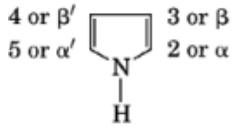
Kirk-Othmer Encyclopedia of Chemical Technology.

PYRROLE AND PYRROLE DERIVATIVES

Pyrrole [109-97-7], a five-membered, heterocyclic system, is a fundamental structural subunit of many of the most important biological molecules, eg, heme, the chlorophylls, the bile pigments, some naturally occurring antibiotics, many alkaloids, and some enzymes. Pyrrole was first obtained in 1834 from the destructive distillation of coal or bone (1). It was characterized in 1858, and its composition was determined in 1870 (2, 3). Early interest in the chemistry of pyrrole began with the discovery that indole (benzopyrrole) is the fundamental nucleus of indigo. Ring positions in pyrrole **(1)** are designated by number or Greek letter.

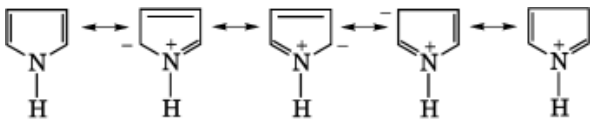


(1)

1. Physical Properties

Pyrrole is a colorless, slightly hygroscopic liquid which, if fresh, emits an odor like that of chloroform. However, it darkens on exposure to air and eventually produces a dark brown resin. It can be preserved by excluding air from the storage container, preferably by displacement with ammonia to prevent acid-catalyzed polymerization. A review of the physical and theoretical aspects of pyrrole is found in Reference 4. Some physical properties of pyrrole are listed in Table 1.

Pyrrole has a planar, pentagonal (C_{2v}) structure and is aromatic in that it has a sextet of electrons. It is isoelectronic with the cyclopentadienyl anion. The π-electrons are delocalized throughout the ring system, thus pyrrole is best characterized as a resonance hybrid, with contributing structures **(1–5)**. These structures explain its lack of basicity (which is less than that of pyridine), its unexpectedly high acidity, and its pronounced aromatic character. The resonance energy which has been estimated at about 100 kJ/mol (23.9 kcal/mol) is intermediate between that of furan and thiophene, or about two-thirds that of benzene (5).



(1) **(2)** **(3)** **(4)** **(5)**

The contributions from the canonical forms have been calculated, and the contributions from the equivalent polar structures **(2)** and **(3)** dominate those of **(4)** and **(5)** (6). Thus, electrophilic substitution is predicted

Table 1. Physical Properties of Pyrrole

Property	Value
melting point, °C	−23.4
boiling point, °C	129.8
critical temperature, °C	366
density, d_4^{20}, g/mL	0.970
refractive index, n_D^{20}	1.5085
dielectric constant at 20°C, ϵ	8.00
flash point, closed cup, °C	39

to occur in the α-position, and this is proven experimentally in most cases. Nitrosation and selenocyanation occur at the β-position (7, 8).

Many of the physical characteristics of pyrrole indicate at least partial association. In particular, the boiling point is 98°C higher than that of furan. It has been postulated that various associated dimeric and higher structures occur because of hydrogen bonding (9, 10).

Pyrrole is soluble in alcohol, benzene, and diethyl ether, but is only sparingly soluble in water and in aqueous alkalies. It dissolves with decomposition in dilute acids. Pyrroles with substituents in the β-position are usually less soluble in polar solvents than the corresponding α-substituted pyrroles. Pyrroles that have no substituent on nitrogen readily lose a proton to form the resonance-stabilized pyrrolyl anion, and alkali metals react with it in liquid ammonia to form salts. However, pyrrole (pK_a = ca 17.5) is a weaker acid than methanol (11). The acidity of the pyrrole hydrogen is greatly increased by electron-withdrawing groups, eg, the pK_a of 2,5-dinitropyrrole [32602-96-3] is 3.6 (12, 13).

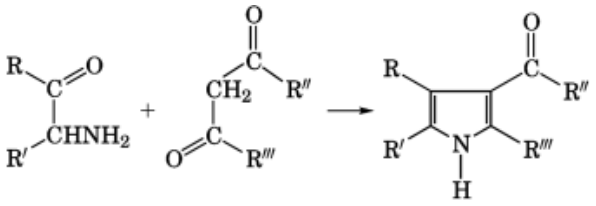
The dipole moment varies according to the solvent; it is ca 5.14×10^{-30} C·m (ca 1.55 D) when pure and ca 6.0×10^{-30} C·m (ca 1.8 D) in a nonpolar solvent, such as benzene or cyclohexane (14, 15). In solvents to which it can hydrogen bond, the dipole moment may be much higher. The dipole is directed toward the ring from a positive nitrogen atom, whereas the saturated nonaromatic analogue pyrrolidine [123-75-1] has a dipole moment of 5.24×10^{-30} C·m (1.57 D) and is oppositely directed. Pyrrole and its alkyl derivatives are π-electron rich and form colored charge-transfer complexes with acceptor molecules, eg, iodine and tetracyanoethylene (16).

Infrared spectra of pyrrole and its derivatives have been described in detail (13). The N–H absorption of nonassociated pyrroles varies predictably with the substituents and is related to the acidity of the pyrrole. It has been used as evidence for intermolecular association, which results from hydrogen bonding, between pyrrole units. Nuclear magnetic resonance studies have provided evidence for ring currents (17). The concentration and temperature dependence of the hydrogen chemical shifts have been used to estimate the enthalpy of self-association as −6.7 kJ/mol in pyrrole (18). The effect of substituents upon the various chemical shifts has also been reported (19). Pyrrole gives an intense molecular ion in its mass spectrum. Smaller fragments result primarily from ring-size reduction.

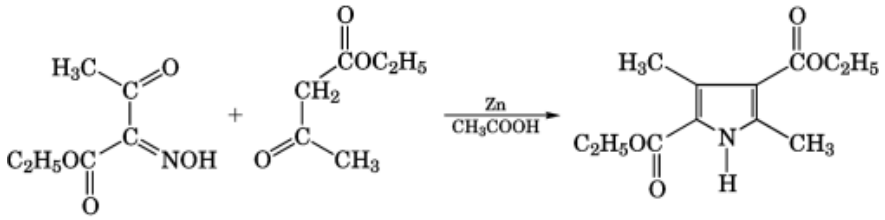
2. Syntheses of Pyrroles

2.1. Knorr Synthesis

Condensation of an α-aminoketone with a carbonyl compound was first reported by Knorr (20). This reaction and its modifications are among the most important and widely used methods for the synthesis of pyrroles.

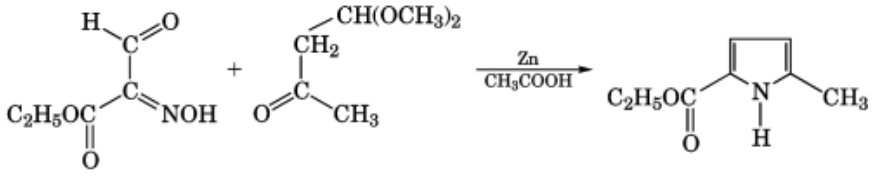


Because the α-aminoketone is subject to self-condensation, the condensation with a β-dicarbonyl derivative **(6)** is usually carried out by generating the α-aminoketone *in situ* through reduction of an oximino derivative **(7)**; zinc in glacial acetic acid is used as the reductant. For example, Knorr's pyrrole [2436-79-5] **(8)** forms from **(6)** and **(7)**.



(7) **(6)** **(8)**

Modifications include the use of β-ketoaldehydes as acetals, eg **(9)**, which leads to loss of the formyl group (21); the product in this example is 5-ethoxycarbonyl-2-methylpyrrole [3284-51-3].

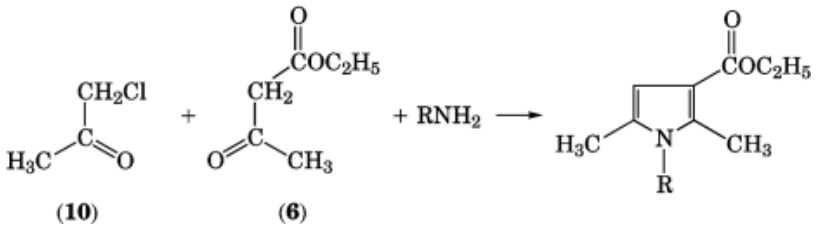


(7) **(9)**

The Knorr synthesis is not particularly sensitive to the nature of R and R‴, ie, they may be alkyl, acyl, aryl, or carbalkoxy without significantly affecting the yield. Similarly, good yields are obtained if R′ and R″ are acyl or carbalkoxy, but poor yields are obtained if they are alkyl or aryl.

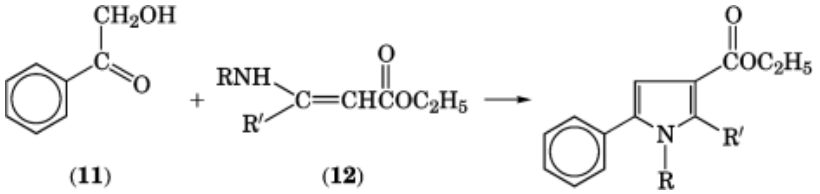
2.2. Hantzsch and Feist Syntheses

The Hantzsch synthesis of pyrroles involves condensation of an α-haloketone **(10)** with a β-keto ester **(6)** in the presence of ammonia or an amine (22).



(10) (6)

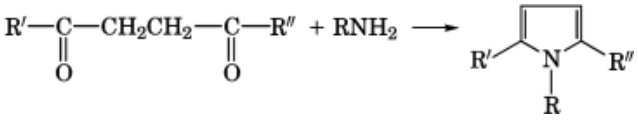
The Feist synthesis is similar to the Hantzsch method and involves condensation of acyloins, eg **(11)**, with aminocrotonic esters, eg **(12)**, in the presence of zinc chloride (23).



(11) (12)

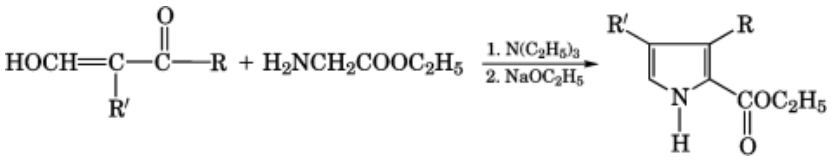
2.3. Paal-Knorr Synthesis

The condensation of a 1,4-diketone, for example, with ammonia or a primary amine generally gives good yields of pyrroles; many syntheses have been reported (24). The lack of availability of the appropriate 1,4-diketone sometimes limits the usefulness of the reaction.

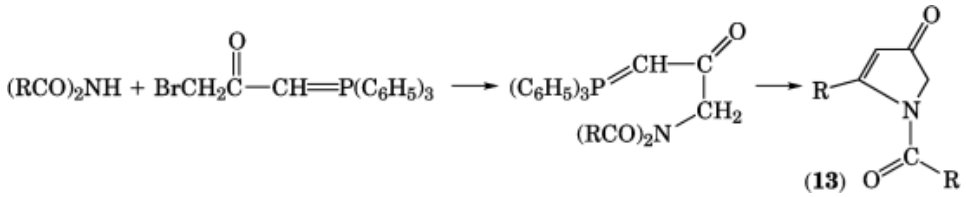


2.4. Other Methods

Newer methods for forming pyrrole and related heterocyclic rings include the formation of substituted pyrrole 2-carboxylate esters by condensation of β-dicarbonyl compounds with glycinate esters (25).

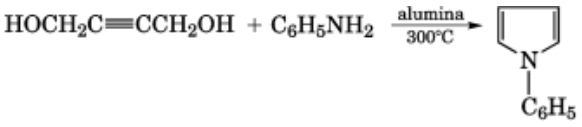


A Wittig-type reaction has been used to obtain N-protected 3-hydroxypyrroles, which exist as the pyrrolenone **(13)** tautomers (26).

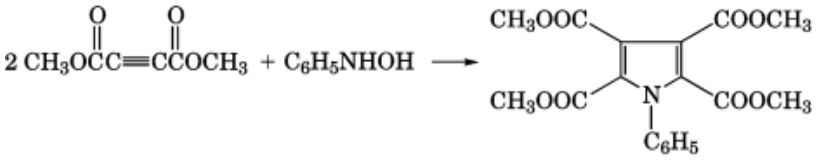


(13)

Acetylenic compounds have often been used as precursors to certain pyrroles. Thus, 2-butyne-1,4-diol reacts with aniline in the presence of alumina to produce *N*-phenylpyrrole [635-90-5] (27).

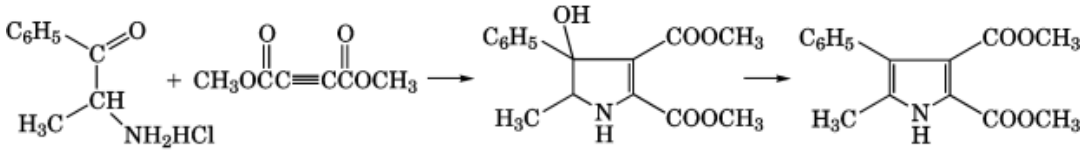


Acetylenedicarboxylic esters also react with phenylhydroxylamines to give pyrroles (28), eg, *N*-phenylpyrrole-2,3,4,5-tetracarboxylic acid, tetramethyl ester [37802-39-4] **(14)**.



(14)

α-Aminoketones and acetylenic carbonyl compounds cyclize and dehydrate to give pyrroles in high yields by a Michael-type addition (29), eg, dimethyl 5-methyl-4-phenylpyrrole-2,3-dicarboxylate [53252-73-6] **(15)** in the following.



(15)

3. Pyrrolines and Pyrrolidines

The pyrrolines or dihydropyrroles can exist in three isomeric forms: 1-pyrroline (3,4-dihyro-2*H*-pyrrole [5724-81-2]) **(16)** is an unstable material that resinifies upon exposure to air; 2-pyrroline (2,3-dihydro-1*H*-pyrrole [638-31-3]) **(17)** is even more unstable; only 3-pyrroline (2,5-dihydro-1*H*-pyrrole [109-96-6]) **(18)** is reasonably stable. 3-Pyrroline boils at 91°C and has a density of 0.9097 g/cm^3 and a refractive index of 1.4664.

(16)

(17)

(18)

Pyrrolidine [123-75-1] (tetrahydropyrrole) **(19)** is a water-soluble strong base with the usual properties of a secondary amine. An important synthesis of pyrrolidines is the reaction of reduced furans with excess amine or ammonia over an alumina catalyst in the vapor phase at 400°C. However, if labile substituents are present on the tetrahydrofurans, pyrroles may form (30).

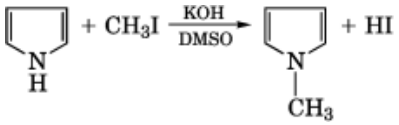
(19)

Pyrrolidines also can be obtained by reaction of 1,4-dihydroxyalkanes with amines in the presence of dehydrating agents at elevated temperatures or by reaction of primary amines with 1,4-dihaloalkanes. The dry distillation of 1,4-butanediamine dihydrochloride also generates pyrrolidine. Pyrroles can also be catalytically hydrogenated to pyrrolidines.

4. Reactions of Pyrroles

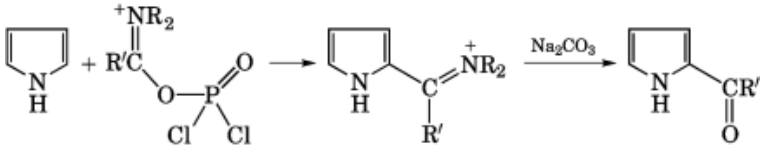
In keeping with its aromatic character, pyrrole is relatively difficult to hydrogenate, it does not ordinarily serve as a diene for Diels-Alder reactions, and does not undergo typical olefin reactions. Electrophilic substitutions are the most characteristic reactions, and pyrrole has often been compared to phenol or aniline in its reactivity. Acids strong enough to form salts with pyrrole destroy the aromaticity and cause polymerization.

N-Alkylpyrroles may be obtained by the Knorr synthesis or by the reaction of the pyrrolyl metallates, ie, Na, K, and Tl, with alkyl halides such as iodomethane, eg, 1-methylpyrrole [96-54-8]. Alkylation of pyrroles at the other ring positions can be carried out under mild conditions with allylic or benzylic halides or under more stringent conditions (100–150°C) with CH_3I. However, unless most of the other ring positions are blocked, polyalkylation and polymerization tend to occur. N-Alkylation of pyrroles is favored by polar solvents and weakly coordinating cations (Na^+, K^+). More strongly coordinating cations (Li^+, Mg^{2+}) lead to more C-alkylation.



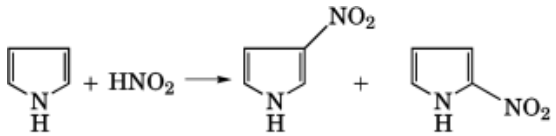
N-Acylation is readily carried out by reaction of the alkali metal salts with the appropriate acid chloride. C-Acylation of pyrroles carrying negative substituents occurs in the presence of Friedel-Crafts catalysts. Pyrrole and alkylpyrroles can be acylated noncatalytically with an acid chloride or an acid anhydride. The formation of trichloromethyl 2-pyrryl ketone [35302-72-8] (**20**, R′ = CCl_3) is a particularly useful procedure because the ketonic product can be readily converted to the corresponding pyrrolecarboxylic acid or ester by treatment with aqueous base or alcoholic base, respectively (31).

The most generally useful method for acylation or formylation of pyrroles is the Vilsmeier-Haack reaction (32, 33). The pyrrole is treated with the phosphoryl complex of *N,N*-dialkylamide and the intermediate imine salt is hydrolyzed.



(**20**)

Nitration of pyrroles by the usual methods leads to extensive degradation. However, nitration can be achieved with an equimolar nitric acid–acetic anhydride mixture at low temperatures. In the case of pyrrole, the reaction leads predominantly to substitution at the β-position (34), ie, in the following: 51% 3-nitropyrrole [5930-94-9] **(21)** and 13% 2-nitropyrrole [5919-26-6] **(22)**.



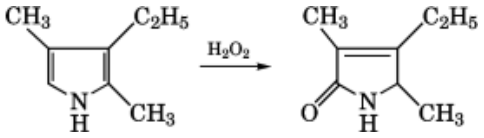
(**21**) (**22**)

Halogenation reactions usually involve pyrroles with electronegative substituents. Mixtures are usually obtained and polysubstitution products, ie, tetrahalopyrroles, predominate. The monohalopyrroles are difficult to prepare and are not very stable in air or light.

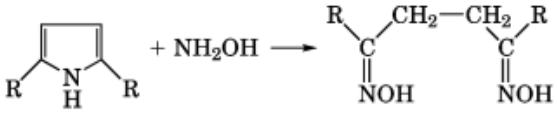
The following rules pertain to electrophilic substitution in pyrroles (35): (*1*) an electron-withdrawing substituent in the α-position directs substitution to the β'- and α'-positions, (*2*) an electron-releasing substituent in the α-position directs substitution to the neighboring β-position or to the α'-position, (*3*) an electron-withdrawing substituent in the β-position leads to substitution in the α'-position, and (*4*) an electron-releasing substituent in the β-position tends to direct substitution into the neighboring α-position.

Pyrrole can be reduced catalytically to pyrrolidine over a variety of metal catalysts, ie, Pt, Pd, Rh, and Ni. Of these, rhodium on alumina is one of the most active. Less active reducing agents have been used to produce the intermediate 3-pyrroline (36). The 2-pyrrolines are ordinarily obtained by ring-closure reactions. Nonaromatic pyrrolines can be reduced easily with H_2 to pyrrolidines.

Pyrrole oxidizes in air to red or black pigments of uncertain composition. More useful is the preparation of 2-oxo-Δ^3-pyrrolines, which is best carried out by oxidation of the appropriate pyrrole with H_2O_2 in pyridine (37), eg, 3,5-dimethyl-ethyl-3-pyrrolin-2-one [4030-24-4] from 2,4-dimethyl-3-ethylpyrrole [517-22-6]. Perbenzoic acid oxidizes *N*-methylpyrrole to *N*-methylsuccinimide (38).

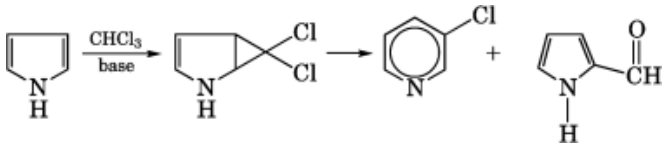


Ring openings of pyrrole commonly occur at the carbon–nitrogen bond. Treatment of pyrrole or 2,5-dimethylpyrrole [625-84-3] (**23**, R = CH_3) with hydroxylamine leads to ring opening and formation of dioximes **(31)** (39).



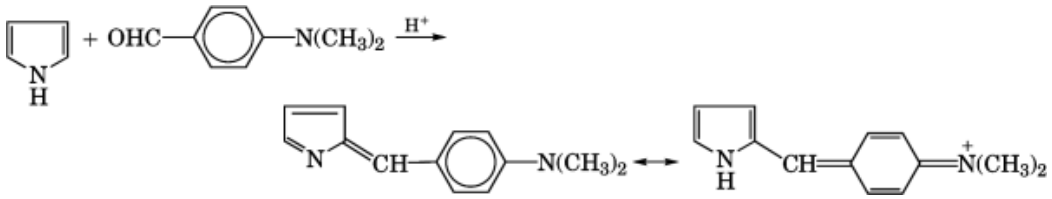
(**23**)

Reaction of pyrrole with carbenes yields enlarged ring systems as well as 2-formylpyrrole [1003-29-8] (40).



4.1. Analytical and Test Methods

In addition to the modern spectroscopic methods of detection and identification of pyrroles, there are several chemical tests. The classical Runge test with HCl yields pyrrole red, an amorphous polymer mixture. In addition, all pyrroles with a free α- or β-position or with groups, eg, ester, that can be converted to such pyrroles under acid conditions undergo the Ehrlich reaction with *p*-(dimethylamino)benzaldehyde to give purple products.

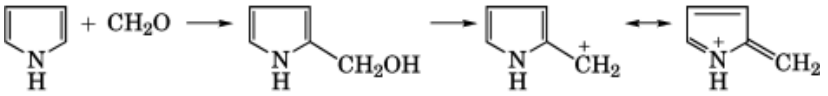


Both pyrrole and indole react with selenium dioxide in the presence of nitric acid to give a deep violet solution. Very small quantities (ca 4×10^{-5} g) of pyrrole can be detected by this method.

5. Functional Derivatives

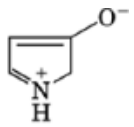
5.1. Hydroxypyrroles

Pyrroles with nitrogen-substituted side chains containing hydroxyl groups are best prepared by the Paal-Knorr cyclization. Pyrroles with hydroxyl groups on carbon side chains can be made by reduction of the appropriate carbonyl compound with hydrides, by Grignard synthesis, or by insertion of ethylene oxide or formaldehyde. For example, pyrrole plus formaldehyde gives 2-hydroxymethylpyrrole [27472-36-2] **(24)**. The hydroxymethylpyrroles do not act as normal primary alcohols because of resonance stabilization of carbonium ions formed by loss of water.



(1) **(24)**

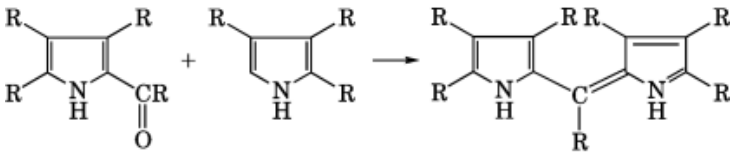
The α-hydroxypyrroles, which exist primarily in the tautomeric pyrrolin-2-one form, can be synthesized either by oxidation of pyrroles that are unsubstituted in the α-position or by ring synthesis. β-Hydroxypyrroles also exist primarily in the keto form but do not display the ordinary reactions of ketones because of the contributions of the polar form **(25)**. They can be readily O-alkylated and -acylated (41).



(25)

5.2. Aldehydes and Ketones

Pyrrole aldehydes and ketones are somewhat less reactive than the corresponding benzenoid derivatives. The aldehydes do not undergo Cannizzaro or Perkin reactions but condense with a variety of compounds that contain active methylene groups. They also react with pyrroles under acidic conditions to form dipyrrylmethenes **(26)**. The aldehydes can be reduced to the methyl or carbinol structures. The ketones undergo normal carbonyl reactions.



(26)

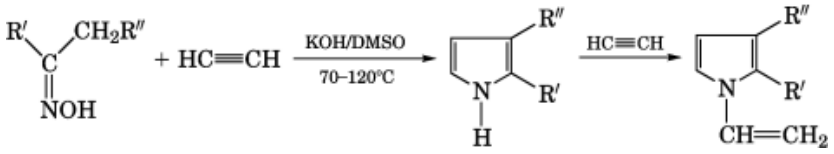
5.3. Pyrrole Carboxylic Acids and Esters

The acids are considerably less stable than benzoic acid and often decarboxylate readily on heating. However, electron-withdrawing substituents tend to stabilize them toward decarboxylation. The pyrrole esters are important synthetically because they stabilize the ring and may also act as protecting groups. Thus, the esters

can be utilized synthetically and then hydrolyzed to the acid, which can be decarboxylated by heating. Often β-esters are hydrolyzed more easily than the α-esters.

5.4. Vinyl Pyrroles

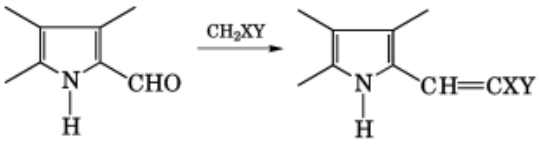
Relatively new synthetic routes based on a one-pot reaction between ketoximes and acetylene in an alkali metal hydroxide–dimethyl sulfoxide (DMSO) system have made vinyl pyrroles accessible. It requires no pyrrole precursors and uses cheap and readily available ketones (42).



The 1-vinylpyrroles are highly reactive and are sensitive to oxygen. Conjugation of the vinyl group with the aromatic ring leads to a greater susceptibility to electrophilic attack. *N*-Vinylpyrroles have been shown to react additively with alcohols, diols, and hydrosilanes.

N-Vinyl polymers may be used for the preparation of semiconductors (qv). Derivatives of others have biological activity, eg, a derivative of 2-phenyl-1-vinylpyrrole, 2-phenyl-1-(propargyloxyethyl)pyrrole, stimulates motor activity and increases excitation, etc (42) (see *n*-VINYL AMIDES).

2-Vinylpyrroles and 3-vinylpyrroles can be prepared by the base-catalyzed condensation of the corresponding formyl pyrroles with activated methylene groups, CH_2XY, where X, Y = COR, COOH, CN, etc.

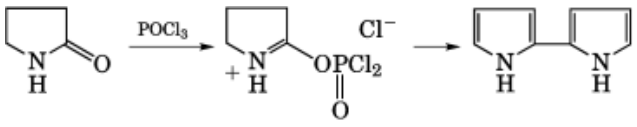


5.5. Condensed Pyrroles

Pyrroles can be condensed to compounds containing two, three, or four pyrrole nuclei. These are important in synthetic routes to the tetrapyrrolic porphyrins, corroles, and bile pigments and to the tripyrrolic prodigiosins. The pyrrole nuclei are joined by either a one-carbon fragment or direct pyrrole–pyrrole bond.

5.6. Bipyrroles

Although four different types of bipyrroles, ie, 1,1′-, 2,2′-, 2,3′-, and 3,3′-, are known, the most important is 2,2′-bipyrrole [10087-64-6], which can be made by the Vilsmeier condensation of 2-pyrrolidinone [616-45-5] **(27)** (43).

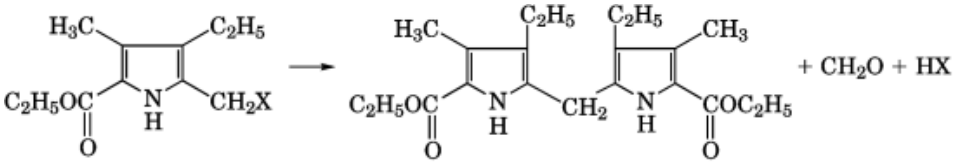


(27)

Other syntheses utilize α-bromo or α-iodo compounds, which condense on heating with copper (44).

5.7. Dipyrrylmethanes

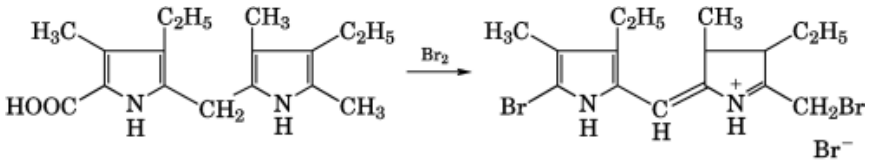
The most important dipyrrylmethanes are the 2,2′derivatives. The parent compound is not very stable, but electron-withdrawing substituents increase its stability considerably. Symmetrical dipyrrylmethanes, eg, the diethyl ester of 5,5′-methylenebis(4-ethyl-3-methyl)pyrrole-2-carboxylic acid [6305-93-7] **(28)**, can be synthesized by acid-catalyzed self-condensation of α-halomethyl-, α-acetoxymethyl-, or α-methoxymethylpyrroles (45). Unsymmetrical dipyrrylmethanes are obtained through condensation of α-bromomethyl- or α-hydroxymethylpyrroles with a pyrrole that has an open α- or β-position.



(28)

5.7.1. Dipyrrylmethenes

Oxidation of the dipyrrylmethanes, eg, 5-carboxy-3,4′-diethyl-4,3′,5′-trimethyl-2,2′-dipyrrylmethane [26030-65-9] **(29)**, by bromine or sulfuryl chloride yields dipyrrylmethenes, eg **(30)** [80294-31-1].



(29) **(30)**

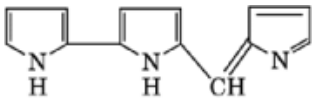
5.8. Polypyrroles

Highly stable, flexible films of polypyrrole are obtained by electrolytic oxidation of the appropriate pyrrole monomers (46). The films are not affected by air and can be heated to 250°C with little effect. It is believed that the pyrrole units remain intact and that linking is by the α-carbons. Copolymerization of pyrrole with *N*-methylpyrrole yields compositions of varying electrical conductivity, depending on the monomer ratio. Conductivities as high as $10^4/(\Omega\cdot m)$ have been reported (47) (see Electrically conductive polymers).

Because of its physical properties, polypyrrole has been cited as a unique building block for intelligent polymeric materials, ie, it has characteristics which make it capable of sensing, information processing, and response actuation (48).

5.9. Natural Products

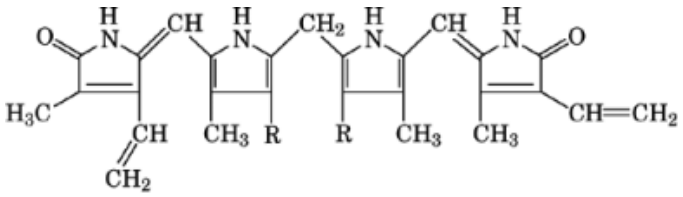
The prodigiosins are antibacterial and antifungal orange-red pigments based on the basic pyrryl–dipyrrylmethene unit [22187-69-5] **(31)**.



(31)

5.9.1. Bile Pigments

The oxidative degradation of heme yields open-chain tetrapyrrole as a waste product in humans and other higher animals. The yellow color of the skin in jaundice victims is caused by the presence of bilirubin [635-65-4] (**32**, R = $(CH_2)_2COOH$).



(32)

5.10. Phthalocyanines

The pyrrole ring system is also the fundamental structural unit of the important group of blue and blue-green pigments known as the phthalocyanines (see Phthalocyanine compounds).

6. Pyrrolidinones and Derivatives

2-Pyrrolidinone (2-pyrrolidone, butyrolactam or 2-Pyrol) **(27)** was first reported in 1889 as a product of the dehydration of 4-aminobutanoic acid (49). The synthesis used for commercial manufacture, ie, condensation of butyrolactone with ammonia at high temperatures, was first described in 1936 (50). Other synthetic routes include carbon monoxide insertion into allylamine (51, 52), hydrolytic hydrogenation of succinonitrile (53, 54), and hydrogenation of ammoniacal solutions of maleic or succinic acids (55–57). Properties of 2-pyrrolidinone are listed in Table 2. 2-Pyrrolidinone is completely miscible with water, lower alcohols, lower ketones, ether, ethyl acetate, chloroform, and benzene. It is soluble to ca 1 wt % in aliphatic hydrocarbons.

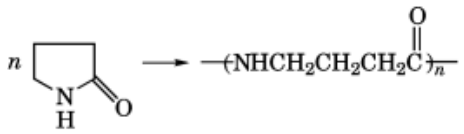
6.1. Reactions of 2-Pyrrolidinone

Pyrrolidinone undergoes the reactions of a typical lactam, eg, ring opening, attack on the carbonyl group, and replacement of hydrogens alpha to the carbonyl group. Many of the reactions involve the amide. 2-Pyrrolidinone can be polymerized with anionic catalyst systems to polypyrrolidinone (nylon-4) **(33)**, which is a high molecular weight linear polymer of potential interest as a textile fiber, film former, and molding compound (58, 59) (see Polyamides).

Table 2. Properties of 2-Pyrrolidinone

Property	Value
melting point, °C	25.6
boiling point, °C	
at 0.133 kPa[a]	103
1.33 kPa[a]	122
13.2 kPa[a]	181
101.3 kPa[a]	245
density (l), g/cm^3	
d_4^{25}	1.107
d_4^{50}	1.087
refractive index	1.4860
viscosity, at 25°C, mPa·s(= cP)	13.3
flash point, open cup, °C	129.41

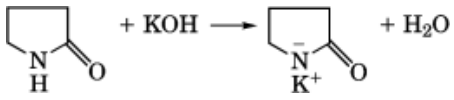
[a]To convert kPa to mm Hg, multiply by 7.5.



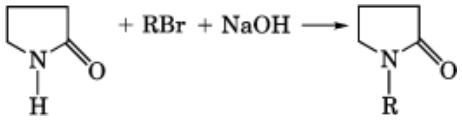
(27) (33)

Strong acids or bases catalyze the hydrolysis of 2-pyrrolidinone to 4-aminobutanoic acid [γ-aminobutyric acid [56-12-2] (GABA)]. GABA is involved in the functioning of the brain and nervous system and is of considerable interest as a potential dietary supplement (60).

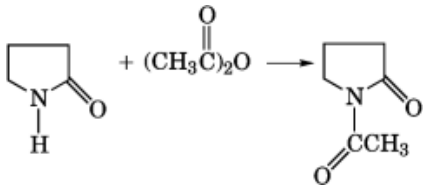
2-Pyrrolidinone forms alkali metal salts by direct reaction with alkali metals or their alkoxides or with their hydroxides under conditions in which the water of reaction is removed. The potassium salt prepared *in situ* serves as the catalyst for the vinylation of 2-pyrrolidinone in the commercial production of *N*-vinylpyrrolidinone. The mercury salt has also been described, as have the N-bromo and N-chloro derivatives (61, 62).



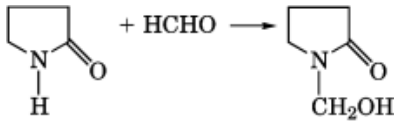
2-Pyrrolidinone can be alkylated by reaction with an alkyl halide or sulfate and an alkaline acid acceptor (63, 64). This reaction can be advantageously carried out with a phase-transfer catalyst (65). Alkylation can also be accomplished with alcohols and either copper chromite or heterogenous acid catalysts (66, 67).



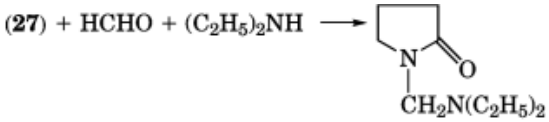
Treatment of 2-pyrrolidinone with an acid anhydride or acyl halide results in N-acylation.



The amide nitrogen readily adds across the carbonyl group of an aldehyde yielding N-hydroxyalkyl-substituted pyrrolidinones (68), eg, *N*-methylol-2-pyrrolidinone [15438-71-8] **(34)**. In the presence of secondary amines or alcohols, the hydroxyl groups are replaced (69), eg, if diethylamine is present the product is *N*-diethylaminomethyl-2-pyrrolidinone [66297-50-5] **(35)**.

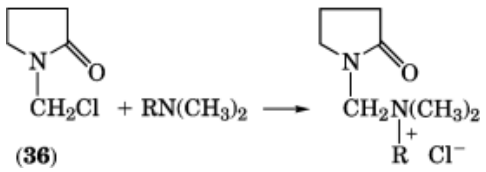


(27) **(34)**



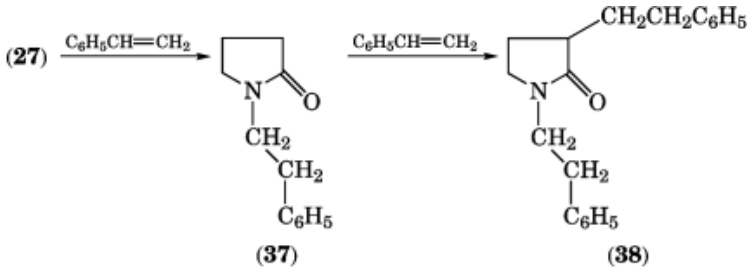
(35)

Treatment of *N*-hydroxymethylpyrrolidinone **(34)** with a chlorinating agent, eg, thionyl chloride, produces chloromethyl pyrrolidinone **(36)**, a powerful alkylating agent useful for introducing the methylpyrrolidinonyl group into surface-active materials via quarternization of long-chain surface-active amines (70).



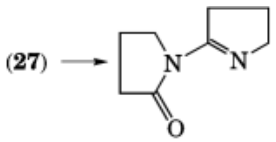
(36)

2-Pyrrolidinone is readily N-alkylated by styrene to give *N*-(2-phenyethyl)2-pyrrolidinone [10135-23-6] **(37)**. Additional styrene alkylates the 3-position (71) yielding 1,3-bis(2-phenylethyl)-2-pyrrolidinone [60548-73-7] **(38)**.



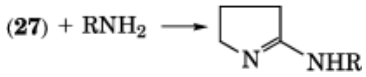
(37) **(38)**

High temperature hydrogenation with a cobalt catalyst gives pyrrolidine, **(27)** + H_2 ⟶ **(19)** (72). Under dehydrating conditions, 2-pyrrolidinone condenses with itself to form 1-(Δ1′-pyrrolin-2-yl)-2-pyrrolidinone [7060-52-8] **(39)** (73).

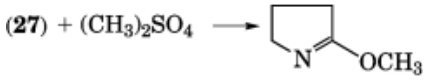


(39)

2-Pyrrolidinone can also condense with primary or secondary amines.



Under suitable conditions, O-alkylation rather than N-alkylation takes place, eg, to form 2-methoxy-1-pyrroline [5264-35-7] **(40)** (74–76).

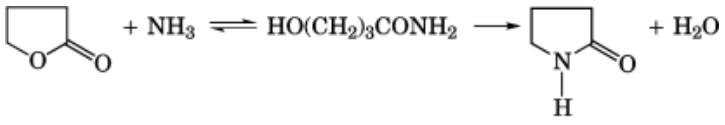


(40)

6.2. Manufacture

There are two main 2-pyrrolidinone producers. International Specialty Products (ISP) (GAF Corporation) has manufacturing facilities in Calvert City, Kentucky, and Texas City, Texas, and BASF manufactures it at Ludwigshafen, Germany. Both producers consume most of their production in the manufacture of 1-vinyl-2-pyrrolidinone.

Butyrolactone **(41)** and a moderate excess of ammonia are passed through a reactor at ca 250°C and 8–9 MPa (80–90 atm). Yields of 90–95% have been reported (77). The reaction proceeds in two steps, but the intermediate 4-hydroxybutyramide **(42)** is not ordinarily isolated. Improved yields are obtained if the reaction is carried out in the gas phase on a magnesium silicate catalyst (250–290°C, 0.4–1.4 MPa), owing to supression of the undesirable by-product 4-(*N*-2-pyrrolidonyl)butyramide (78).



(41) **(42)** **(27)**

6.3. Shipment and Storage

2-Pyrrolidinone is available in steel drums and in aluminum or stainless-steel tank cars and tank trailers. Because of its high freezing point, bulk shipments are in tanks with heating coils. Heating with hot water rather

than steam avoids product discoloration. Steel (qv), stainless steel, and aluminum are satisfactory materials for storage containers. Because 2-pyrrolidinone is hygroscopic, it must be protected from atmospheric moisture.

6.4. Specifications and Analytical Methods

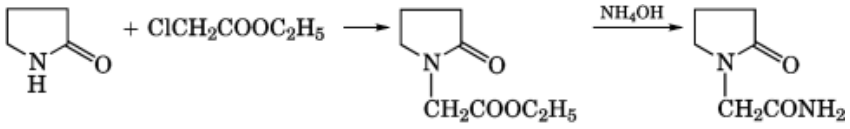
The purity of 2-pyrrolidinone is determined by gas chromatography and is specified as 98.5 wt % minimum. Maximum moisture content is specified as 0.5 wt %. Typical purities are much higher than specification.

6.5. Health and Safety Factors

Results of acute oral toxicity studies of 2-pyrrolidinone on white rats and guinea pigs show the LD_{50} to be 6.5 mL/kg. Skin patch tests on 200 human subjects indicate that 2-pyrrolidinone is a skin irritant, but there is no indication of sensitizing action. It is a mild eye irritant (79).

6.6. Uses

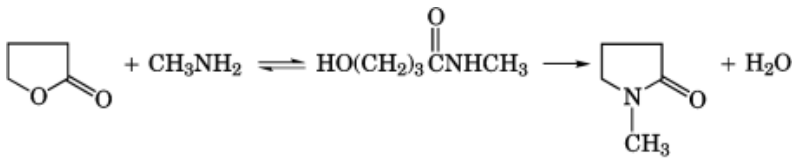
Because of the labile hydrogen on the nitrogen, 2-pyrrolidinone is not as good a solvent as 1-methylpyrrolidinone. Nevertheless, moderate amounts are sold as solvents and as plasticizers (qv) and coalescing agents for polymer emulsion coatings. There is also continuing interest in 2-pyrrolidinone as a monomer for polypyrrolidinone and as a source of 4-aminobutanoic acid. Significant quantities of 2-pyrrolidinone react with ethyl chloroacetate in the preparation of Piracetam (1-acetamido-2-pyrrolidinone [7491-74-9]) **(43)**, which is useful for treatment of motion sickness, epilepsy, etc (80). The main use of 2-pyrrolidinone is, however, as an intermediate for the manufacture of 1-vinyl-2-pyrrolidinone.



(43)

6.7. 1-Methyl-2-Pyrrolidinone

N-Methyl-2-pyrrolidinone [872-50-4] **(44)** (NMP or methyl-2-pyrrolidone, M-Pyrol) was first reported in 1907 as prepared by alkylation of 2-pyrrolidinone with methyl iodide (81). The present commercial route, ie, condensation of butyrolactone with methylamine, was first described in 1936 (50).



(44)

Other preparative routes include hydrogenation of succinonitrile in the presence of methylamine and hydrogenation of solutions of maleic or succinic acid and methylamine (82, 83). Properties are listed in Table 3. 1-Methyl-2-pyrrolidinone is completely miscible with water, lower alcohols, lower ketones, ether, ethyl acetate, chloroform, and benzene. It is moderately soluble in aliphatic hydrocarbons and dissolves many organic and inorganic compounds.

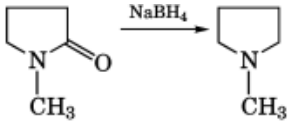
Table 3. Properties of 1-Methyl-2-Pyrrolidinone

Property	Value
freezing point, °C	−24.4
boiling point, °C	
at 0.133 kPa[a]	41
1.33 kPa[a]	79
13.3 kPa[a]	136
101.3 kPa[a]	202
density, g/cm^3, d_4^{25}	1.028
refractive index, n_D^{25}	1.65
flash point, open cup, °C	95
solubility parameter, δ	11

[a]To convert kPa to mm Hg, multiply by 7.5.

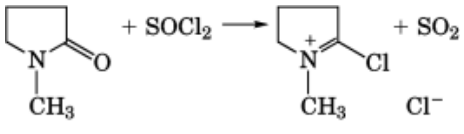
6.7.1. Reactions

Although usually a stable and unreactive solvent, 1-methyl-2-pyrrolidinone can undergo a number of characteristic chemical reactions. In particular, these involve ring opening, attack on the carbonyl group, or replacement of hydrogens alpha to the carbonyl group. Although it is very resistant to hydrolysis under neutral conditions, with strong acids or bases 1-methyl-2-pyrrolidinone can be hydrolyzed to 4-methylaminobutyric acid. Borohydride reduction under suitable conditions yields 1-methylpyrrolidine [120-94-5] **(45)** (84).

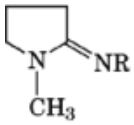


(44) **(45)**

1-Methyl-2-pyrrolidinone reacts with chlorinating agents, eg, $COCl_2$, $SOCl_2$, $POCl_3$, and PCl_5, etc, to form the salt (85), which then reacts with a variety of compounds (86–88). For example, reaction of **(46)** with primary amine (RNH_2) yields imines **(47)**, and reaction with alkoxides (RONa), the corresponding ketals **(48)**. Hydroxylamine plus **(46)** gives *N*-methyl-2-pyrrolidone oxime [35197-40-1] **(49)**, and the reaction of **(46)** with H_2S replaces the keto oxygen with sulfur **(50)**. Methyl-2-thiopyrrolidinone [10441-57-3] **(50)** can also be prepared by reaction of 1-methyl-2-pyrrolidinone with sulfur or carbon disulfide at high temperatures and pressures (89, 90).



(44) **(46)**



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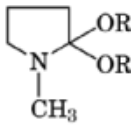

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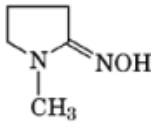
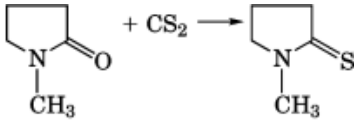


(49)



(44) (50)

6.7.2. Manufacture

1-Methyl-2-pyrrolidinone **(44)** is manufactured at the same sites and by essentially the same process as described for 2-pyrrolidinone **(27)**. In general, capacity for 2-pyrrolidinone and *N*-methylpyrrolidinone (NMP) involves the same equipment with only moderate differences in auxiliaries.

In addition to ISP and BASF, ARCO has begun producing 1-methyl-2-pyrrolidinone at a plant in Texas. NMP is also made in Japan (Mitsubishi) and in Russia. Annual U.S. production (1991) has been estimated by OSHA at 36,000–39,000 t.

6.7.3. Shipment, Storage, and Price

1-Methyl-2-pyrrolidinone is available in tank cars or tank trailers as well as in drums. Shipping containers are normally of unlined steel. Rubber hose is unsuitable for handling; standard steel pipe or braided steel hose is acceptable. Ordinarily 1020 carbon steel (0550) is satisfactory as a storage material. Stainless-steel 304 and 316, nickel, and aluminum are also suitable. Methylpyrrolidinone is hygroscopic and must be protected from atmospheric moisture. In September 1994, NMP was listed at $3.89/kg.

6.7.4. Specifications and Analytical Methods

The purity of 1-methyl-2-pyrrolidinone is determined by gas chromatography and is specified as 99.5 wt % minimum. Maximum moisture content is specified as 0.05 wt % by ir spectroscopy.

6.7.5. Health and Safety Factors

1-Methyl-2-pyrrolidinone is less toxic than many other dipolar aprotic solvents. The LD_{50} for white rats is 4.2 mL/kg. Although it does not appear to be a sensitizing agent, prolonged contact with skin should be avoided. It is a moderate eye irritant.

6.7.6. Uses

1-Methyl-2-pyrrolidinone is a dipolar aprotic solvent. It has a high dielectric constant and is a weak proton acceptor. All of its commercial uses involve its strong and frequently selective solvency. It has replaced other solvents of poorer stability, higher vapor pressures, greater flammabilities, and greater toxicities.

Table 4. N-Substituted 2-Pyrrolidinones

N-substituent	CAS Registry Number	Bp, °C	Mp, °C
ethyl	[2687 – 91 – 4]	212	−77
vinyl	[88 – 12 – 0]	215	13
hydroxyethyl	[3445 – 11 – 2]	309	26
isopropyl	[3772 – 26 – 7]	219	−28
butyl	[3470 – 98 – 2]	244	−106
hexyl	[4838 – 65 – 7]	276	−52
cyclohexyl	[6837 – 24 – 7]	292	15
octyl	[2687 – 94 – 7]	307	−26
dodecyl	[2687 – 96 – 9]	361	10

The largest use of NMP is in extraction of aromatics from lube oils. In this application, it has been replacing phenol and, to some extent, furfural. Other petrochemical uses involve separation and recovery of aromatics from mixed feedstocks; recovery and purification of acetylenes, olefins, and diolefins; removal of sulfur compounds from natural and refinery gases; and dehydration of natural gas.

Large amounts of NMP are consumed in the polymer industry as a medium for polymerization and as a solvent for finished polymers. Polymers that are soluble in NMP are poly(vinyl acetate), poly(vinyl fluoride), polystyrene, nylon and aromatic polyamides and polyimides (qv), polyesters (qv), acrylics, polycarbonates (qv), cellulose derivatives, and synthetic elastomers. 1-Methyl-2-pyrrolidinone is also useful for cleaning and stripping of magnetic wire coatings and electronic parts as well as in agricultural applications for preparing emulsifiable concentrates. Its low toxicity has allowed it to displace chlorinated solvents in many of these applications as well as in paint and finish removers (qv), where it is gaining increasing popularity (91).

6.8. Higher 1-Alkyl-2-Pyrrolidinones

The hydrophilicity of the pyrrolidinone ring system when combined with the hydrophobicity of a longer chain alkyl group leads to compounds with surfactant properties which enhance the water solubility of hydrophobic materials. Two of these, 1-octyl-2-pyrrolidinone and 1-dodecyl-2-pyrrolidinone, have been made available commercially. These surface-active pyrrolidinones (Surfadones) are finding applications in several areas. They are excellent wetting agents and interact with anionic surfactants to exhibit synergistic effects on both static and dynamic surface-tension reductions (92). 1-Octyl-2-pyrrolidinone is used in hard-surface cleaners, in fountain solutions (graphic arts), and for pigment dispersions (qv) (93, 94). It is also used for preparing emulsifiable concentrates in agricultural applications (95) and it inhibits crystallization. 1-Dodecyl-2-pyrrolidinone is used in some shampoos.

A number of other N-substituted 2-pyrrolidinones have been offered commercially or promoted as developmental products. These materials offer different and sometimes unique solvency properties. All are prepared by reaction of butyrolactone with suitable primary amines. Principal examples are listed in Table 4.

Several N-substituted pyrrolidinones eg, ethyl, hydroxyethyl and cyclohexyl, are used primarily in specialized solvent applications where their particular physical properties are advantageous. For example, mixtures of 1-cyclohexyl-2-pyrrolidinone and water exhibit two phases at temperatures above 50°C; below that temperature they are miscible in all proportions. This phenomenon can be used to facilitate some extractive separations. Mixtures of 1-alkyl-pyrrolidinones that are derived from coconut and tallow amines can be used at lower cost in certain applications where they may be used instead of the pure 1-dodecyl-2-pyrrolidinone and 1-octadecyl-2-pyrrolidinone.

6.9. 1-Vinyl-2-Pyrrolidinone

1-Vinyl-2-pyrrolidinone (VP) (1-ethenyl-2-pyrrolidinone, *N*-vinyl-2-pyrrolidone, and V-Pyrol) is manufactured by ISP in the United States and by BASF in Germany by vinylation of 2-pyrrolidinone with acetylene. It forms the basis for a significant specialty polymer and copolymer industry and consumes the primary portion of all 2-pyrrolidinone manufactured (see *n*-VINYL MONOMERS AND POLYMERS).

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