# THE CHEMISTRY OF THE 2-IMIDAZOLINES AND IMIDAZOLIDINES

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## I. INTRODUCTION

A number of naturally occurring substances have been found to contain the imidazole nucleus. Some of these compounds and their synthetic derivatives possess therapeutic value. Although review articles have been published dealing with amidines (112), benzimidazole (136), and biologically active imidazoles (47), no summary of the chemistry of 2-imidazolines and imidazolidines has previously appeared.

The numbering system used for imidazole (I) is extended to imidazolines (II) and imidazolidines (III), which are dihydroimidazoles and tetrahydroimidazoles, respectively (see page 594). As depicted here, the No. 1 position is assigned to the nitrogen connected through single bonds to two carbon atoms of the ring and the No. 3 position to the nitrogen connected to one carbon by a double bond. In some of the older literature, however, either of the two nitrogen atoms

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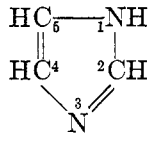
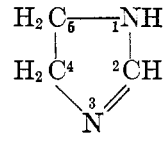
is used as a starting point for numbering. The alternate numbering is sometimes designated in parentheses, as, for example, 4(5)-methylimidazole. In some instances the 2-position is designated as the $\mu$-position, the 4-position as $\alpha$, and the 5-position as $\beta$.



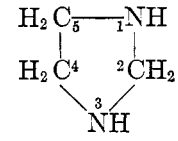
I

Imidazole



II

2-Imidazoline



III

Imidazolidine

The term glyoxaline, a common name sometimes used for imidazole, was originated in 1858 by Debus, who obtained from glyoxal and ammonia a compound possessing an imidazole structure (32). Thus, imidazolines may be referred to as dihydroglyoxalines and imidazolidines as tetrahydroglyoxalines. Imidazoles are also known as iminazoles.

The present review has been restricted to 2-imidazolines and imidazolidines. Other dihydroimidazoles, such as 3-imidazoline and 4-imidazoline, whose double bond is not located between a nitrogen and the No. 2 carbon of the ring, are uncommon and have been omitted. Likewise, no attempt has been made to include numerous closely related keto, thioketo, or imine-type compounds such as imidazolidones, imidazolones, and derivatives of hydantoin, allantoin, creatinine, or parabanic acid. The literature has been reviewed through the 1952 volume of *Chemical Abstracts*.

## II. 2-Imidazolines

### A. Synthesis of 2-imidazolines

Although the most widely used methods of preparing 2-imidazolines involve ring-closure of 1,2-diamines or 1,2-diamine derivatives with carboxylic acids or derivatives of these acids, this heterocyclic ring system may be formed by several other synthetic approaches.

#### *1. From 1,2-diamines*

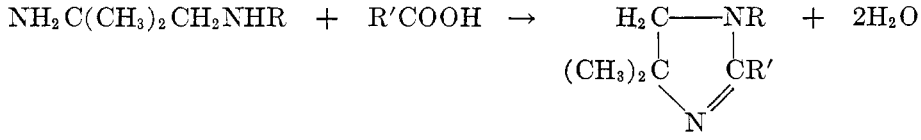
##### (a) By reaction with monocarboxylic acids

The reaction of ethylenediamine with acetic acid affords only a 19 per cent yield of 2-methyl-2-imidazoline (18). Heating other 1,2-diprimary diamines, such as 2,3-dimethyl-2,3-butanediamine or 1,2-butanediamine, with acetic acid gives 10–15 per cent yields of the diacetyl derivatives of the respective diamines with very little or none of the 2-imidazolines (100).

Early investigators reported the preparation of 2-methyl-2-imidazoline by distillation of a mixture of ethylenediamine hydrochloride with an excess of sodium acetate (8, 70, 80). The yield, however, was only 8 per cent. Waldmann and Chwala (127) have made an extensive study of the preparation of 2-imidaz-

olines from high-molecular-weight carboxylic acids and either free aliphatic 1,2-diamines or a mixture of these amines and their mineral acid salts. These reactions were carried out by heating the reactants at 200–300°C. Condensing agents such as aluminum chloride, phosphorus trichloride, stannic chloride, and phosphorus pentoxide have been employed (113) and a variety of 1,2-diamines have been used (127, 133).

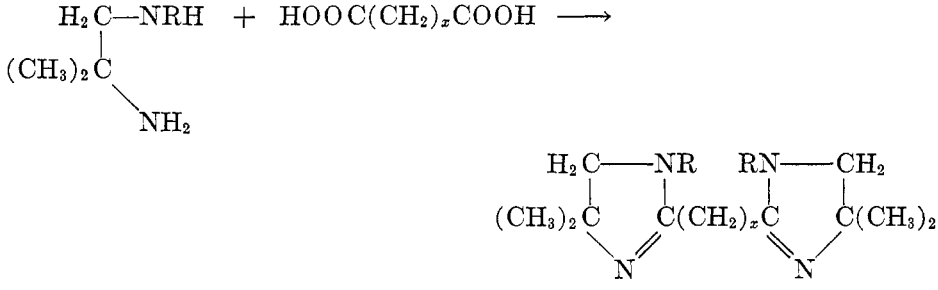
A number of 1,2-substituted-4,4-dimethyl-2-imidazolines have been prepared by heating 1,2-diamines containing one primary and one secondary amino group with organic acids in the presence of benzene. The mixtures were heated under conditions to remove water by azeotropic distillation (100, 125).



Molecular complexes of these 2-imidazolines with 1 or 2 moles of carboxylic acids were also formed. The complexes could readily be converted to the 2-imidazolines by treatment with dilute alkali.

(b) By reaction with dicarboxylic acids

1,2-Diamines containing one primary and one secondary amino group have been found to react with dibasic acids containing four or more carbon atoms to give bisimidazolines and their molecular complexes with the dibasic acids (101).



$x$ = 2 or more.

When the above reaction was attempted with oxalic acid there was formed a low yield of the product which would have been obtained by heating formic acid and the 1,2-diamine. Also, when this type of reaction was attempted with malonic acid, the product obtained was the same as from acetic acid and the 1,2-diamine. This behavior was attributed to the reaction of one of the carboxyl groups of the oxalic or malonic acid in the usual manner with subsequent decarboxylation of the other.

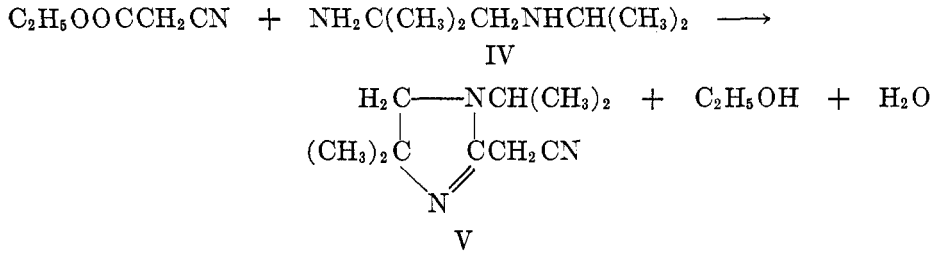
Chwala (19) reported that di- or polycarboxylic acids react at temperatures of about 280°C. with a mixture of 1,2-diamines and their salts in the presence of

strong mineral acids to yield products containing more than one 2-imidazoline ring per molecule. When the sodium salt of terephthalic acid is treated with an aliphatic 1,2-diamine, the expected imidazoline ring is formed at each carboxylic acid group (51).

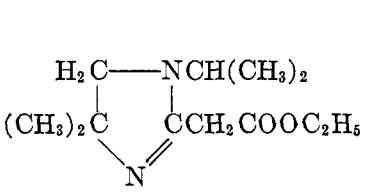
(c) By reaction with esters

2-Imidazolines may be prepared in 60–70 per cent yields by refluxing ethylenediamine with an ester and removing the alcohol and water formed by distillation (92). This type of reaction probably proceeds by initial amide formation, followed by loss of water and cyclization to the 2-imidazoline structure.

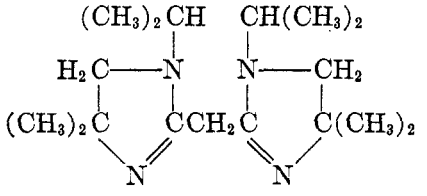
Pachter and Riebsomer (95) found that cyanoacetic ester reacts with *N*-(2-aminoisobutyl)isopropylamine (IV) to produce 2-cyanomethyl-2-imidazoline (V).



When IV was treated with malonic ester, ethyl 1-isopropyl-4,4-dimethyl-2-imidazolinyl-2-acetate (VI) resulted.

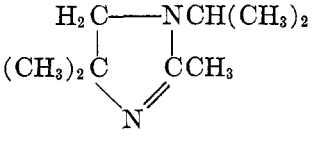


VI

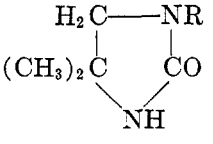


VII

None of the expected bisimidazoline (VII) was formed. When compound VI was treated with various 1,2-diamines of the same type as IV except for variation of the group attached to the secondary nitrogen, the bisimidazoline (VII) was not formed, but instead a 2-imidazoline (VIII) and a 2-imidazolidone (IX) resulted (43, 95).

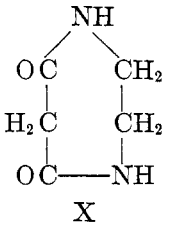


VIII

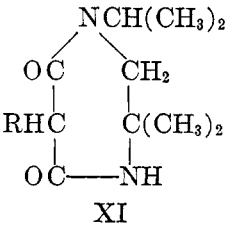


IX

Freund (48) and later Dox (41) reported that ethylenediamine and malonic ester reacted to form a seven-membered ring compound (X).



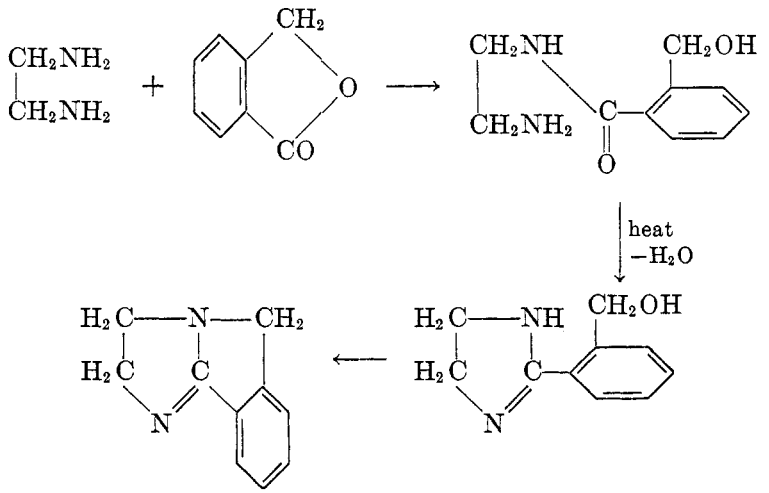
X



XI

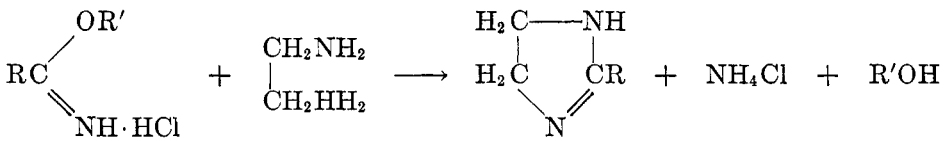
Pachter and Riebsomer found that when *N*-(2-aminoisobutyl)isopropylamine (IV) was treated with a substituted malonic ester, diazepines of type XI were formed.

The cyclization of phthalide with ethylenediamine in the presence of acetic anhydride as a dehydrating agent has been reported (10).



(d) By reaction with imino-ethers

The heating of iminoalkyl ethers or their hydrochlorides with 1,2-diamines is a satisfactory method of preparing 2-imidazolines.

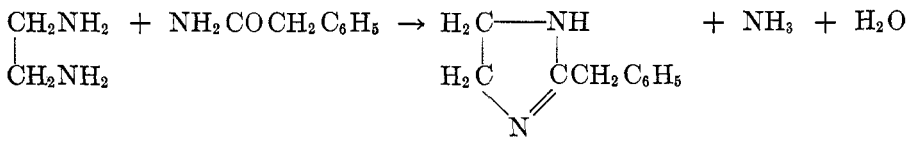


R′ may be any alkyl group but is generally ethyl. Examples are given in the literature with a variety of R groups; $ClCH_2$— (114, 115); $Cl(CH_2)_3$— (116); $HOCH_2$— (69); $C_6H_5CONH(CH_2)_2$— (66); $C_6H_5NHCH_2$— (117); —$C_6H_4C_6H_4$— (25, 51); $C_{15}H_{31}$— (14); $C_{17}H_{35}$— (14); X— (119) and $XO(CH_2)_n$—, where X stands for a substituted or an unsubstituted phenyl, naphthyl, or quinolyl radical (the substituent being alkyl, alkenyl, hydroxy, or alkoxy) and *n* stands for numbers

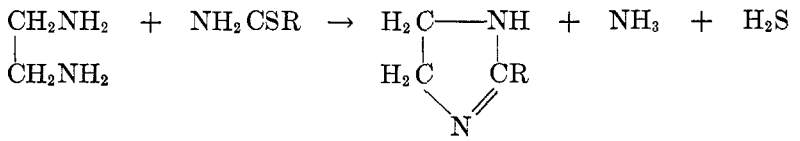
1 through 6 (37, 118, 119); YZCHO$(CH_2)_n$—, where Y is aryl, Z is H, an aryl radical, or an alkaryl radical, and $n$ again stands for a small integer (39).

(e) By reaction with amides

Arylacetamides have been treated in the absence of mineral acids or condensing agents with an excess of anhydrous ethylenediamine at 150–200°C. to yield 2-imidazolines (88).



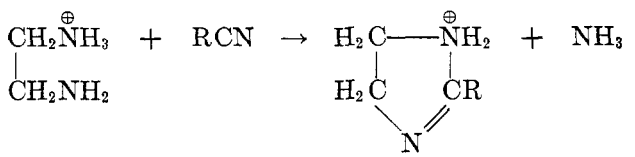
This same type of reaction has been carried out with a number of thioamides.



Examples may be found in which R is $C_6H_5$— (46), $C_6H_5CH_2$— (73), $C_6H_5CHCH_3$— (72), 1-$C_{10}H_7CH_2$— (73), 2,1-$CH_3C_{10}H_6CH_2$— (73), $C_6H_5(C_6H_5CH_2)NCH_2$— (65), and $(C_6H_5)_2CHOCH_2$— (38).

(f) By reaction with nitriles

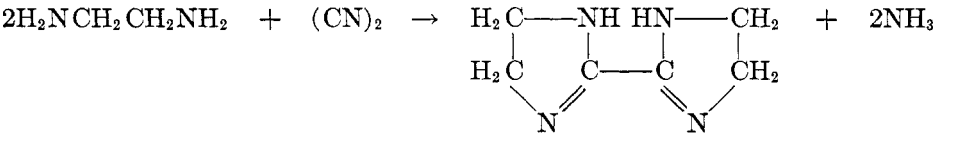
It has been shown that 2-substituted-2-imidazolines may be prepared in excellent yields (often 90 per cent) by heating aromatic or aliphatic nitriles and the salts of 1,2-diamines at 140–250°C. (94).



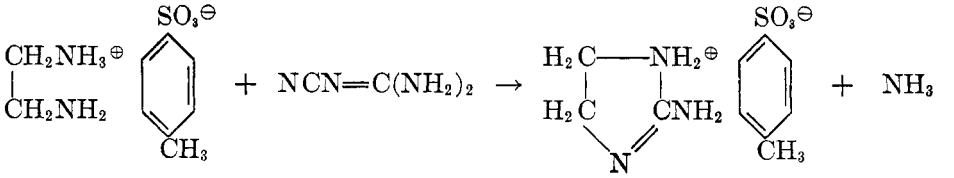
Although some reactive nitriles have been found to yield 2-imidazolines with the free 1,2-diamine base, this reaction is usually too slow to be useful. With sulfonic acid salts of the 1,2-diamines a homogeneous reaction mixture is formed which can be heated to high temperatures. While the hydrochlorides also produce good yields of the desired 2-imidazoline, their use is less desirable because the initial reaction mixtures are heterogeneous and the reaction slower. Either the mono- or the diacid salts of the 1,2-diamine may be used. When this method is applied to dinitriles, the bisimidazolines are readily formed.

The presence of hydrogen sulfide has been found to be advantageous in the preparation of 2-imidazolines from 1,2-diamines and aliphatic or aromatic nitriles (23, 27, 85). In some instances these reactions are carried out under conditions in which hydrogen sulfide is formed, as by hydrolysis of a sulfide (24). Cyanogen

and ethylenediamine have been found to produce a bisimidazoline in low yield (135).

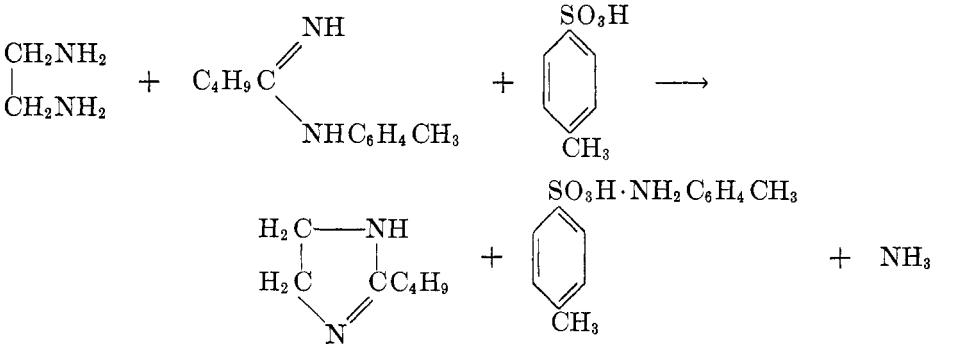


When dicyandiamide and 2-aminoethylammonium *p*-toluenesulfonate are heated at 140°C., 2-amino-*p*-toluenesulfonate-2-imidazoline is formed with the evolution of ammonia (108, 111).

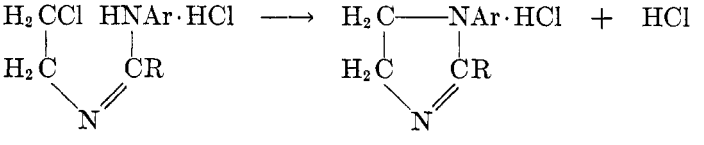


(g) By reaction with amidines and guanidines

It has been shown that *N*-substituted amidine salts may be heated with 1,2-diamines to yield 2-imidazolines and ammonia (110). This is in accord with the suggestion that amidines may be intermediates in some of the reactions of nitriles and salts of 1,2-diamines to form 2-imidazolines (94).

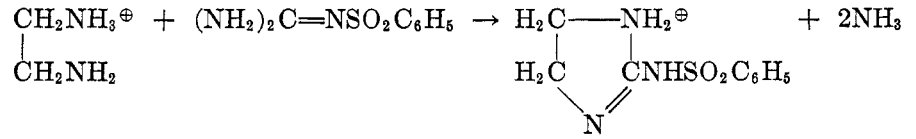


This reaction has also been used to produce bisimidazolines (135). *N'*-Substituted-*N*-(2-chloroethyl)amidinium chloride can be cyclized to a 1-aryl-2-imidazoline (96).



When a mixture of guanidine *p*-toluenesulfonate and ethylenediamine is heated, ammonia is liberated and 2-amino-*p*-toluenesulfonate-2-imidazoline is

formed. Accordingly, when benzenesulfonamidoguanidine is used, 2-(benzenesulfonamido)-2-imidazoline results (109).



*2. From monoacyl and diacyl 1,2-diamines*

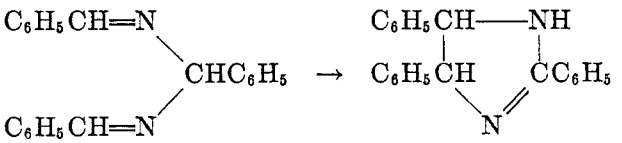
Hill and Aspinall (56) found that many aromatic monoacylethylenediamines undergo dehydration and cyclization to 2-imidazolines merely on distillation, while lime was necessary to cyclize the alkyl monoacylethylenediamines in satisfactory yields. In extending this work Aspinall (6) studied the differences in ease of preparation of various 2-imidazolines. Several patents have been issued on the use of lime to bring about this same type of ring-closure (76, 77).

Other workers have shown that it is possible to obtain 70 per cent yields of 2-alkyl-2-imidazolines by refluxing a mixture of 1 mole of the methyl or ethyl ester of a carboxylic acid with 3 moles of 90–100 per cent ethylenediamine. The time required for the acylation of ethylenediamine with the ester may be estimated by collecting the alcohol distilled from the reaction mixture (79).

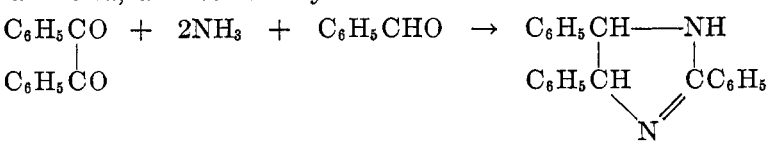
The preparation of 2-imidazolines from diacetylethylenediamine was thoroughly investigated by Chitwood and Reid (18), who found that the highest yields were obtained when diacetylethylenediamine was heated with magnesium powder at 270°C., although such diverse reagents as hydrochloric acid, sodium hydroxide, magnesia, zinc, or sodium metal also promote the reaction to a limited extent. It was, however, not possible to cyclize diformylethylenediamine to a 2-imidazoline. King and McMillan (68) have used a catalytic amount of magnesium to obtain a 94 per cent yield of 2-methyl-2-imidazoline from diacetylethylenediamine. Hofmann (58) distilled diacetylethylenediamine in a current of hydrogen chloride to yield this same imidazoline.

*3. From carbonyl-containing compounds and ammonia*

Aromatic aldehydes react with ammonia to yield hydroamides which may be cyclized on heating to 2,4,5-triaryl-2-imidazolines (120, 123).

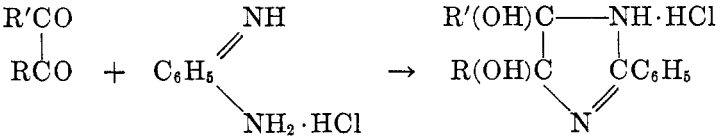


Further heating can produce triarylimidazoles through dehydrogenation. It has been reported by Strain (124) that furfural and ammonia undergo the same type of reaction. Radziszewski (98) has prepared 2,4,5-triphenyl-2-imidazoline from benzil, ammonia, and benzaldehyde.

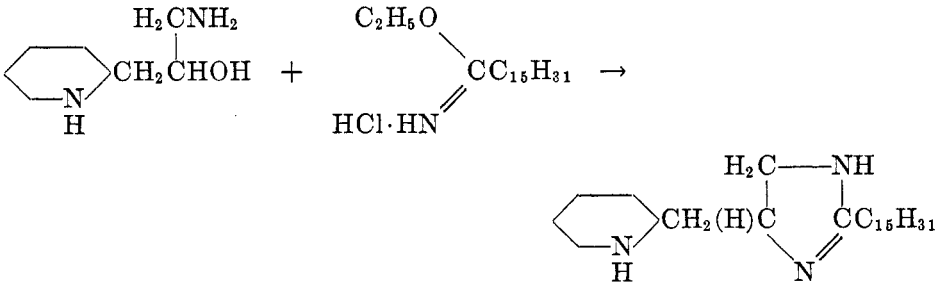


*4. Miscellaneous syntheses*

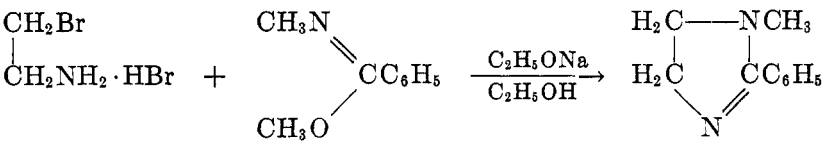
Benzamidine hydrochloride has been reported to react in aqueous sodium acetate with glyoxals, such as dimethylglyoxal or phenylglyoxal, to yield 2-imidazoline derivatives. These compounds are precipitated as the hydrochlorides by adding an excess of hydrochloric acid (29, 36, 129).



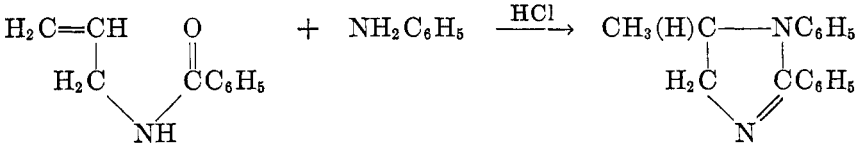
An imino alkyl ether and a β-hydroxy primary amine have been reported by Drozdov and Bekhli (42) to yield 2-imidazolines.



It has been shown that an alkyl-substituted imino alkyl ether reacts with a β-bromo primary amine hydrobromide to give a poor yield of a 2-imidazoline (121).

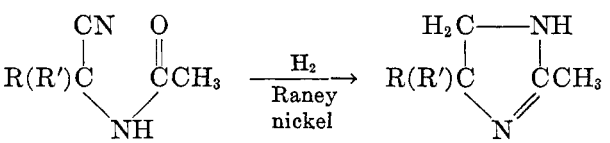


Clayton (28) has shown that *N*-allylbenzamide reacts with aniline in the presence of hydrochloric acid to yield a 2-imidazoline.

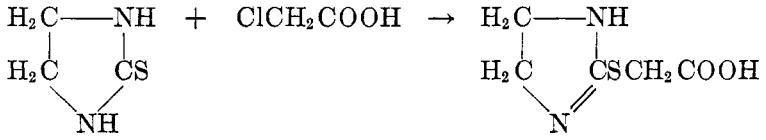


It has been reported by Diels (35) that monoöximes of α,β-diketones react with aldehydes in the presence of ammonia to yield 2-imidazolines.

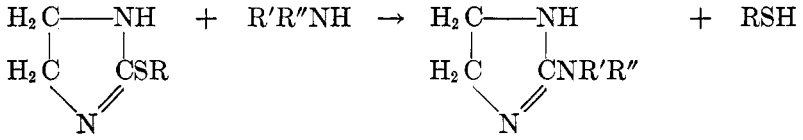
2-Imidazolines have been prepared in yields as high as 94 per cent by reducing the monoacetyl derivatives of α-aminonitriles (53, 54).



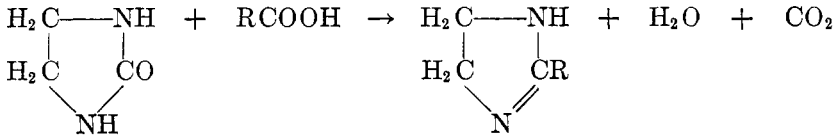
It has been shown that 2-imidazolidinethione and chloroacetic acid react to form 2-imidazolinyl alkyl thioethers (67).



Alkyl ethers of 2-imidazolidinethione have been found to react with primary or secondary amines to form *N*-substituted amino-2-imidazolines (60, 61).



An unusual method of preparing 2-imidazolines consists in heating to a high temperature a mixture of a 2-imidazolidone and a monocarboxylic acid other than formic acid (62).



It has been shown that compounds containing two or more imidazoline groups in each molecule may be prepared in yields as high as 85 per cent when this method is applied to di- or polycarboxylic acids having at least eight carbon atoms (63, 74, 75).

### B. PHYSICAL PROPERTIES OF 2-IMIDAZOLINES

2-Imidazolines unsubstituted at the nitrogen of the 1-position show a greater solubility in polar solvents than the 1-alkyl- or 1-aryl-substituted derivatives. 2-Methyl-2-imidazoline is hygroscopic and very soluble in water, alcohol, and chloroform and less so in benzene, carbon tetrachloride, and petroleum ether. The solubility of 2-substituted-2-imidazolines in polar solvents decreases with increasing length of the 2-substituted alkyl group. 2-Undecyl-2-imidazoline is only slightly soluble in water (18). Alcohol, amine, or sulfonic acid groupings are often introduced into 2-imidazolines to increase their water solubility.

2-Imidazolines which are unsubstituted in the 1-position are solids or heavy viscous oils, while compounds substituted in this position are most frequently liquids. This phenomenon, which is explained by association, is also found to be true of bisimidazolines.

Ultraviolet absorption spectra studies of 2-imidazolines show the presence of the carbon-to-nitrogen double bond (44).

## C. CHEMICAL PROPERTIES OF 2-IMIDAZOLINES

### *1. Salt formation*

In accordance with their cyclic amidine structure 2-imidazolines form monohydrogen halide salts and titrate potentiometrically as monoacid bases. They also form complexes with salts of silver, copper, and cobalt. The insoluble salts which are formed with gold or platinum ions may be used for identification purposes, as may the picrates (18). Aromatic isocyanates have also been shown to be useful in the identification of 2-imidazolines (55).

It has been found that 2-imidazolines form stable distillable complexes with organic acids, most of which contain 2 moles of acid in combination with 1 mole of 2-imidazoline. The 2-imidazolines may be liberated from such complexes by treatment with strong bases (100).

Quaternary salts of 2-imidazolines may be prepared in 46–96 per cent yield by heating with alkyl or aralkyl halides with or without a solvent (28). Interest in the germicidal properties of quaternary ammonium salts has prompted the preparation of a number of these substances. King and McMillan (68) have shown that when 2-methyl-2-imidazoline is treated with an alkyl halide, in addition to the expected alkylation product the alkyl halide of the quaternary salt of the alkylated 2-methyl-2-imidazoline is produced. They found that 1,2-dialkyl-2-imidazolines show a greater tendency to quaternize than 2-alkyl-2-imidazolines when the alkyl group already present in the 1-position is identical with that of the alkyl halide added.

### *2. Ring-opening*

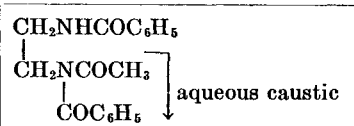
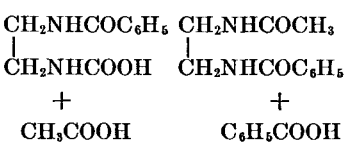
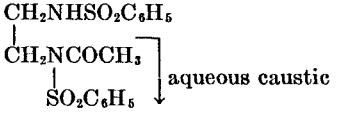
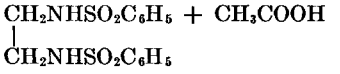
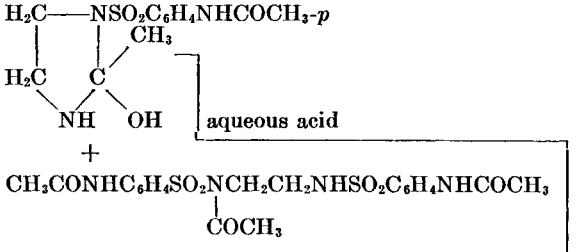
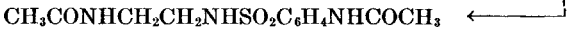
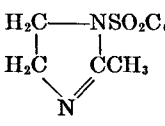
Since 2-imidazolines are cyclic amidines, it is not surprising to find them susceptible to hydrolysis. Minimum requirements for cleavage of the 2-imidazoline ring have not been reported; however, certain 2-imidazolines have been hydrolyzed to 1,2-diamines in yields as high as 70–80 per cent by heating with concentrated hydrochloric acid in a sealed tube or by refluxing with a 30 per cent potassium hydroxide solution (54).

2-Imidazolines may undergo ring-opening when treated with carboxylic or sulfonic acid chlorides. Ladenburg (81) found that a carbonate solution of 2-methyl-2-imidazoline reacts with benzoyl chloride to yield *N*-benzoyl-*N'*-acetylbenzoylethylenediamine, which on treatment with caustic gives further decomposition to dibenzoylethylenediamine and acetic acid (table 1). Aspinall's (7) studies of the reaction of benzoyl chloride with 2-substituted-2-imidazolines showed the presence of additional hydrolysis products besides those reported by Ladenburg. Triacyldiamines resulting from the ring-opening of 2-imidazoline rings were found to decompose in aqueous caustic, expelling some of each of the two groups attached to the diacylated nitrogen atom, rather than only eliminating the one originating from the 2-position of the 2-imidazoline ring (table 1).

Ring-opening reactions with benzenesulfonyl chloride were found to be similar, except that, as expected, the hydrolysis of monoacyldisulfonyldiamines with caustic eliminated exclusively the substituent originating from the 2-position of the 2-imidazoline ring.

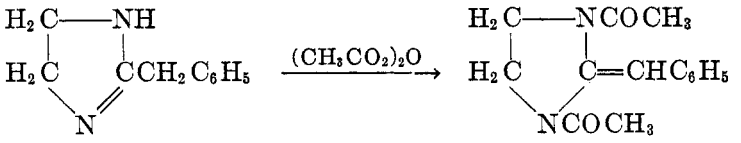
TABLE 1

*Reaction of 2-methyl-2-imidazoline with acid chlorides*

| Acid Chloride | Conditions | Product | References |
|---|---|---|---|
| $C_6H_5COCl$ | In aqueous carbonate |  | (7, 81) |
| $C_6H_5COCl$ | In aqueous caustic |  | (7) |
| $C_6H_5SO_2Cl$ | In aqueous carbonate |  | (7) |
| $C_6H_5SO_2Cl$ | In aqueous caustic |  | (7) |
| *p*-$CH_3CONHC_6H_4SO_2Cl$ | In aqueous caustic at 0–10°C. |  | (137) |
| *p*-$CH_3CONHC_6H_4SO_2Cl$ | In aqueous caustic at 60°C. |  | (137) |
| *p*-$O_2NC_6H_4SO_2Cl$ | In benzene followed by quenching in water |  | (137) |

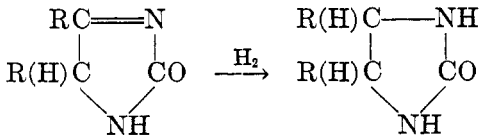
Zienty (137) obtained a hydroxyimidazolidine by treating 2-methyl-2-imidazoline with *N*-acetylsulfanilyl chloride in the presence of water and an equivalent of alkali. The usual derivative typical of secondary amines was formed when this same 2-imidazoline was treated with *p*-nitrobenzenesulfonyl chloride (table 1).

When 2-benzyl-2-imidazoline or 2-(diphenylaminomethyl)-2-imidazoline is treated with an acid chloride in the presence of sodium hydroxide or sodium bicarbonate, reactions similar to those shown in table 1 for 2-methyl-2-imidazoline are reported (83). When 2-benzyl-2-imidazoline is treated with an excess of acetic anhydride, a shift in the double bond apparently occurs, with the formation of 1,3-diacetyl-2-benzylidineimidazolidine.




*3. Hydrogenation and dehydrogenation*

Imidazoles may be reduced with hydrogen over a catalyst to 2-imidazolines, but the remaining nitrogen-to-carbon double bond is extremely resistant to further hydrogenation (52, 128, 134). When present in imidazolones this bond is easily reduced (134).




2-Imidazolines may be dehydrogenated to imidazoles by heating at 150–250°C. over metal catalysts such as powdered nickel, iron, platinum, palladium, copper, or silver (49, 78). 2-Imidazolines substituted and unsubstituted in the 1-position have been dehydrogenated to the corresponding imidazoles in 80–90 per cent yields using a nickel–petroleum paste (79). Potassium amide has been used in the dehydrogenation of amarine (2,4,5-triphenyl-2-imidazoline) to lophine (2,4,5-triphenylimidazole) (124).

*4. Halogenation*

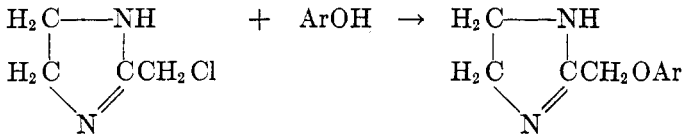
Little attention has been given to the halogenation of the 2-imidazoline structure. Chitwood and Reid (18) reported that treatment of 2-methyl-2-imidazoline with bromine in cold chloroform solution yields the hydrobromide of the monobrominated base, in which the bromine is thought to be attached to a nitrogen atom. It was hoped to remove the bromine as hydrobromic acid, but ethylenediamine was formed instead, owing to the hydrolysis of the 2-imidazoline in aqueous alkali.

When 2-(hydroxymethyl)-2-imidazoline is treated with phosphorus pentachloride or thionyl chloride in the presence or absence of a solvent a quantitative yield

of 2-(chloromethyl)-2-imidazoline is produced. The latter compound is a valuable intermediate in the synthesis of antihistamine agents (26, 69).

*5. Miscellaneous reactions*

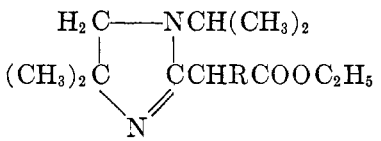
2-Imidazolines possessing antihistamine activity have been prepared by the alkylation of phenols with 2-(chloromethyl)-2-imidazoline (30, 31, 37).



When primary or secondary aromatic amines are used in this reaction, 2-(aminoalkyl)-2-imidazolines are obtained (21, 22, 88, 126).

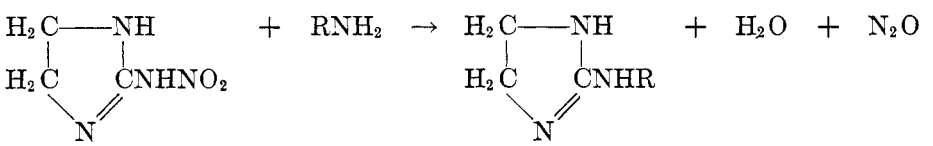
2-Imidazolines unsubstituted at the 1-position or containing one or more exchangeable hydrogen atoms present in substituted imido, amido, or hydroxyl groups, may be treated with epoxides, monohalogen derivatives of polyhydric alcohols, or a variety of other halides (1, 20, 34).

It has been found that the sodium derivative of ethyl 1-isopropyl-4,4-dimethyl-2-imidazolinyl-2-acetate may be alkylated with various halides to yield compounds of the type of XII, which on decarboxylation and hydrolysis afford 2-alkyl-1-isopropyl-4,4-dimethyl-2-imidazolines (95, 106).



XII

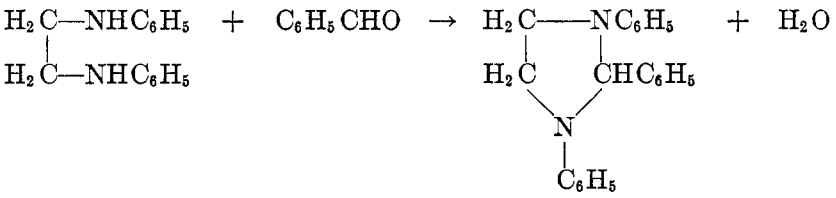
When 2-nitramino-2-imidazoline is refluxed with an aliphatic primary amine a 2-alkylamino derivative is obtained (87).



## III. Imidazolidines

### A. Synthesis of imidazolidines

The principal method of synthesis of imidazolidines is through the reaction of aldehydes with aliphatic 1,2-diamines in which both amino groups are secondary. Early work by Moos (91) showed that *N*,*N*′-diphenylethylenediamine and benzaldehyde yield triphenylimidazolidine.

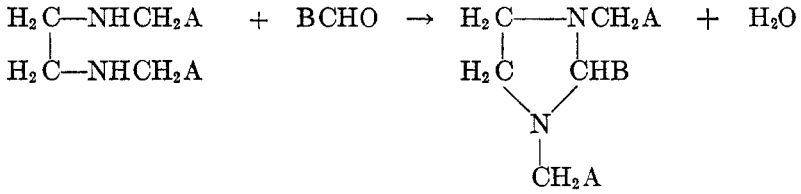


Aliphatic 1,2-diamines in which both amino groups are primary always react with aromatic aldehydes to form bis(arylidene)imines instead of imidazolidines (84, 122).

$$ArCHO + NH_2(CH_2)_nNH_2 \rightarrow ArCH{=}N(CH_2)_nN{=}CHAr$$

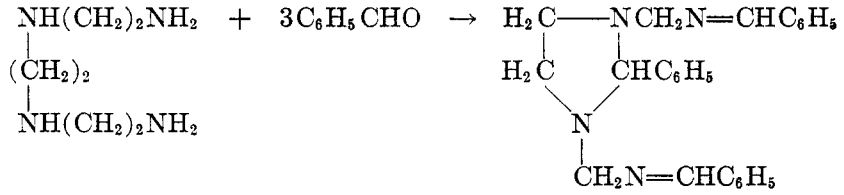
Aliphatic diprimary 1,2-diamines usually react with aliphatic aldehydes in the same manner (71).

The Schiff bases prepared from 1,2-diprimary diamines and aldehydes may be reduced by sodium and ethyl alcohol (82), sodium amalgam (3), or catalytically with platinum oxide and hydrogen (11) to 1,2-disecondary diamines. The 1,2-diamines formed in this manner have been used to prepare a large number of imidazolidine derivatives (3, 4, 82, 99).

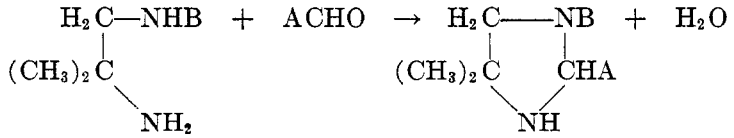


This reaction appears to be quite general, since groups A and B may be aliphatic, aromatic, or heterocyclic.

It has been shown by van Alphen (4) that a polyamine containing both primary and secondary amino groups reacts with an aldehyde as follows:



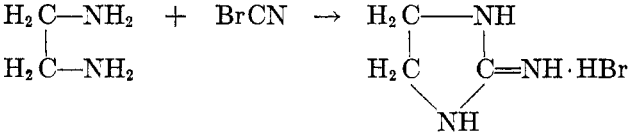
1,2-Diamines containing one primary and one secondary amino group have been found to form imidazolidines in approximately 70 per cent yields.



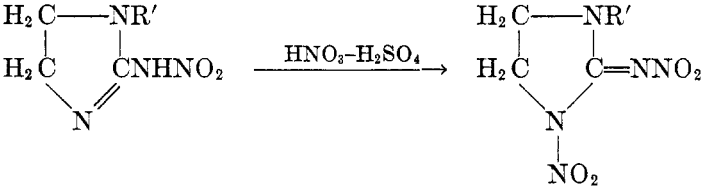
The course of this reaction was found to be independent of the nature of groups A and B (102).

Ketones usually cannot be substituted for aldehydes in their reactions with 1,2-diamines to prepare imidazolidines. Lob (82) was unable to obtain a reaction between 1,2-bis(benzylamino)ethane and acetone or acetophenone even when the reaction mixture was heated in a closed tube at 200–210°C. A method of differentiating between aldehydes and ketones has been reported which is based on the preparation of solid derivatives with 1,2-bis (*p*-methoxybenzylamino)ethane and aldehydes. Acetone was the only ketone found to react with this 1,2-diamine (11). Ethylenediamine does not usually react with ketones to yield imidazolidines; however, imidazolidine formation has been reported with cyclohexanone (9). No reaction was found between 1,2-diamines containing one primary and one secondary amino group and common ketones, such as acetone and acetophenone (102).

The reaction of 1,2-diamines with cyanohalogens such as cyanobromide or cyanoiodide to prepare 2-iminoimidazolidines has been employed by Schenck (104) and Pierron (97).



When 1-substituted-2-nitramino-2-imidazolines are treated with a mixture of nitric and sulfuric acids an imidazolidine is formed (86).



R′ = alkyl group.

There are a few less widely studied reactions in which imidazolidines were obtained. It is claimed that the hydrobromides or hydrochlorides of mandelimidic acid esters can be refluxed with alkylenediamines to yield derivatives of imidazolidine carbinol hydrochlorides (15). It has been reported by Brook (16) that when *N*,*N*′-diisobutylideneëthylenediamine was hydrogenated a mixture of *N*,*N*′-diisobutylethylenediamine and 1,3-diisobutyl-2-isopropylimidazolidine was obtained.

### B. PROPERTIES OF IMIDAZOLIDINES

Imidazolidines are easily hydrolyzed. 1,3-Dibenzyl-2-phenylimidazolidine is immediately hydrolyzed to benzaldehyde and 1,2-bis(benzylamino)ethane with 10 per cent aqueous hydrochloric or sulfuric acid, but is unattacked by 10 per cent caustic soda. This compound may be oxidized with aqueous potassium permanganate to yield benzoic acid and benzamide.

Imidazolidines may be either oils or crystalline solids. They are readily soluble in common organic solvents and insoluble in water.

The stereochemistry of several imidazolidines has been studied through electric moment measurements (45). Ultraviolet absorption spectra studies of a number of imidazolidines have been made and in several cases used to confirm their structures (44).

## IV. Uses of 2-Imidazolines and Imidazolidines

Many 2-imidazolines substituted in the 2-position by either alkyl, aryl, or aralkyl groups show a definite effect on the circulatory system. 2-Benzyl-2-imidazoline, which is known as "Priscol," is an important vasodilator, while "Privine" [2-(1-naphthylmethyl)-2-imidazoline] and "Otrivine" [2-(anilinomethyl)-2-imidazoline] are useful vasoconstrictors. A number of compounds, such as 2-(benzhydryloxymethyl)-2-imidazoline, have been found to be strong histamine antagonists.

Certain 2-imidazolines may be used as surface-active agents in the emulsification of oil and water for lubrication and other industrial purposes (93, 131). Salts of 2-imidazolines with aromatic monosulfonic acids are used as demulsifying agents (12). Demulsifiers have also been prepared by heating 2-imidazolines containing amino alkylene or hydroxy alkylene groups with urea or urea derivatives (33).

2-Heptadecyl-2-imidazoline, 2-heptadecyl-1-(hydroxyethyl)-2-imidazoline, and related derivatives are successful surface-active agents in foliage fungicides (57, 90, 103). The surface activity and the basic character of some 2-imidazoline derivatives have made them useful in the beneficiation of acidic minerals. Certain 2-imidazolines or their soluble salts are used for textile finishing and softening of cellulosic fibrous material (105, 132).

2-Imidazoline derivatives are reported to inhibit corrosion against brines, weak inorganic acids, organic acids, carbon dioxide, and hydrogen sulfide (13, 50, 59), to prevent or inhibit clogging tendencies of fuel oils (17), and to improve the adherence of asphalt to wet aggregate (89).

Imidazolidines substituted with a hydropyranyl ring are useful as insecticides, as ingredients in pharmaceutical products, and as ingredients in compounding or vulcanizing rubber (130).

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