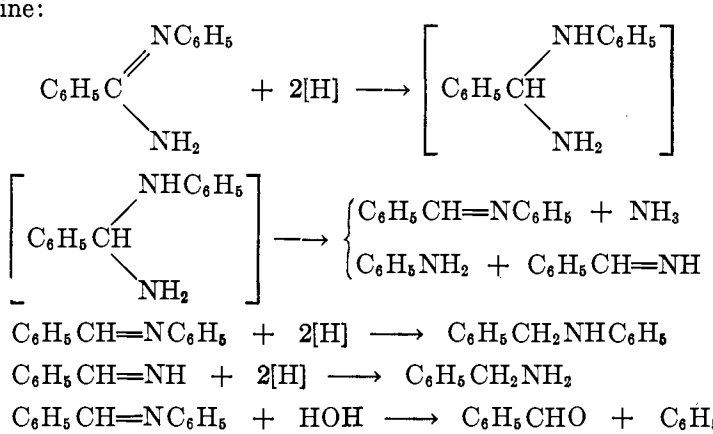
Thus Pyman (135) was able to reduce *N*-methyl-*N'*-benzylbenzamidine, an amidine which could not be hydrolyzed by boiling with 20 per cent sodium hydroxide.



Beckmann and Fellrath (9) have reduced a trisubstituted amidine.

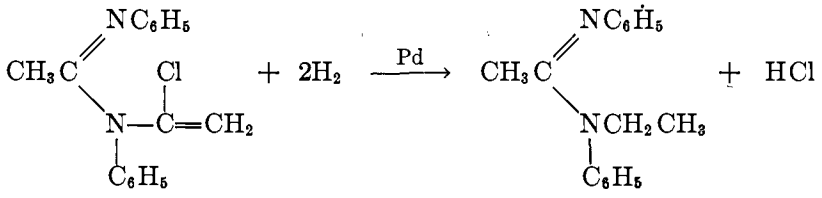


In 1880 Bernthsen and Szymanski (14) reported the isolation of a reduction product from *N*-phenylbenzamidine which they termed *dihydrophenylbenzamidine*. Later investigators suggested that the reported dihydro derivative was probably the unchanged amidine (74). Kirsanov and Ivaschchenko further studied the reduction of *N*-phenylbenzamidine, using sodium amalgam and acetic acid in absolute alcohol (74). Employing an isolation procedure which involved an aqueous acid treatment, they recovered approximately 74 per cent of unchanged amidine as well as smaller amounts of benzaldehyde, aniline, benzylaniline, and benzylamine. To explain the formation of these compounds they proposed the following reactions, which involve an unstable dihydrophenylbenzamidine:



Houben (62) mentions that an *N*,*N*′-diphenyl-substituted amidine may be reduced to an aldehyde; an alcoholic solution of the amidine is refluxed in the presence of sodium, and the reaction mixture is worked up after treatment with dilute hydrochloric acid.

von Braun, Jostes, and Heymons (18) cited an example in which an amidine was not reduced catalytically. Thus, when *N*-α-chlorovinyl-*N*, *N*′-diphenylacetamidine was treated with hydrogen under slight pressure at room temperature in the presence of palladized charcoal and dilute acid, the amidine linkages were not changed but halogen was removed and the vinyl group reduced.



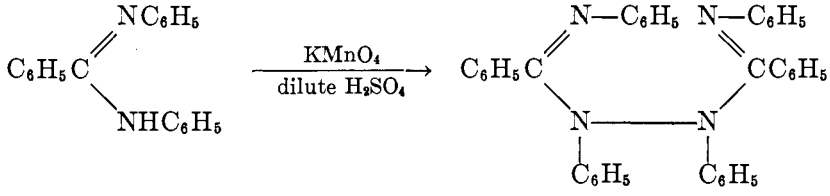
Kubiczek (77), however, claims that the statement of von Braun *et al.* that amidines cannot be hydrogenated by hydrogen and palladized charcoal is not true, at least for all amidines. He treated *N*,*N'*-di-*m*-tolylbenzamidine with hydrogen and palladium black at 18°C. as above for 34 hr., and isolated *m*-toluidine and toluene. The hydrogenation is so slow that it may easily be overlooked.

Henle (58) reduced benzamidine hydrochloride to ammonia and benzylamine in a yield of 38 per cent by treating a cooled aqueous solution of the salt with sodium amalgam and hydrochloric acid.

Beckmann and Fellrath (9) studied the reduction of amidines, using zinc dust and acetic acid; some reduction occurred but unchanged amidine was also recovered.

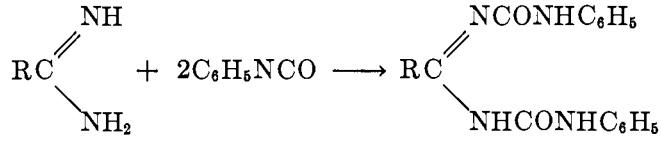
18. Oxidation of amidines

Joshi, Khanolkar, and Wheeler (70) have shown that *N*,*N'*-diphenylbenzamidine may be oxidized with potassium permanganate and dilute sulfuric acid at 100°C. to form *s*-diphenyldi(phenyliminobenzyl)hydrazine. The results were extended to show that the reaction is general for diaryl-substituted benzamidines.



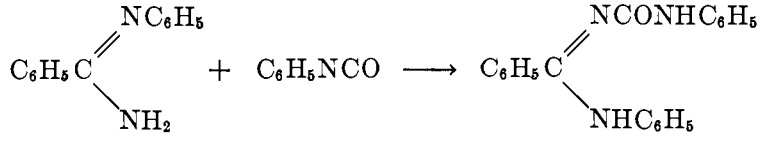
19. Formation of substituted ureas

As early as 1889 Pinner (109, 115, 121) demonstrated that both aromatic and aliphatic amidines can easily be made to react with phenyl isocyanate to form the corresponding phenylureides.

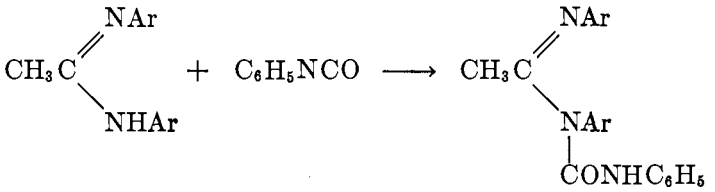


A solution of the amidine in anhydrous ether or benzene is treated with a solution of phenyl isocyanate at room temperature. The derivative either separates at once (175) or else the solvent is then removed and the residue crystallized from acetone or alcohol (121).

Wheeler (175) and Walther and Grossmann (172) have prepared the phenylureides of monosubstituted amidines.

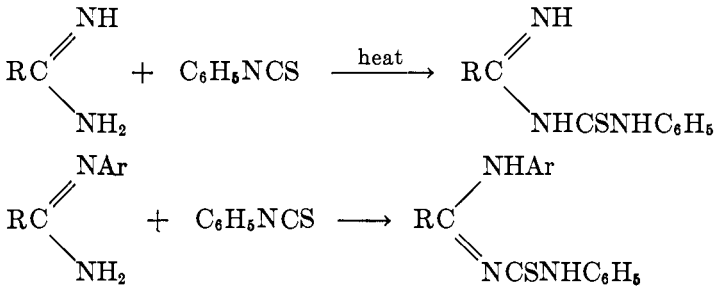


Hill and Rabinowitz (60) have characterized various symmetrical disubstituted amidines by conversion to the corresponding phenylureides.



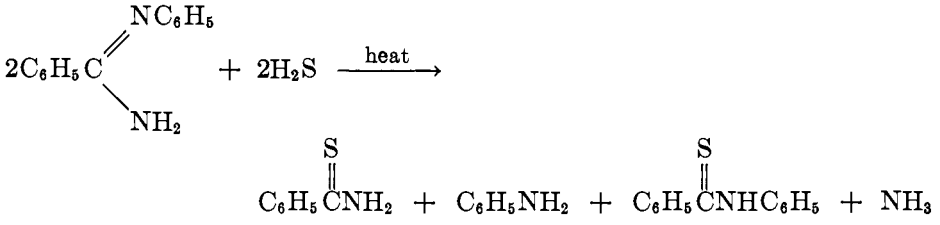
The yields of the derivatives are good, and the melting points are generally not too high.

Pinner (115) and others (172, 175) have also prepared derivatives of amidines by the use of phenyl isothiocyanate.

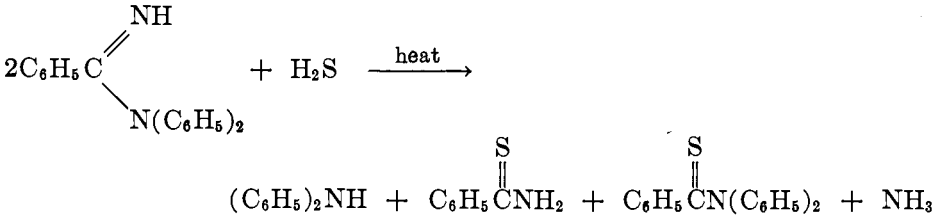


20. Formation of thioamides

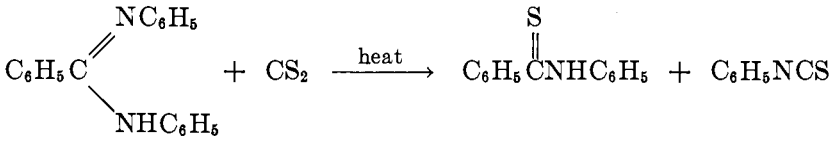
Bernthsen has studied the action of hydrogen sulfide and carbon disulfide on various amidines (12). Thioamides were produced in all of the reactions studied. When *N*-phenylbenzamidine was heated to 120°C. in the presence of hydrogen sulfide gas, the following reaction took place:



Thus the reaction between amidines and hydrogen sulfide is analogous to the reaction between amidines and water. *N*,*N*-Diphenylbenzamidine likewise reacts with hydrogen sulfide at 130°C.



Amidines can be caused to react with carbon disulfide under the influence of heat (12). *N*-Phenylbenzamidine reacts to form *N*-phenylthiobenzamide and other products; *N*,*N*′-diphenylbenzamidine reacts as follows:

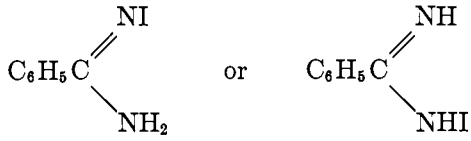


21. Reaction with halogens

In 1893 Beckmann and Fellrath (9) reported that *N*-methyl-*N*-phenyl-*N*′-benzylbenzamidine ($C_{21}H_{20}N_2$) reacted with bromine. The color of the bromine disappeared as it was added to a chloroform solution of the amidine, and a heat of reaction was noticed. The product was colorless after crystallization from ethanol and had the empirical formula of $C_{21}H_{20}N_2Br_2$. The authors reported that the compound acted like a hydrobromide ($C_{21}H_{19}N_2Br \cdot HBr$), and that oxidation with dilute potassium permanganate produced bromine-free products: benzoic acid, benzylamine, and methylaniline. Beckmann and Fellrath did not attempt to draw any conclusions from the results, but thought that one bromine atom had replaced a hydrogen in a side chain.

Dains and Griffin (36) observed that *N*,*N*′-diphenylformamidine could absorb bromine to form a yellow addition product. This product could be hydrolyzed with dilute potassium hydroxide to yield aniline, *p*-bromoaniline, and *p*-bromoformanilide. These authors also made no attempt to draw any conclusions from the experiments.

Bougault and Robin (16) in 1920 reported that benzamidine hydrochloride reacts with an iodine–potassium iodide solution in the presence of sodium hydroxide to form an iodoamidine, a pale yellow solid. The authors suggest that this reaction may be useful in the identification of amidines, since the product is stable in the air. The following formulas were proposed for *N*-iodobenzamidine:



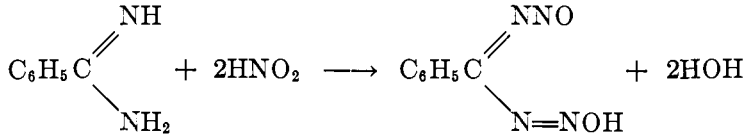
In 1923 Robin (139) further reported that a sodium hypochlorite solution could be used as well, producing a white chloroamidine immediately. Various aromatic amidines were used in like experiments. An excess of cold sodium hydroxide solution or an acidic potassium iodide solution regenerates the amidine.

22. Effect of nitrous acid

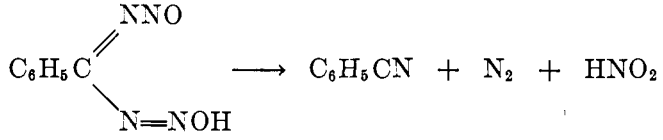
Since unsubstituted amidines are strong bases, one might expect the amino group to react similarly to that in primary amines. Lossen, Mierau, Kobbert, and Grabowski (89, 90) have studied the action of nitrous acid on amidines and the results indicate that the analogy cannot be extended very far.

When an aqueous solution of benzamidine hydrochloride and an equimolecular amount of sodium nitrite is concentrated to dryness, the nitrite salt is formed along with benzonitrile and benzamide.

When the hydrochloride of benzamidine is treated with an excess of sodium nitrite and hydrochloric acid, there is formed a dinitroso derivative which possesses both acid and basic properties.

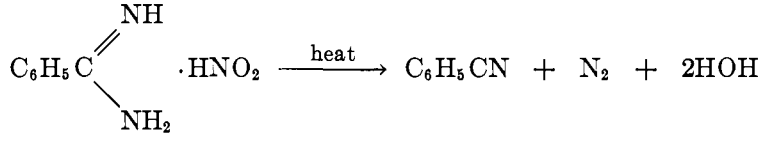


In general, these amphoteric derivatives decomposed very easily as follows:

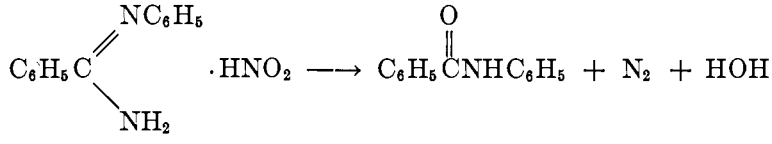


The dioxytetrazotic acids could not be prepared successfully in the free state, but the acid or basic salts could be isolated and analyzed since they proved to be more stable. The dry metallic salts decomposed with explosive violence. The formation of the dioxytetrazotic acids is characteristic only of the unsubstituted amidines.

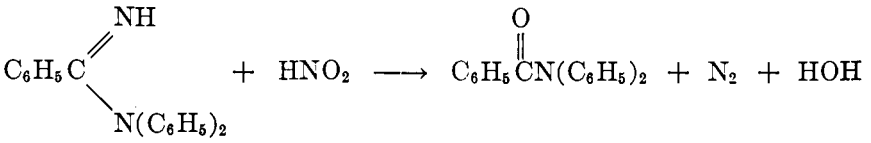
Nitrite salts of amidines are sufficiently stable to be isolated. The hydrochloride and a silver nitrite solution are allowed to react and the solvent removed at 30–40°C. after separation of the silver chloride. Benzamidine nitrite decomposes upon heating to form benzonitrile.



The nitrite of *N*-ethylbenzamidine can be formed from the hydrochloride and silver nitrite; this nitrite can be crystallized from ethanol and ether, but an attempt to use water resulted in decomposition. The heating of an aqueous solution of *N*-phenylbenzamidine nitrite produced the following decomposition.

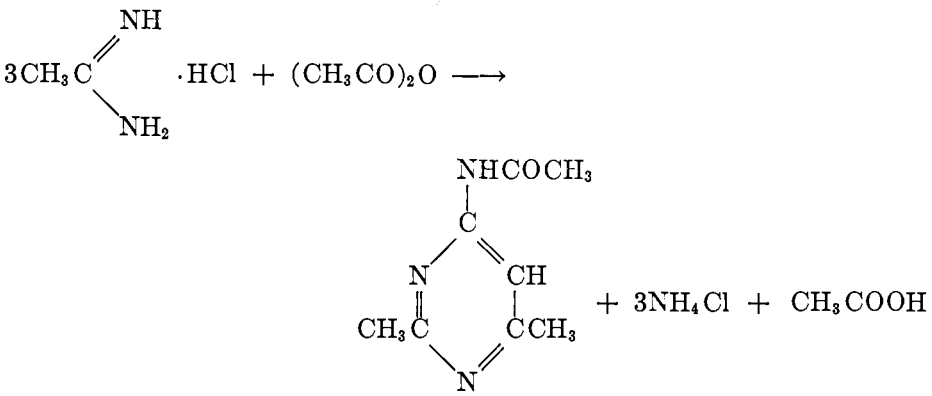


Lossen *et al.* (90) also report that *N*,*N'*-diphenylbenzamidine is not changed by the action of nitrous acid and that the nitrite salt could not be formed. All attempts to prepare the nitrite of *N*,*N*-diphenylbenzamidine resulted in the formation of diphenylbenzamide.

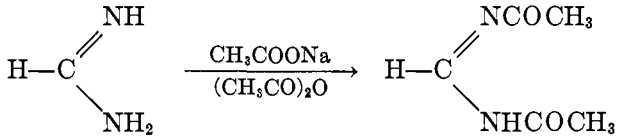


23. Action of acetic anhydride

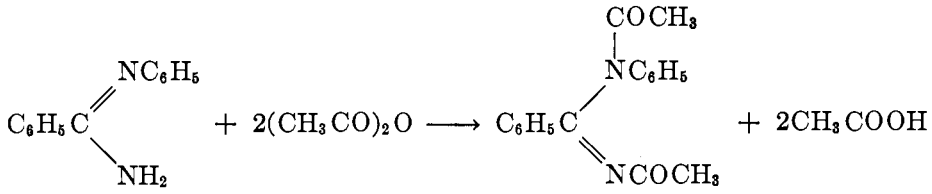
According to Pinner (109) aliphatic unsubstituted amidines decompose when heated in the presence of acetic anhydride to form dialkylaminopyrimidines. Thus, acetamidine hydrochloride forms 2,4-dimethyl-6-acetylaminopyrimidine when heated with sodium acetate and acetic anhydride at 185°C. (115).



Aromatic unsubstituted amidines form triazines under the same conditions. Pinner (112) has reported that formamidine acetate forms a diacetyl derivative when treated with acetic anhydride.

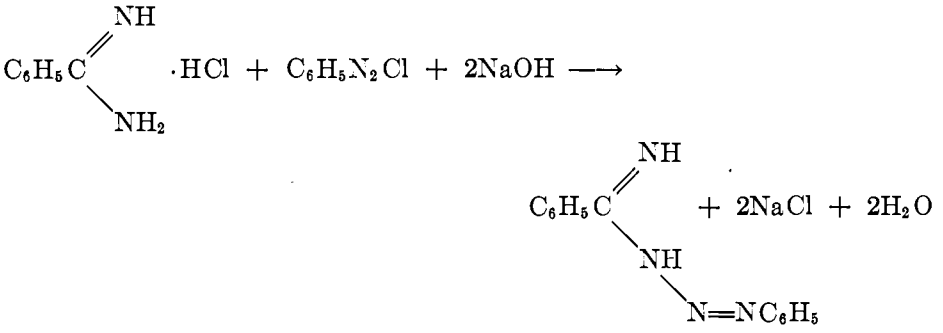


Lottermoser (91) obtained the diacetyl derivative of *N*-phenylbenzamidine by heating with acetic anhydride.



24. Reaction with diazonium salts

Pinner has reported (109, 115) that benzenediazonium chloride reacts with unsubstituted amidines to form azo derivatives.



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