CYCLIC HYDROXYLAMINES; A REVIEW OF PREPARATIVE METHODS AND PROPERTIES

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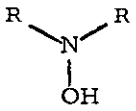
The preparation of cyclic hydroxylamines by various methods is discussed. These methods include (a) direct N-oxidation of amines, (b) reduction of cyclic nitrones, (c) addition to cyclic nitrones, (d) reductive and non-reductive cyclization reactions, as well as other miscellaneous methods.

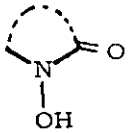
The physical and chemical properties of cyclic hydroxylamines which are also discussed are (a) solubility and salt formation, (b) qualitative and quantitative analysis, (c) molecular spectroscopy and mass spectrometry, (d) stability, (e) tautomerism, (f) oxidation, (g) reduction, (h) alkylation reactions, (i) acylation and sulfonation reactions, (j) reactions with nucleophilic reagents, and (k) reactions with electrophilic reagents. Some comments on the biological importance of cyclic hydroxylamines and related compounds are included in an introductory section.

Cyclic hydroxylamines (which will also be referred to as cyclic N-hydroxy compounds) are disubstituted hydroxylamines (I) in which

the N-hydroxy function is incorporated within a cyclic system (II).

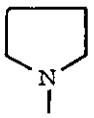

(I)


(II)


(III)

Although cyclic hydroxamic acids (III) are also cyclic N-hydroxy compounds, no attempt is made to include them in the following discussion since they have recently been reviewed.[1,2]

Simple examples of cyclic hydroxylamines are N-hydroxypyrrolidine (IV), N-hydroxypyrazole (V) and N-hydroxyisoxazolidine (VI) to which reference will be made later. In certain instances, cyclic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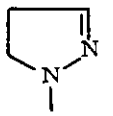
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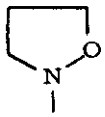
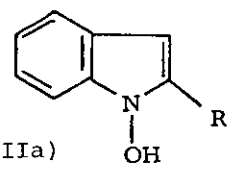
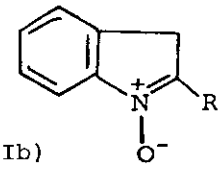

(VI)

N-hydroxy compounds exist in tautomeric equilibrium with a corresponding N-oxide (e.g. VIIa⇌VIIb). Some aspects of this tautomerism will be discussed in detail later.

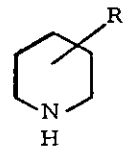

(VIIa)


(VIIb)

Until the beginning of the last decade, very little attention was paid to the chemistry and biochemistry of hydroxylamines. Recent studies have been generally confined to aromatic hydroxylamines especially those found to be metabolites of carcinogenic amines. A comprehensive review of the chemistry of aliphatic and aromatic hydroxylamines, which also included some cyclic hydroxylamines, was published recently.[3] Also, Weisburger and Weisburger[4]

briefly summarized the chemistry of these compounds in their discussion which dealt mainly with the biochemical formation as well as pharmacological and toxicological properties of hydroxylamines and hydroxamic acids.

Some hydroxylamines are of biological importance. N-Hydroxylation is now a well recognized metabolic pathway,[4,5] but until recently, biochemical N-hydroxylation studies were mostly confined to aromatic amines especially those which demonstrated carcinogenic activity. Some aliphatic amines were also studied but relatively little success was achieved in demonstrating N-hydroxylation. Beckett and Al-Sarraj,[6] however, showed that certain aliphatic amines do yield hydroxylamines metabolically. So do secondary amines in which the nitrogen atom is a part of the ring system. Compounds based on the piperidine (VIII), morpholine (IX) and



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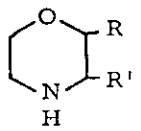

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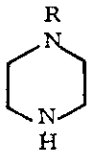

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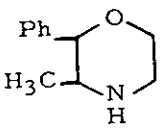
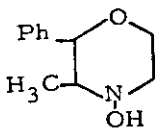


XI



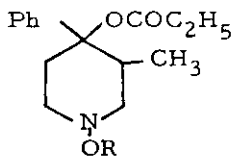
XII

piperazine (X) structures were found to be metabolized *in vitro* to the corresponding hydroxylamines. One of these, phenmetrazine (XI), has been shown to oxidize to N-hydroxyphenmetrazine (XII) *in vivo* in various animals. It was also shown[6] that compounds structurally more complex than (VIII) also form hydroxylamines metabolically. For example, pipradrol, normorphine, norcodeine and nortriptyline

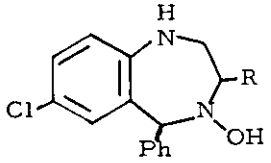
are metabolized to their corresponding hydroxylamines. It is not yet known, however, whether metabolic N-hydroxylation of all these compounds increases toxicity or whether it is sometimes a detoxification reaction.

In addition to this flow of biochemical work, numerous reports on the pharmacological activity of cyclic N-hydroxy compounds have recently started to appear in the literature. Although studies in this area were limited and the early results were not outstanding,[7,8] recent studies describe diverse activities such as analgesic, adrenolytic, tranquilizing, muscle relaxant, anticonvulsant, antimicrobial and antiprotozoal properties for this type of compound.

Some α- and β-1-alkoxy-3-methyl-4-phenyl-4-propionoxypiperidines (XIII) were synthesized[9] and examined for analgesic activity in rats. Two of these compounds (XIII, R=CH_3 or C_2H_5) showed strong oral activity but also many toxic manifestations. N-Hydroxybenzodiazepine derivatives such as (XIV) have been screened for potential



XIII

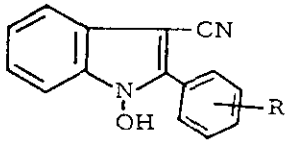


XIV

central nervous system (CNS) depressant activity.[10] Some related N-hydroxybenzodiazepines were also evaluated as anticonvulsants.[11]

The N-hydroxyindole derivatives (XV) were found[12] to possess CNS-depressant as well as adrenolytic activity. N-Alkyloxybenzimidazole derivatives (XVI) also showed CNS-depressant, muscle relaxant and tranquilizing properties.[13,14] A variety of related compounds such as O-ethers of 1-hydroxyindoles and 1-hydroxybenzi-

midazole 3-oxides were found[14] to be generally less active than (XVI).



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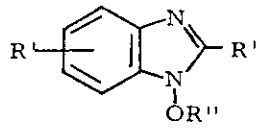
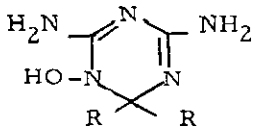
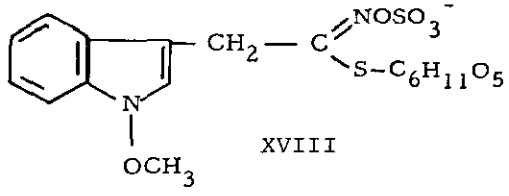


XVI

The antimicrobial properties of some O-ethers of 4,6-diamino-1, 2-dihydro-1-hydroxy-1,3,5-triazines (XVII) were described by Mamalis et al.[15] These compounds were found to be active in vitro against a wide range of bacteria. Later investigations showed that these ethers possessed unexpected antimalarial properties even against



XVII

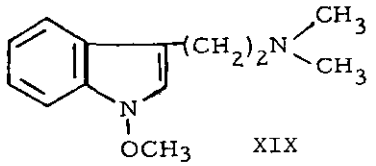


XVIII

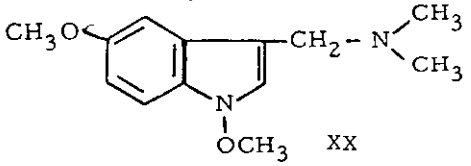
resistant strains of Plasmodium berghei. A related bis-triazine ether also showed trypanocidal activity of a high order in mice.[8]

The recent isolation of some derivatives of cyclic hydroxylamines from some plant and animal species demonstrated that these compounds exist in nature and stimulated further chemical and biological interest in cyclic hydroxylamines. All compounds isolated are derivatives of indole. A glucoside (XVIII) which was named neoglucobrassicin was isolated[16] from Brassica napobrassica. This glucoside was identified on the basis of products formed by enzymatic cleavage, acid hydrolysis and hydrogenolysis with Raney nickel. Subsequently, a tryptamine alkaloid, 1-methoxy-3-(2-dimethylaminoethyl)indole (XIX) which was given the name lespedamine was isolated from the leaves of Lespedeza bicolor var. japonica.[17] A related

N-methoxyindole derivative identified as 1,5-dimethoxy-3-(dimethylaminomethyl)indole (XX) was found to be the major alkaloid in



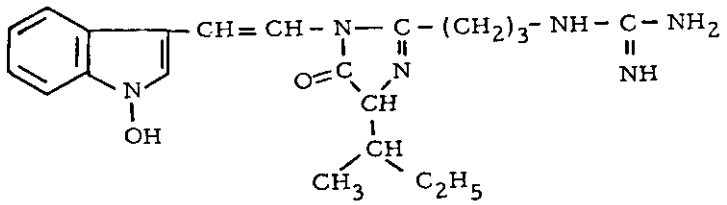
XIX



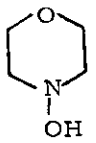
XX

Gymnacranthera paniculata var. zippeliana.[18] Both (XIX) and (XX) were identified by their spectra and by their ease of reduction to the corresponding amines (NH for $N\text{-}OCH_3$).

Chemical studies[19] on Cypridina luciferin, a crystalline substance isolated from the firefly, C. hilgendorfii, tentatively suggested that it was an N-hydroxyindole derivative (XXI), but subsequent studies[20] showed that the N-hydroxy group was absent.



XXI



XXII

PREPARATION OF CYCLIC HYDROXYLAMINES

Cyclic hydroxylamines have been prepared by various methods from a variety of precursors. These methods are conveniently grouped together for discussion in the following sections:

A) Preparation of cyclic hydroxylamines by direct N-oxidation of the corresponding amines.

B) Reduction of cyclic nitrones

C) Addition to cyclic nitrones

D) Formation of cyclic hydroxylamines by reductive or non-reductive

cyclization reactions.

E) Miscellaneous preparations.

(A) Direct N-Oxidation of Secondary Cyclic Amines:

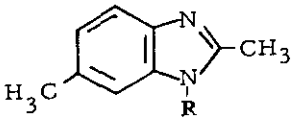
Reactions of this type are rarely used for the preparation of cyclic hydroxylamines, possibly due to the expected side reactions which might accompany the N-oxidation process. However, this method can be useful for the preparation of certain N-hydroxy compounds which might be difficult to obtain by other synthetic routes.

In most of these reactions hydrogen peroxide is employed with or without a catalyst as the oxidizing agent. 1-Hydroxymorpholine (XXII) was obtained by the oxidation of morpholine with different concentrations of hydrogen peroxide but the yields were generally poor.[21-23] 1-Hydroxypiperidine and 1-hydroxypyrrolidine were similarly prepared.[22] An attempt to improve the yield of these compounds by catalyzing the reaction with methyl formate was unsuccessful,[24] but formic acid[25] and silicotungstic acid[26] were successfully used for this purpose.

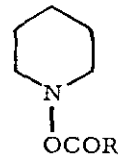
An early report[27] that indole-magnesium bromide reacted with hydrogen peroxide to give 1-hydroxyindole was recently discounted by Kawana *et al.*[28] These investigators and others[29] failed to oxidize some cyclic amines to the corresponding hydroxylamines by means of hydrogen peroxide. Similarly, no cyclic N-hydroxy compounds were formed when ferric chloride was used,[28,30] although Houff *et al.*[31] reported earlier the oxidation of indole-3-acetic acid to the corresponding N-hydroxyindole using this reagent.

The use of percarboxylic acids for the N-oxidation of tertiary amines is very common and a considerable number of N-oxides have

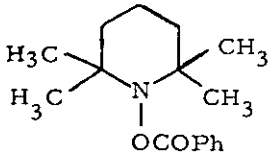
been prepared by this method. Recently, Beckett and Salami[32] claimed that one of these acids (m-chloroperbenzoic acid) successfully oxidized phenmetrazine (XI) to 1-hydroxyphenmetrazine (XII). An earlier attempt[33] to use percarboxylic acids for the preparation of 1-hydroxy-2-phenylbenzimidazole from the corresponding amine failed. The related compound, 2,6-dimethylbenzimidazole (XXIIIa) was said[34] to be oxidized by bromine to the corresponding hydroxylamine (XXIIIb).



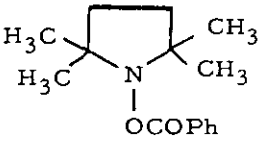
XXIII a, R=H b, R=OH



XXIV a, R=CH_3 b, R=Ph



XXV

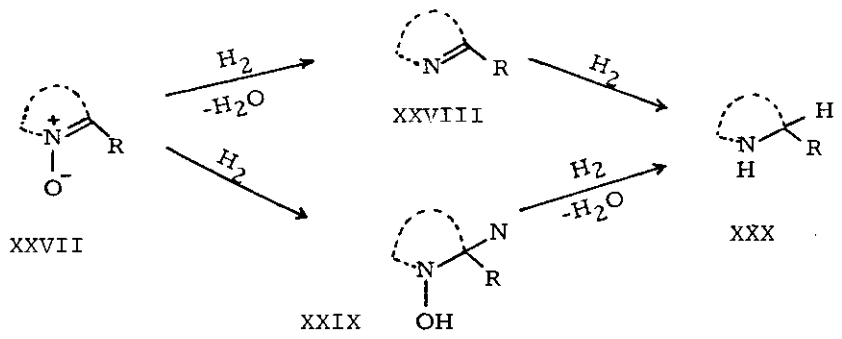


XXVI

N-Acetoxy and N-benzoyloxypiperidines (XXIV) can be prepared from piperidine by the action of acetyl and benzoyl peroxides respectively.[35] 1-Benzoyloxy-2,2,6,6-tetramethylpiperidine (XXV) and 1-benzoyloxy-2,2,5,5-tetramethylpyrrolidine (XXVI) were similarly prepared. Hydrolysis of (XXV) and (XXVI) gave rise to the corresponding N-hydroxy compounds.[36]

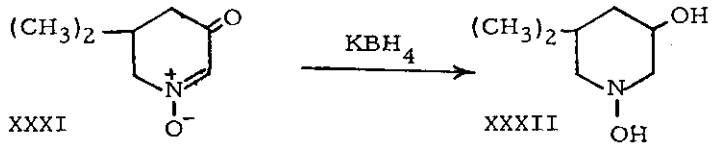
(B) Reduction of Cyclic Nitrones

Reduction of nitrones (XXVII) to the corresponding secondary amines (XXX) can proceed by two different pathways. The intermediate imines (XXVIII) or hydroxylamines (XXIX) have been isolated. Deoxygenation to (XXVIII) is generally achieved using triphenyl-



phosphene, phosphorous trichloride, phosphorus oxychlorides, sulfur dioxide, zinc and acetic acid as well as catalytic hydrogenation. Zinc and mineral acids reduce the nitrone group to the secondary amine stage (XXX). Reductions with complex metal hydrides lead, in most cases, to the formation of hydroxylamines.

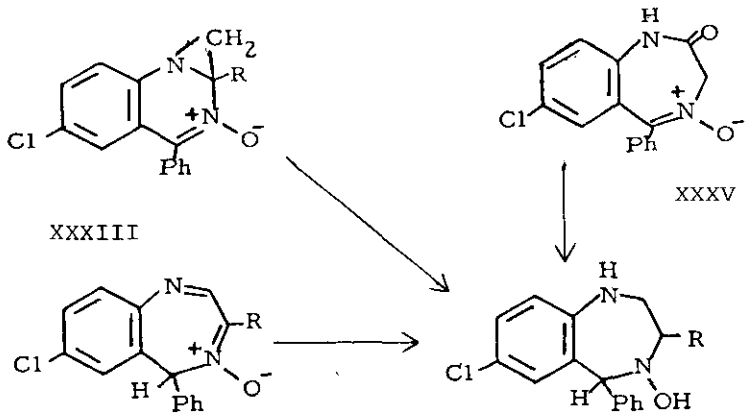
1,5-Dihydroxy-3,3-dimethylpiperidine (XXXII) was prepared by the reduction of (XXXI) using potassium borohydride.[37] The same



reagent was used for the reduction of Δ'-pyrroline 1-oxides to the corresponding 1-hydroxypyrrolidines.[38]

The N-hydroxybenzodiazepine (XIV, R=H) was prepared by reducing nitrones (XXXIII) or (XXXIV) with sodium borohydride in ethanol or diglyme.[39] Reduction of the former was accompanied by cleavage of the aziridine ring. These reactions were also successful using tetramethylammonium borohydride.[11]

The use of lithium aluminum hydride for the reduction of cyclic nitrones to the corresponding hydroxylamines was first reported by

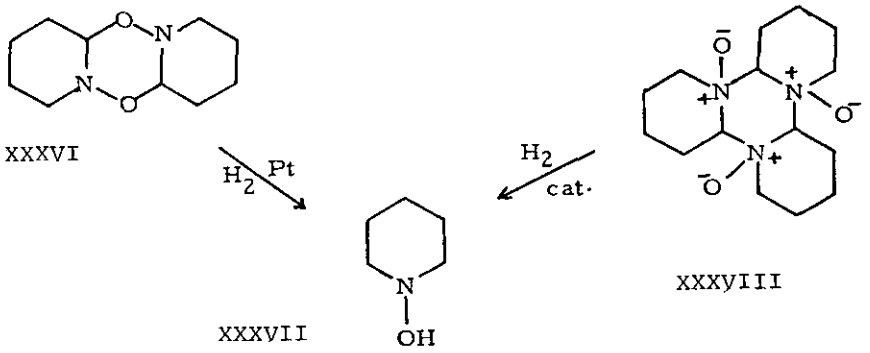


XXXIII XXXV

XXXIV XIV

Exner.[40] There have been claims that reduction stops at the hydroxylamino stage even when excess reagents and fairly vigorous conditions are used.[24] Among the N-hydroxy compounds prepared in this way are 1-hydroxypyrrolidine from Δ'-pyrroline 1-oxide[24] and 7-chloro-4-hydroxy-5-pyenyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (XIV, R=H) from the lactam-nitrone (XXXV).[41] 7-Chloro-2-methylamino-4-hydroxy-5-phenyl-4,5-dihydro-3H-1,4-benzodiazepine was prepared similarly.[42]

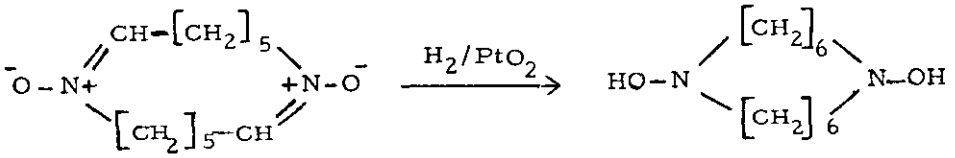
The dimeric 1,2,3,4-tetrahydropyridine 1-oxide (XXXVI) did not react with lithium aluminum hydride. However, it could be reduced



XXXVI XXXVIII

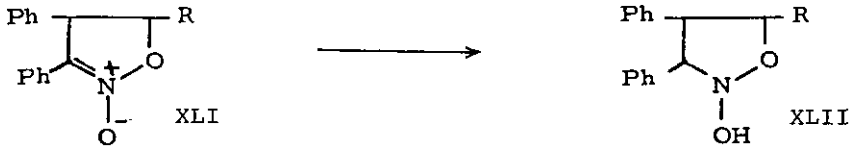
XXXVII

catalytically over platinum in acidic methanol to give 1-hydroxypiperidine (XXXVII).[43] Catalytic hydrogenation of the trimer (XXXVIII) afforded the same N-hydroxy compound.[43] The dimeric nitrone (XXXIX) was also hydrogenated in the presence of Adam's catalyst to give 1,8-dihydroxy-1,8-diazacyclotetradecane (XL). Further hydrogenation of (XL) over Raney nickel yielded the corresponding amine.[44,45]

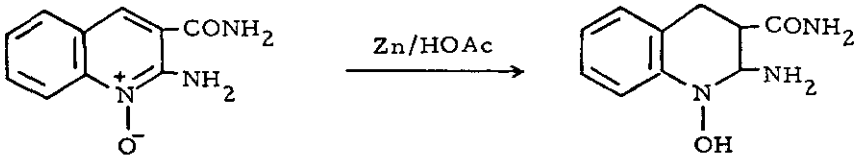


XXXIX XL

More powerful chemical reagents are employed occasionally for the reduction of nitrones to hydroxylamines. The N-hydroxyisoxazoline (XLII) was formed when the isoxazoline 1-oxide (XLI) was reduced with zinc and acetic acid or with sodium iodide and acetic acid.[46] Similarly, the N-hydroxytetrahydroquinoline (XLIV) was prepared by the zinc and acetic acid reduction of (XLIII).[47] In

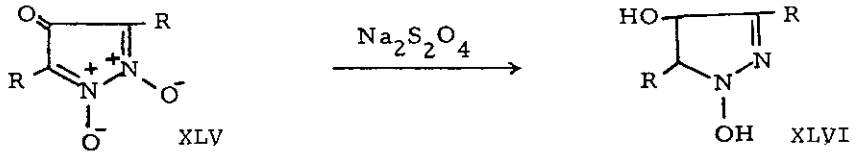


XLI XLII



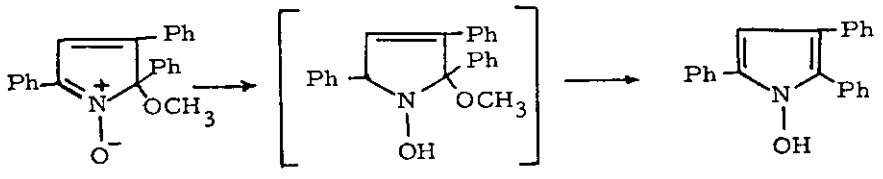
XLIII XLIV

contrast, the dioxide derivatives were reduced with sodium hydrosulfite to 1,4-dihydroxypyrazoles (XLVI) but when reduction was performed with zinc and acetic acid, 4-hydroxypyrazoles (XLVI, N-H for N-OH) were formed.[48]

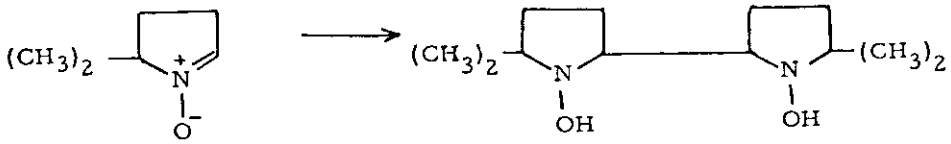


XLV XLVI

Reduction of the cyclic nitrone (XLVII) was accompanied by an elimination of methyl alcohol and yielded 1-hydroxy-2,3,5-triphenylpyrrole (XLVIII). This reduction was achieved using sodium-potassium alloy, and alkyl or aryl magnesium bromides.[49] Sodium-potassium alloy was also reported[50] to reductively dimerize 5,5-dimethyl-Δ'-pyrroline-1-oxide (XLIX) to the 1,1'-dihydroxy-2,2'-bipyrrolidinyl derivative (L).



XLVII XLVIII



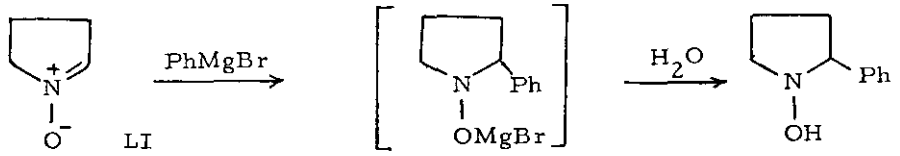
XLIX L

(C) Addition to Cyclic Nitrones:

Grignard reagents add across the double bond of cyclic nitrones leading, in certain instances, to the formation of stable cyclic hydroxylamines. Some α-alkyl and α-aryl-N-hydroxy compounds are prepared in this way from pyrrolidine 1-oxides, piperidine 1-oxides,

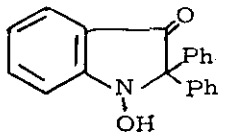
pyridine 1-oxides and quinoline 1-oxides.

1-Hydroxy-2-phenylpyrrolidine (LII) was the product of the reaction of Δ'-pyrroline 1-oxide (LI) and phenylmagnesium bromide.[24] Other N-hydroxypyrrolidines are prepared similarly.[38,51] The

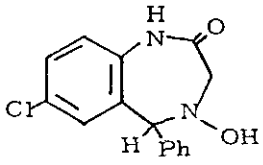


LI LII

tetrahydropyridine 1-oxide dimer (XXXVI), which is resistant to a number of nitrone reactions such as reduction with lithium aluminum hydride or with sulfur dioxide, reacted readily with phenylmagnesium bromide to give 1-hydroxy-2-phenylpiperidine.[43] 2,2-Diphenyl-3-oxo-1-hydroxyindoline (LIII) and 7-chloro-4-hydroxy-5-phenyl-1,3,4,5-tetrehydro-2H-1,4-benzodiazepin-2-one (LIV) were prepared similarly.[10,52]

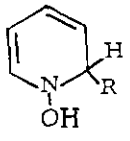


LIII

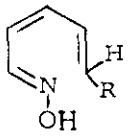


LIV

Addition of Grignard reagents to pyridine 1-oxides and quinoline 1-oxides generally gives α-alkyl and α-aryl pyridines and quinolines,[53,54] and in some instances α-substituted N-oxides.[55,56] When some of these reactions were carried out in tetrahydrofuran, cyclic N-hydroxy compounds were claimed to be formed. 1-Hydroxy-2-phenyl-1,2-dihydropyridine, its 6-methyl homolog, and 1-hydroxy-2-



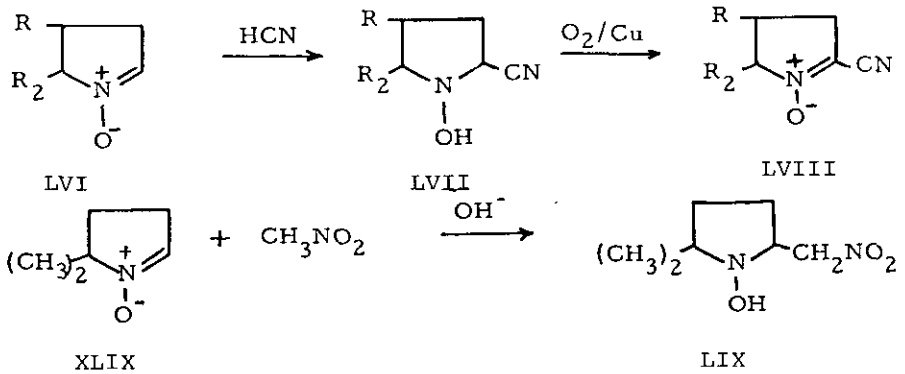
LVa



LVb

phenyl-1,2-dihydroquinoline, for example, were said to be the products of the reaction of phenylmagnesium bromide with pyridine 1-oxide, 2-picoline 1-oxide and quinoline 1-oxide respectively.[56] Subsequent studies, however, have revealed[56a] that the products obtained by the interaction of Grignard reagents with pyridine 1-oxide are conjugated oximes (LVb) and not cyclic hydroxylamines (LVa).

Hydrogen cyanide is reported to add across the double bond of nitrones giving adducts which generally lose water in the presence of bases. This reagent, however, reacted with the pyrroline 1-oxides (LVI) to give 2-cyano-1-hydroxypyrrolidines (LVII) which were stable to alkali, but readily oxidized to cyanonitrones (LVIII).[38] Cyclic nitrones also react with active hydrogen com-

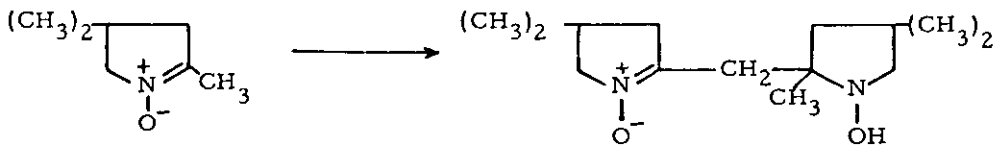


LVI LVII LVIII

XLIX LIX

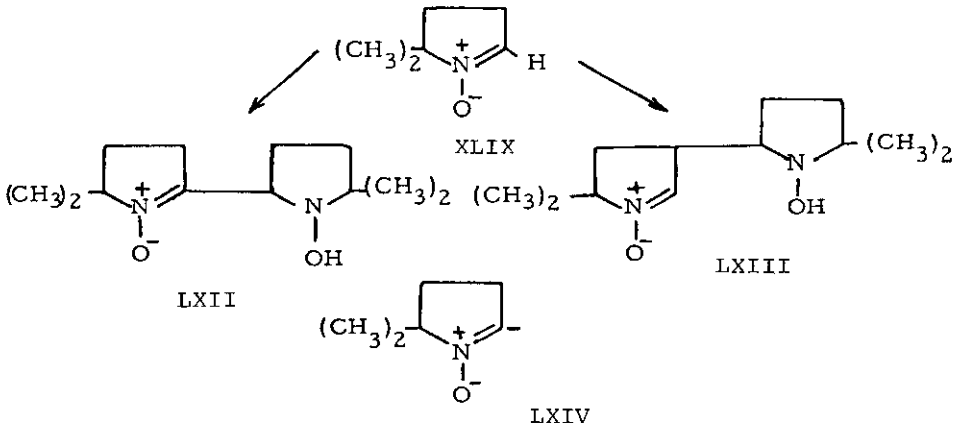
pounds forming simple adducts. For example, treating pyrroline 1-oxides such as (XLIX) with nitromethane, in the presence of base, yielded the 2-nitromethyl-1-hydroxypyrrolidine (LIX).[38,57]

Some nitrones undergo aldol-type reactions. 2,4,4-Trimethyl-Δ'-pyrroline 1-oxide (LX), for example, dimerizes slowly on standing to give the nitrone-hydroxylamine (LXI).[37] Dimerization is also induced and controlled by basic catalysts. The nitrone (XLIX), for example, readily dimerizes under basic conditions.



LX LXI

In the presence of triphenylmethyl sodium, an aldol-type reaction occurred and gave the dimer (LXIII) while a benzoin-type dimerization to (LXII) occurred with sodamide in liquid ammonia. Sodamide in triethylamine gave a mixture of both dimers.[37,58] The benzoin-



XLIX

LXII LXIII

LXIV

type dimerization might be initiated by deprotonation of (XLIX) to form the anion (LXIV).[59]

(D) Cyclization Reactions:

The majority of cyclic hydroxylamines reported in the literature were prepared by cyclization reactions which involve either condensation of two molecules or the intramolecular cyclization of a single compound. These reactions generally utilize nitro or oxime derivatives. Nitroso and hydroxylamino compounds are possible intermediates in many cases and are sometimes used as initial reagents. The mechanisms of these cyclization reactions are seldom

clear and accordingly the discussion of these mechanisms is mostly speculative.

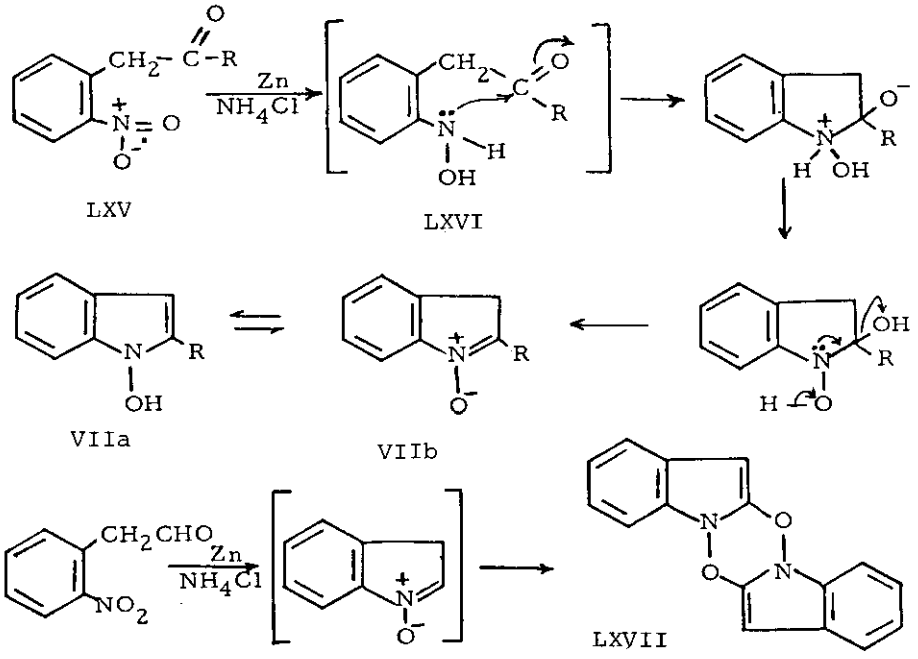
Most often, especially when nitro compounds or oximes are used, an initial reductive step is required prior to cyclization and numerous reducing systems have been employed for this purpose. However, the nitro group may also cyclize without initial reduction to the nitroso or hydroxylamino stages. This alternative route involves nucleophilic attack on the nitrogen atom of the nitro-group; the attacking nucleophile can be an aliphatic carbanion, a reactive aromatic ring or an amino group. These types of reactions were extensively reviewed by Loudon and Tennant.[60]

Cyclization reactions discussed now are classified under two subheadings, reductive and non-reductive cyclizations. In the first, a reducing agent is used, mainly to effect reduction of the oxime or nitro-group to a hydroxylamino or nitroso function. The second group includes those reactions in which the nitro-group's demand for electrons is supplied from within the molecule. Miscellaneous reactions in which cyclization involves quite different mechanisms will also be reviewed.

i - Reductive cyclizations:

Various reducing agents have been employed for the reductive cyclization of oximes and nitro compounds. Zinc and ammonium chloride has been used by several investigators for the preparation of aromatic hydroxylamines from the corresponding nitro compounds. Reduction of o-nitrobenzyl ketones (LXV) with this system was also successful and resulted in the formation of the tautomeric 1-hydroxyindoles (VIIa ⇄ VIIb). The hydroxylamine (LXVI) was postulated

as an intermediate. The same synthetic route was employed in an attempt to prepare the parent N-hydroxyindole, but it led instead to a dimer formulated as (LXVII).[61]



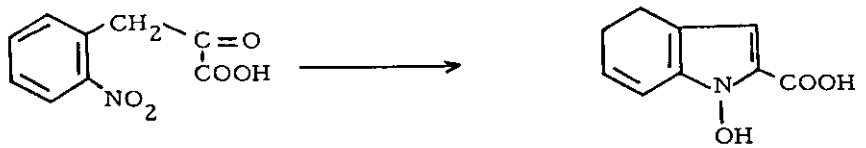
LXV LXVI

VIIa VIIb

LXVII

Reduction of 2-nitrophenylpyruvic acid (LXVIII) with sodium-amalgam offered a means of preparing 1-hydroxyindole-2-carboxylic acid (LXIX).[62] Similar results were obtained when 4-methyl-2-nitrophenylpyruvic acid was reduced. Reduction of (LXVIII) with zinc and acetic acid yielded indole 2-carboxylic acid.

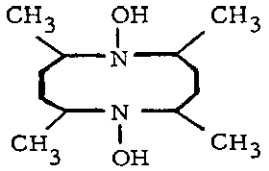
The same N-hydroxyindole (LXIX) was the sole acidic product obtained by the sodium borohydride/palladium-charcoal reduction of



LXVIII LXIX

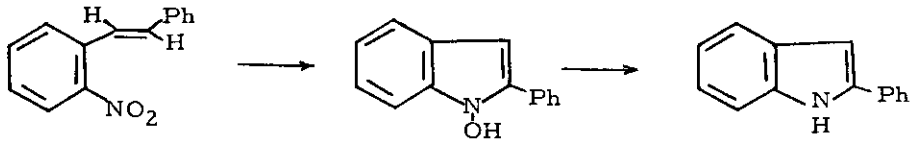
2-nitrophenyl pyruvic acid (LXVIII) or its methyl ester; from the latter a better yield was obtained.[63] Catalytic hydrogenation of the oxime, semicarbazone and phenylhydrazone of 2-nitrophenyl-pyruvic acid over platinum or palladium provided another route to 1-hydroxyindole-2-carboxylic acid.[64] Varying amounts of indole-2-carboxylic acid were also formed along with the hydroxyindole.

Another example of the use of catalytic hydrogenation for preparing cyclic hydroxylamines was reported by Krajcinovic and Vranjican[65] who hydrogenated acetonylacetone dioxime in acidic medium and concluded that one product of the reaction was 1,6-dihydroxy-2,5,7,10-tetramethyl-1,6-diazacyclodecane (LXX).



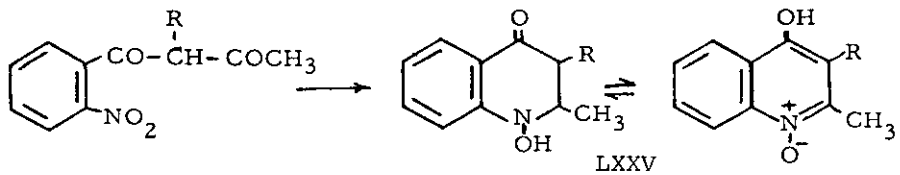
LXX

Reductive cyclization of trans-o-nitrostilbene (LXXI) with triethylphosphite yielded 2-phenylindole (LXXIII) and traces of two other products.[66] When this reaction was interrupted, the intermediate 1-hydroxy-2-phenylindole (LXXII) was isolated, but only in poor yield.



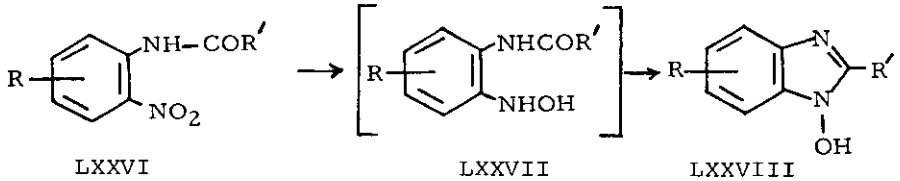
LXXI LXXII LXXIII

The tautomeric N-hydroxyquinolone (LXXV, R=H) was prepared by the stannous chloride/hydrogen iodide reduction of ethyl o-nitrobenzoylacetone (LXXIV, R=H).[67] The related compound (LXXV, R=COOEt) was obtained by the reduction of ethyl o-nitrobenzoylacetoacetate (LXXIV, R=COOEt) with stannous chloride and hydrochloric acid in acetic acid.[68]



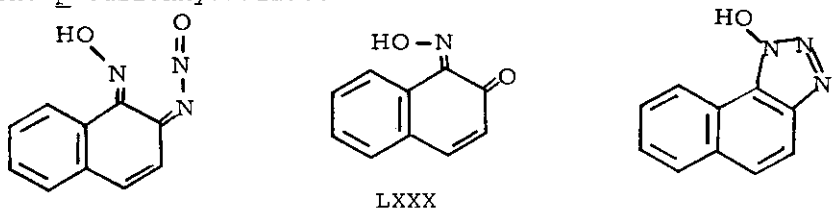
LXXIV LXXV

Reduction of o-nitroanilides (LXXVI) under mild conditions produced 1-hydroxybenzimidazoles (LXXVIII). The hydroxylamine (LXXVII) was postulated as an intermediate. Among the reducing systems used in this type of reaction are zinc and ammonium chloride,[69,70] zinc and hydrochloric acid,[34,71] tin and hydrochloric acid,[72] ammonium sulfide,[69,73,74] sodium dithionite[14,75] and catalytic hydrogenation over palladium.[76]



LXXVI LXXVII LXXVIII

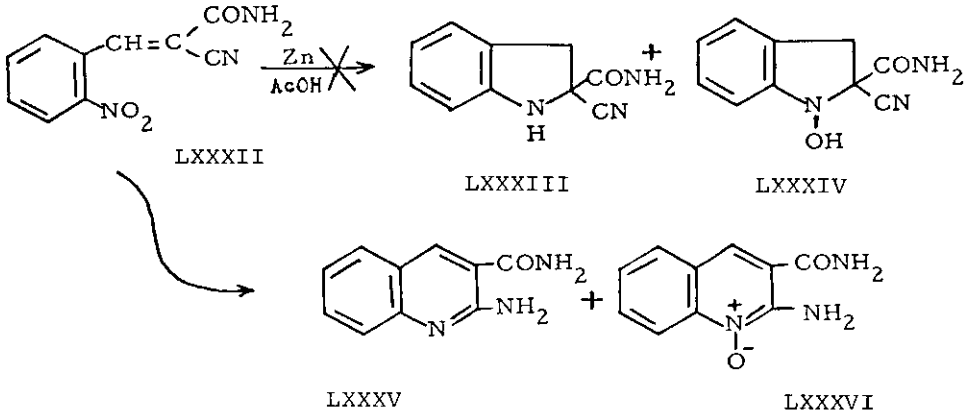
The 1-hydroxybenzotriazole derivative (LXXXI) has been prepared either by the stannous chloride/hydrochloric acid reduction of the potassium salt of the 2-nitrosoimino oxime (LXXIX)[77] or by the interaction of 1,2-naphthoquinone 1-oxime (LXXX) and toluene p-sulfonhydrazide.[78]



LXXIX LXXX LXXXI

An early report[79] that reduction of α-cyano-o-nitrocinnamide (LXXXII) by zinc and acetic acid yielded 2-carbamyl-2-cyanodihydroindole (LXXXIII) and its N-hydroxy derivative (LXXXIV) was later

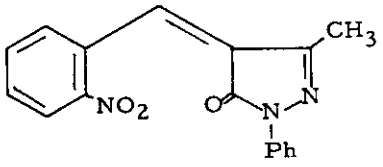
discounted. The products have been reformulated[47,80,81] as 2-aminoquinoline-3-carboxamide (LXXXV) and its N-oxide (LXXXVI).



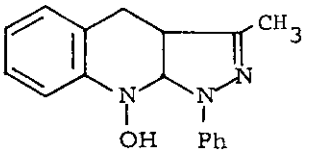
LXXXII LXXXIII LXXXIV

LXXXV LXXXVI

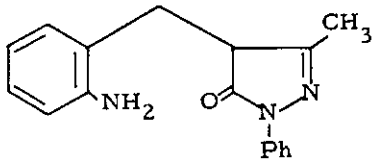
Narang[82] and then Coutts and Edwards[83] claimed that one product of the reduction of 3-methyl-4-(o-nitrobenzylidene)-1-phenyl-2-pyrazolin-5-one (LXXXVII) by various means, including sodium borohydride and palladium-charcoal in ethanol, was the N-hydroxypyrazoloquinoline (LXXXVIII). Other 4-(o-nitrobenzylidene)-pyrazolin-5-ones were said[83] to reduce analogously. Subsequent studies, however, have revealed[84] that the true products of the reduction of (LXXXVII) and its analogs were (o-aminobenzyl)-2-pyrazolin-5-ones (e.g., LXXXIX).



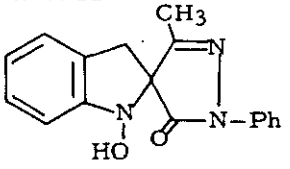
LXXXVII



LXXXVIII



LXXXIX



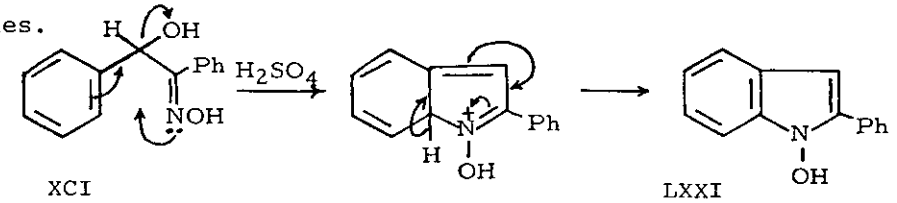
XC

It is well known that metal hydride reductions are often influenced by the nature of the solvent used.[85,86] When the sodium borohydride/palladium-charcoal reduction of (LXXXVII) and its analogs were done in dioxane,[84] a product was obtained, which, on the basis of its physical and chemical properties, is tentatively identified as spiro[(1-hydroxyindoline)-2,4'-(3'-methyl-1'-phenyl-1H-pyrazolin-5'-one)] (XC). Its formation may involve a nitroso intermediate (compare ref. 142a).

ii - Non-reductive cyclizations:

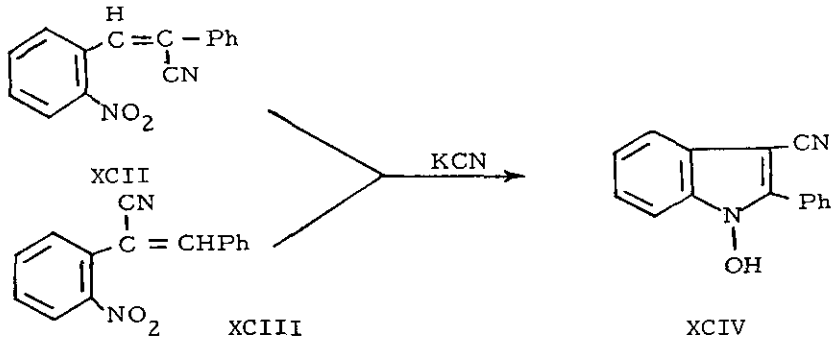
In most cases, cyclizations are catalyzed by acids or bases although some occur under seemingly neutral conditions. A recent review[86a] includes references to the preparation of some cyclic hydroxylamines from oximes.

One of the earliest examples of acid-catalyzed cyclizations was that reported by Fischer and Hütz.[87] Treatment of the benzoin oxime (XCI) with concentrated sulfuric acid resulted in the formation of 1-hydroxy-2-phenylindole (LXXI). A similar procedure was recently employed[28] for the preparation of some related N-hydroxyindoles.



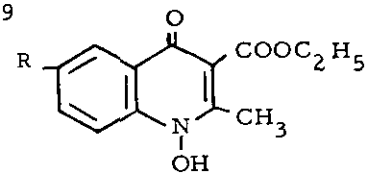
XCI LXXI

The related 3-cyano-1-hydroxy-2-phenylindole (XCIV) was obtained by the action of potassium cyanide on either o-nitro-α-phenylcinnamonitrile (XCII) or α-(o-nitrophenyl)cinnamonitrile (XCIII). Alkaline hydrolysis and decarboxylation of (XCIV) yielded 1-hydroxy-2-phenylindole (LXXI).[88]

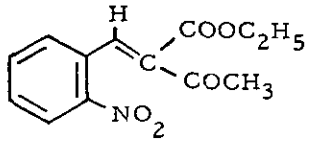


XCIII XCIV

The acid-catalyzed condensation of o-nitrobenzaldehyde with ethyl acetoacetate gave a 1-hydroxyquinolone derivative (XCV, R=H).[88] Analogous results were obtained by replacing ethyl acetoacetate with acetylacetone, benzoylacetone or diethyl acetonedicarboxylate. When hydrogen chloride was used to catalyze the reaction, a chlorine atom was introduced into the product (XCV, R=Cl). However, no brominated derivatives were formed when hydrogen bromide was used. In the presence of quinol, the isolable intermediate (XCVI) may be cyclized even by hydrogen chloride without any uptake of chlorine.[89]



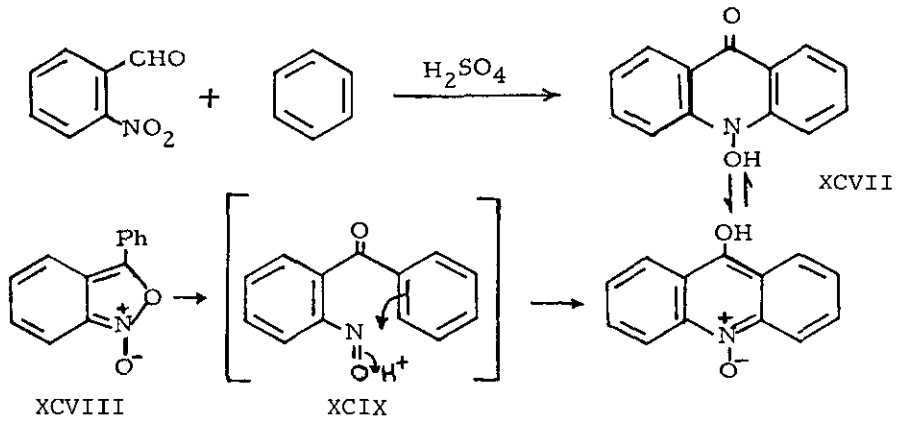
XCV



XCVI

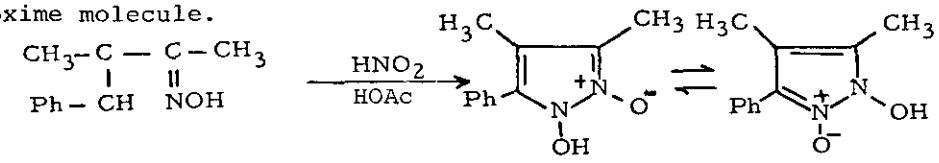
o-Nitrobenzaldehyde reacted with benzene in the presence of sulfuric acid to give 10-hydroxyacridone (XCVII).[90,91] The anthranil oxide (XCVIII) and the nitroso compound (XCIX) were suggested as intermediates.[92]

Nitrosation of 3-methyl-4-phenyl-3-buten-2-one oxime (C) yielded a high melting product which was initially assigned a nitrimine



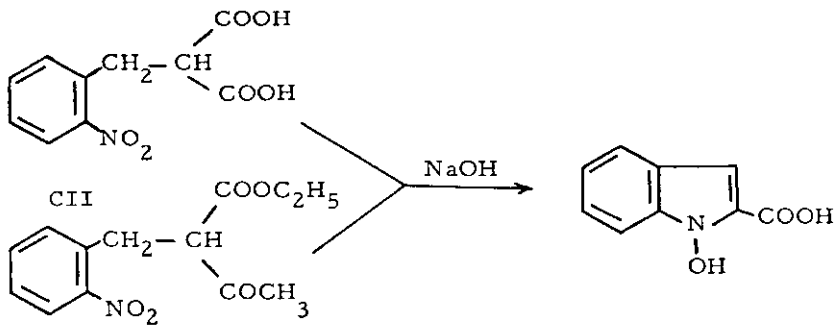
XCVIII XCIX XCVII

structure[93] but was subsequently shown[94] to be the 1-hydroxypyrazole 2-oxide (CIa) or its 2-hydroxy 1-oxide tautomer (CIb). Further studies[48,95,96] showed that the products obtained from this reaction were dependent on the nature of the substituents on the oxime molecule.

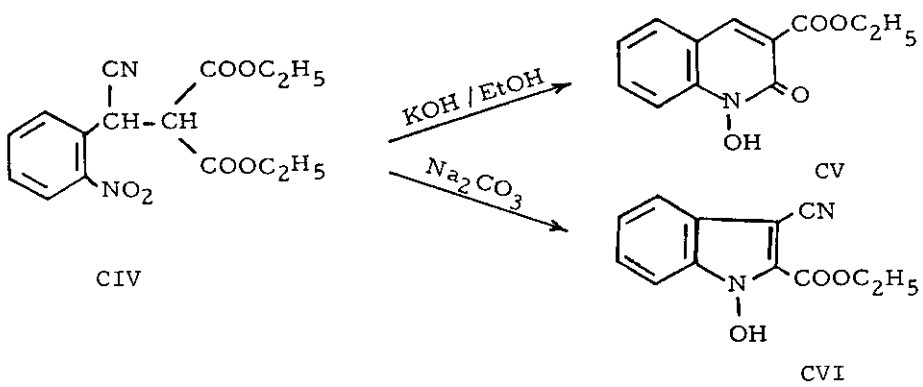


C CIa CIb

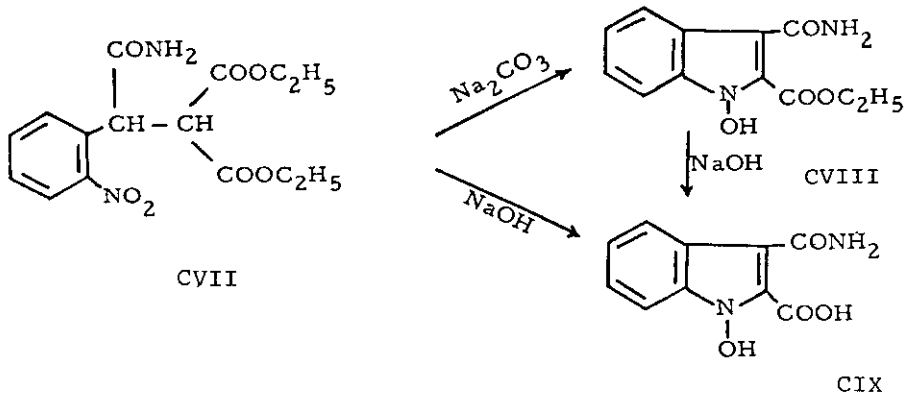
The ability to form cyclic N-hydroxy compounds by base-catalyzed cyclizations has been known for some time. Reissert[97] found that treatment of o-nitrobenzylmalonic acid (CII) with aqueous sodium hydroxide solution yielded 1-hydroxyindole-2-carboxylic acid (LXIX). This compound was also obtained by the action of the same base on ethyl o-nitrobenzylacetoacetate (CIII).[98] The latter reaction occurred so readily that the ethyl ester of (LXIX) was also isolated.



Base-catalyzed cyclizations of diethyl α-cyano-α-2-nitrobenzylmalonate (CIV) and its α-carbamoyl analog (CVII) produced different products depending on the type of base used.[88] Thus, treatment of (CIV) with ethanolic potassium hydroxide yielded a 1-hydroxyquinolone (CV) while the use of aqueous sodium carbonate led to the formation of ethyl 3-cyano-1-hydroxyindole-2-carboxylate (CVI). On the other hand, treatment of the α-carbamoylmalonate



(CVII) with aqueous alkali gave cyclic hydroxylamines (CVIII and CIX). These cyclizations have been explained[88] in terms of intramolecular condensation reactions of carbanions with the nitro groups

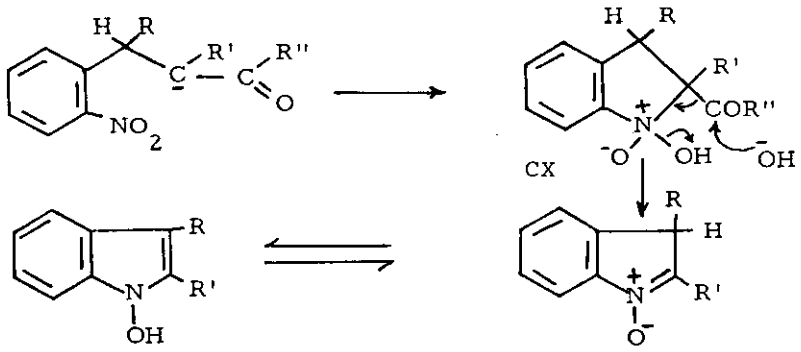


CVII

CIX

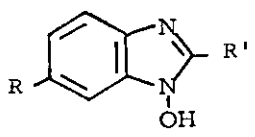
followed by decomposition of the internal condensate (CX).

1-Hydroxybenzimidazoles, including compounds CXI—CXIIIa and



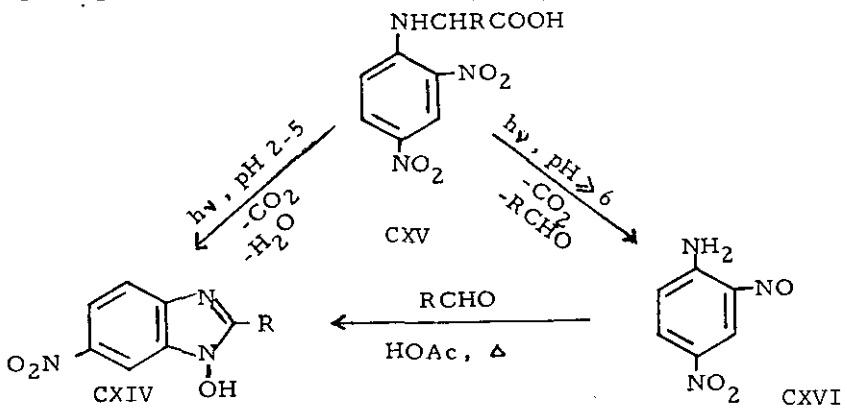
related compounds, are also conveniently prepared from appropriate N-substituted o-nitroanilines by the action of base.[33,99-102]

Other 1-hydroxybenzimidazole derivatives (CXIV) were prepared by

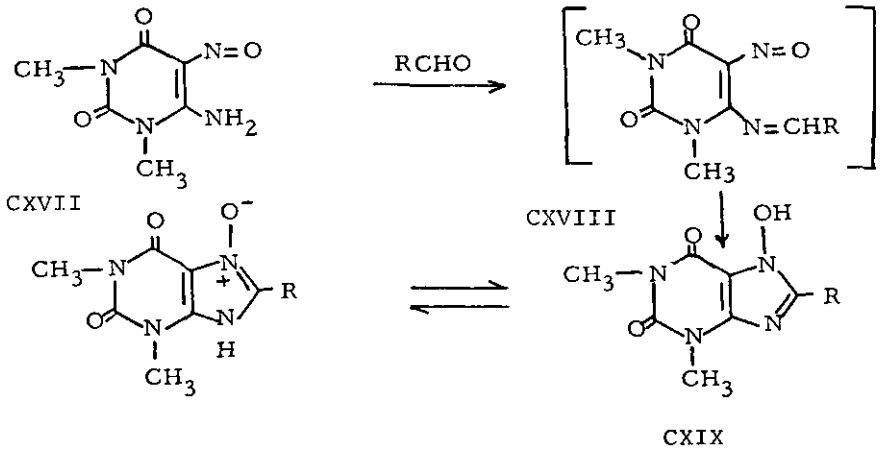


	R	R'
CXI	CH_3	COPh
CXII	NO_2	$COOCH_3$
CXIII	H	Ph
CXIIIa	H	CN

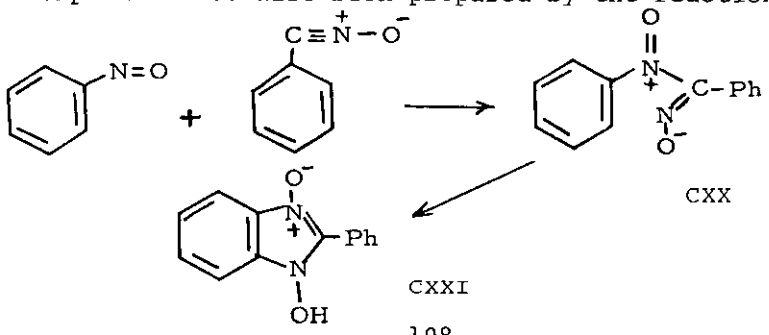
photolysis of 2,4-dinitrophenyl derivatives of α-amino-acids (CXV). This reaction also produced 4-nitro-2-nitrosoaniline (CXVI). The proportions of these two products depended on the pH of the solution.[103,104] Reaction of CXVI with different aldehydes yielded 1-hydroxy-6-nitrobenzimidazoles (CXIV).[105]



Treatment of 1,3-dimethyl-4-amino-5-nitrosouracil (CXVII) with benzaldehyde and dimethylformamide produced an N-hydroxypurine (CXIX) as one of the reaction products. This compound is probably formed by the spontaneous cyclization of the intermediate anil (CXVIII).[106]



1-Hydroxy-2-phenylbenzimidazole 3-oxide (CXXI) was obtained by the interaction of nitrosobenzene with benzonitrile oxide. The intermediate (CXX) has been isolated at low temperature.[107] Related compounds have also been prepared by the reaction of



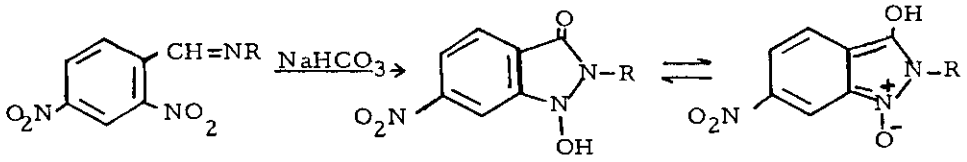
CXX

CXXI

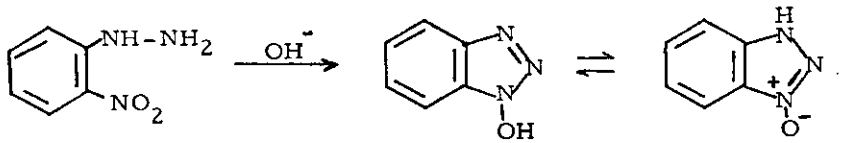
o-quinone dioxime with aldehydes.[108]

1-Hydroxyindazolone derivatives (CXXIIIa) or the tautomeric 3-hydroxyindazole-1-oxides (CXXIIIb) were formed by the isomerization of (2-nitrobenzylidene)anilines (CXXII) in the presence of sodium bicarbonate.[109]

1-Hydroxybenzotriazole (CXXIV) was the product of a base-catalyzed cyclization of o-nitrophenylhydrazine.[110,111] This reaction was extended to the preparation of 1-hydroxy-6-nitrobenzotriazole by the action of hydrazine hydrate on 2,4-dinitrophenyl-



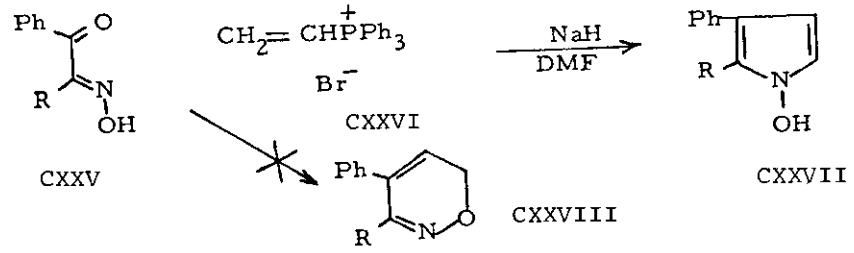
CXXII CXXIIIa CXXIIIb



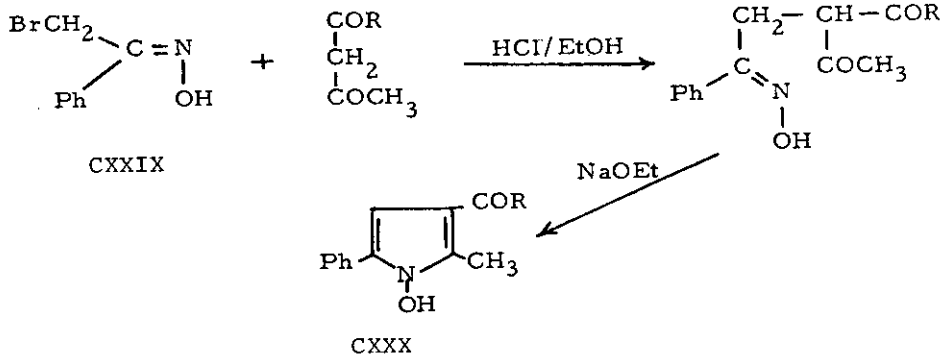
CXXIV

hydrazine.[112] The reaction of hydrazine hydrate with o-halogeno-nitrobenzenes[113] or with o-dinitrobenzenes[114] also gave rise to 1-hydroxybenzotriazoles. Yields varied greatly according to the pH of the reaction media.[115]

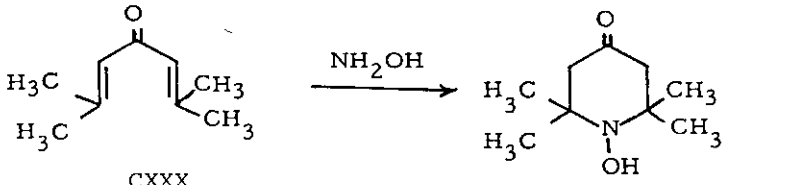
Some monocyclic N-hydroxy compounds can also be prepared by cyclization reactions. 1-Hydroxypyrroles (CXXVII) were formed by the condensation of benzil mono-oximes (CXXV) and vinyltriphenylphosphonium bromide (CXXVI) in a reaction designed for the preparation of 6H-oxazines (CXXVIII).[116] Other substituted N-



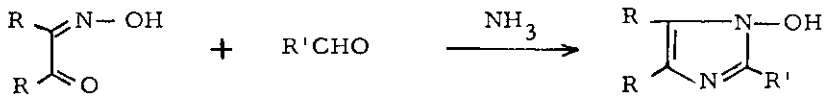
hydroxypyrrole derivatives (CXXX) are the products of the reaction of another oxime (CXXIX) with various β-diketones.[117]



The cyclization of 2,6-dimethylheptadien-4-one (CXXXI) with hydroxylamine offered a means of preparinga 1-hydroxy-4-piperidone derivative (CXXXI).[118]

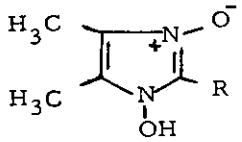


CXXX CXXXI



CXXXII CXXXIII

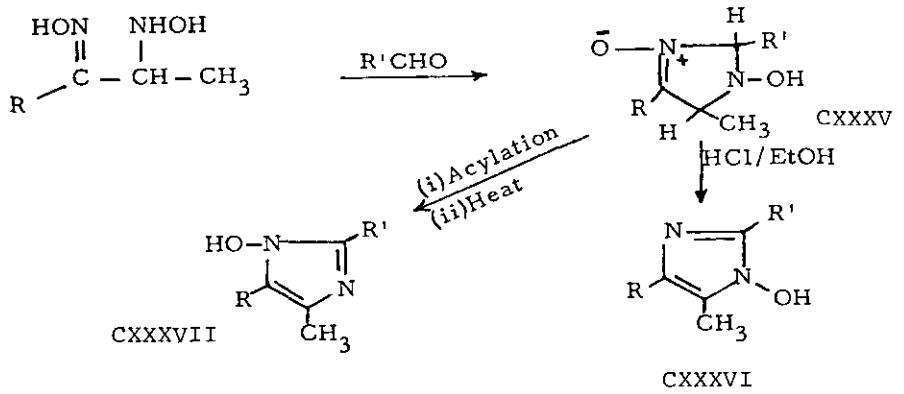
N-Hydroxyimidazoles (CXXXIII) are formed by the reaction of α-dione mono-oximes (CXXXII) with aldehydes in the presence of ammonia.[119,120] This reaction was originally discovered by Diels[121] but the products were allocated inaccurate structures.[122] Alternative preparations of this type of compound were achieved by reacting aldehydes with amino-oximes,[123,124] or by the condensation of 2,3-butanedione mono-oxime with aldoximes. The latter reaction resulted in the formation of substituted 1-hydroxy-imidazole-3-oxides (CXXXIV).[125,126] Similar products have been obtained by



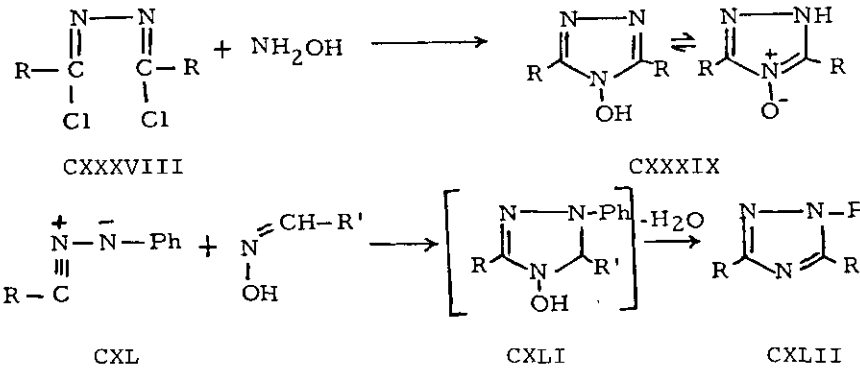
CXXXIV

the reaction of dimethylglyoxime with aldehydes.[127]

α-Hydroxylamino-oximes when reacted with aldehydes yield dihydro-1-hydroxyimidazole 3-oxides (CXXXV). These compounds were readily converted to hydroxylamines (CXXXVI) or (CXXXVII) by acylation followed by heat or by the action of hydrogen chloride in ethanol.[128]

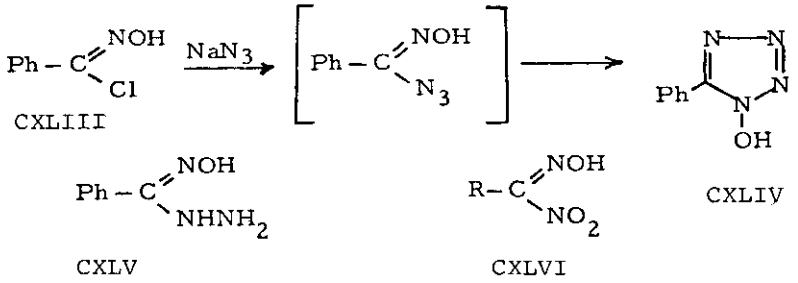


4-Hydroxy-1,2,4-triazoles (CXXXIX) are produced by the reaction of hydroxylamine with dichloro compounds of general structure (CXXXVIII).[129] Also, addition of nitrilimines (CXL) to the C=N double bond of aldoximes produced 4-hydroxy-1-phenyldihydrotriazoles



(CXLI) but these compounds dehydrated spontaneously to give 1,2,4-triazoles (CXLII).[130]

The reaction between hydroxamoyl chloride (CXLIII) and sodium azide gave 1-hydroxy-5-phenyltetrazole (CXLIV).[131] The latter compound was also obtained by the action of nitrous acid on hydroxamoyl hydrazine (CXLV).[132] Some related derivatives were prepared



CXLIII CXLIV

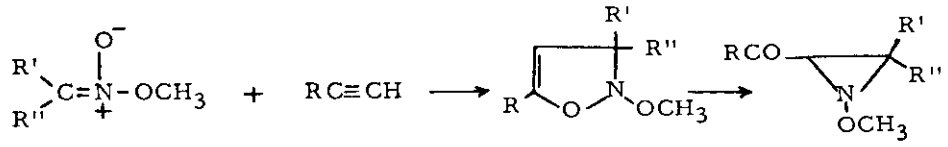
CXLV CXLVI

by the condensation of nitrolic acid (CXLVI) with hydrazoic acid.[133]

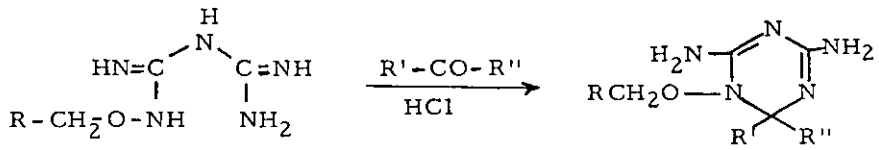
O-Alkyl and O-acyl derivatives of cyclic hydroxylamines are formed by cyclization reactions. Thus, condensation of 1,4-dibromobutane with O-methylhydroxylamine yielded 1-methoxypyrrolidine (CXLVII). 1-Methoxypiperidine was similarly prepared from 1,5-dibromopentane.[134]

CXLVII

N-Methoxyaziridines of the type (CL) were obtained by the reaction of methyl nitronates (CXLVIII) and acetylenes; N-methoxy-4-isoxazolines (CXLIX) were postulated as intermediates.[135]



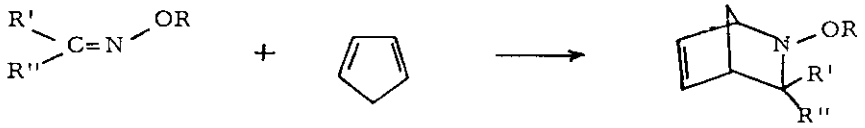
CXLVIII CXLIX CL



CLI CLII

N-Alkoxy and N-aryloxytriazines (CLII) can be prepared by the reaction of the diguanid ethers (CLI) with carbonyl compounds in the presence of hydrochloric acid. Catalytic hydrogenation of (CLII) gave the parent N-hydroxydihydrotriazine (CLII, OH for OCH_2R).[15,136]

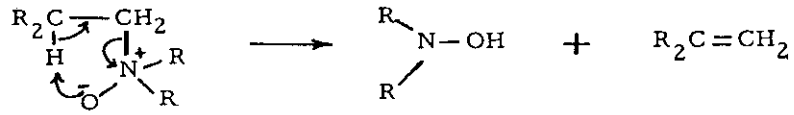
N-Benzoyloxy and N-sulfonyloxy derivatives of 2-azanorbornenes (CLIII) were formed by the addition of cyclopentadiene to various oxime benzoates or sulfonates.[137]



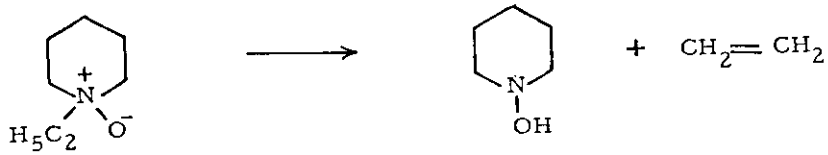
CLIII

(E) Miscellaneous Preparations:

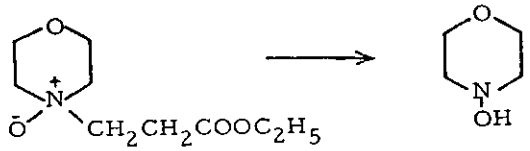
Certain types of amine oxides such as (CLIV) decompose when heated to yield a hydroxylamine plus an olefin. Examples of this



CLIV



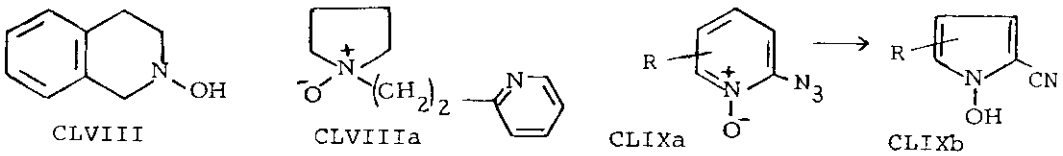
CLV CLVI



CLVII XXII

reaction are reported in the early literature.[138,139] An intramolecular mechanism involving a planar, five-membered cyclic transition state was suggested for this reaction.[140] The report[138] that N-hydroxypiperidine (CLVI) was obtained by pyrolysis of N-ethylpiperidine oxide (CLV) was confirmed by Rogers[141] who extended this work to the preparation of other N-hydroxy compounds. For example, 1-hydroxymorpholine (XXII) was obtained by heating the phthalate salt of ethyl β-morpholinopropionate N-oxide (CLVII) with aqueous ammonia. Similarly, 1-hydroxypiperidine was formed when ethyl β-piperindinepropionate was treated with perbenzoic acid; in this case, the N-oxide benzoate was not separated.

1-Hydroxypyrrolidine (IV) and 2-hydroxy-1,2,3,4-tetrahydroisoquinoline (CLVIII) were similarly prepared by the pyrolysis of N-ethylpyrrolidine N-oxide[24] and N-(carbethoxyethyl-1,2,3,4-tetrahydroisoquinoline) N-oxide[43] respectively. Compound (IV) was also obtained by the pyrolytic decomposition of the N-oxide (CLVIIIa) under reduced pressure.[142] Thermal decomposition of 2-azidopyridine

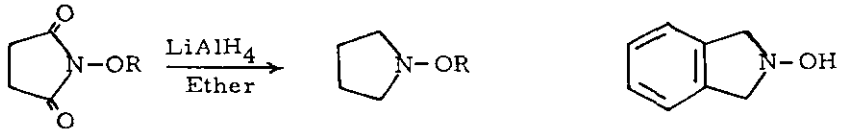


CLVIII CLVIIIa CLIXa CLIXb

1-oxides (CLIXa) is accompanied by ring contraction and yields 2-cyano-1-hydroxypyrroles (CLIXb). This novel reaction is applicable to other ring systems.[142a]

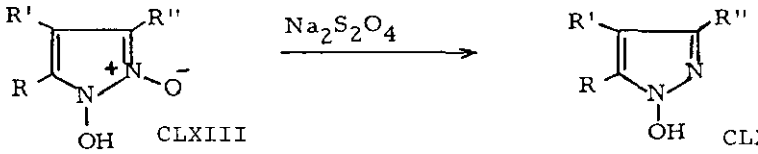
Some cyclic hydroxylamines are prepared by chemical modification of compounds which already have the N-hydroxy function. For example, lithium aluminum hydride reduction of N-hydroxysuccinimide (CLXa) and its O-methyl analog (CLXb) yielded the corresponding derivatives

of pyrrolidine (CLXI).[134] Similar reduction of 3-hydroxyphthalimide gave N-hydroxyisoindoline (CLXII).[143]



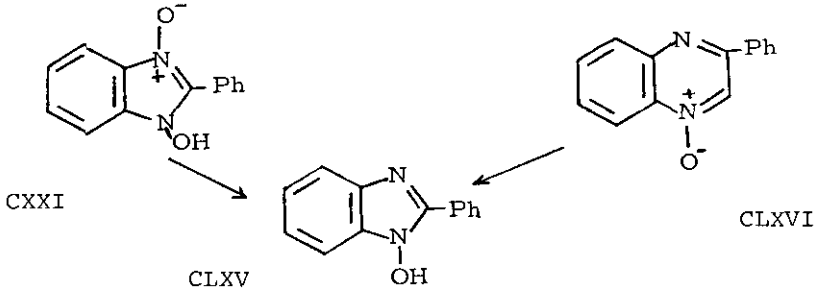
CLX a, R=H b, R=CH_3 CLXI CLXII

Mild reduction of 1-hydroxypyrazole 2-oxides (CLXIII) with sodium dithionite yielded 1-hydroxypyrazoles (CLXIV); zinc and acetic acid reduced both the N-oxy and N-hydroxy functions.[95]



CLXIII CLXIV

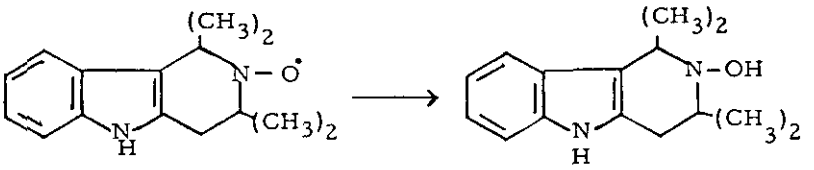
Similarly, cautious reduction of the N-oxide (CXXI) with stannous chloride and hydrochloric acid resulted in the formation of 1-hydroxy-2-phenylbenzimidazole (CLXV).[107] The latter N-hydroxy compound was said to be formed by the action of alkaline hydrogen peroxide on 2-phenylquinoxaline 4-oxide (CLXVI).[144]



CXXI CLXV CLXVI

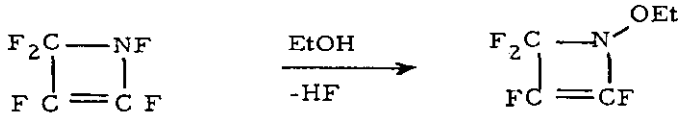
Reduction of the stable free radical (CLXVII) with phenylhydrazine or with hydrogen over platinum yielded 2,2,4,4-tetramethyl-1,-2,3,4-tetrahydro-3-hydroxy-γ-carboline (CLXVIII). The radical was obtained by the catalyzed (Na_2WO_2) hydrogen peroxide oxidation

of the γ-carboline (CLXVIII, H for OH).[145]

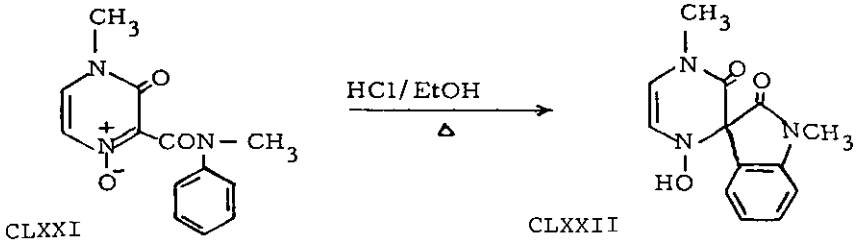


CLXVII CLXVIII

The reaction of ethanol with the pentafluoro compound (CLXIX) causes elimination of one molecule of hydrogen fluoride and the formation of 1-ethoxyaza-2-cycloperfluorobutene (CLXX).[146]



CLXIX CLXX

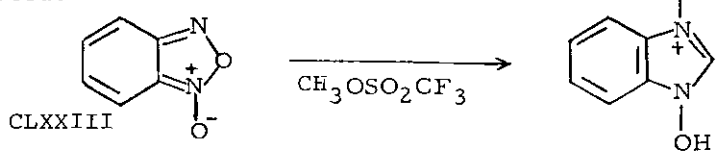


CLXXI CLXXII

10-Hydroxyacridone (XCVII) can be prepared by acid hydrolysis of 9-bromoacridine 10-oxide.[147] A similar hydrolysis of the pyrazine N-oxide (CLXXI) with ethanolic hydrogen chloride gave the hydroxylamino-spirolactam (CLXXII). This compound is believed to be formed by the protonation of the N-oxide followed by intramolecular electrophilic substitution at the o-position of the phenyl ring by the pyrazine 2-C-atom.[29]

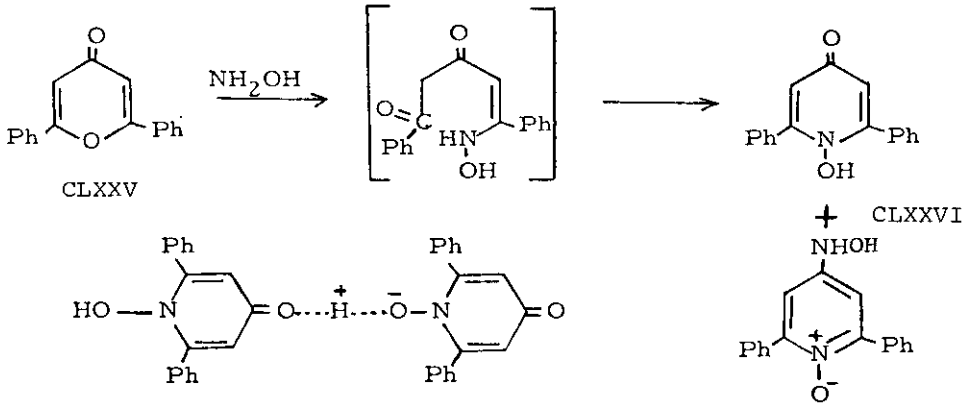
Alkylation of benzofuroxan (CLXXIII) with the powerful alkylating agent, methyl trifluoromethanesulfonate resulted in the isolation of a 1-hydroxybenzimidazole (CLXXIV) rather than the expected

quaternary salt. A mechanism for this rearrangement has been suggested.[108]



CLXXIII CLXXIV

Condensation of 2,6-diphenyl-4-pyrone (CLXXV) with hydroxylamine resulted in ring opening and then reclosure to give 1-hydroxy-2,6-diphenyl-4-pyridone (CLXXVI) and 4-hydroxylamino-2,6-diphenylpyridine 1-oxide (CLXXVII). The i.r. spectrum of (CLXXVI) in chloroform showed that it exists exclusively in the N-hydroxy form. On the other hand, the solid spectrum suggested a polymeric association (CLXXVIII).[148]



CLXXV + CLXXVI

CLXXVIII CLXXVII

PHYSICAL AND CHEMICAL PROPERTIES OF CYCLIC HYDROXYLAMINES

The physical and chemical properties of cyclic hydroxylamines are related to those of their parent amines, but the presence of

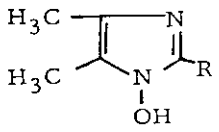
the N-hydroxy function also permits a number of reactions analogous to those found with arylhydroxylamines. There are also some similarities between the chemical reactivity of cyclic hydroxylamines and cyclic hydroxamic acids although the presence of a carbonyl function in the α-position of the latter may have profound effects on their solubility as well as on their chemical behavior. Also, in cases where the cyclic N-hydroxy compound exists in tautomeric equilibrium with the corresponding N-oxide, the properties demonstrated might be related to those of the N-oxides.

(A) Solubility and Salt Formation:

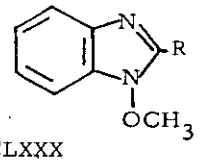
Solubility in aqueous solutions or organic solvents is influenced by the nature of the heterocyclic system incorporating the N-hydroxy function. In many cases, N-hydroxy compounds are acidic and, therefore, soluble in alkali solutions. Stable sodium salts[95,149] as well as potassium, anilinium and hydrazinium salts[112] of some cyclic hydroxylamines have been prepared and identified. Insoluble copper salts of 1-hydroxyisoxazolidines[46,150] and insoluble silver salts of 1-hydroxybenzotriazole[151] are also known. The latter compounds have been used analytically for the determination of silver.[152-154] 1-Hydroxypyrazole 1-oxides form chelates with many divalent elements.[95]

Some cyclic N-hydroxy compounds are basic enough to form acidic salts. For example, 1-hydroxypiperidine and 1-hydroxymorpholine were isolated as hydrochlorides, picrates and acid oxalates.[23,45] A third group of cyclic hydroxylamines contains compounds which are virtually neutral and form no salts. Examples are 1-hydroxy-2-phenylpiperidine[56] and 1-hydroxy-2-methylindole.[155] Minor changes

in structure sometimes alter the acidity and the solubility characteristics of N-hydroxy compounds. For example, 1-hydroxyimidazole (CLXXIX, R=Ph) is amphoteric (pK_a 9.41, pK_b 9.36) while other 1-hydroxyimidazoles such as (CLXXIX, R=CH_3) are not.[120]



CLXXIX



CLXXX

(B) Qualitative and Quantitative Determination:

Cyclic hydroxylamines readily reduce Tollen's and Fehling's solutions.[7,29,156] The former reagent is used as a spray for the detection of N-hydroxy compounds on thin-layer chromatographic plates.[32] Some cyclic hydroxylamines also give a positive test with Schiff reagent.[157] Some of these compounds form a red color when treated with ferric chloride but not as spontaneously as hydroxamic acids with the same reagent. In fact, this color results from the oxidation of cyclic hydroxylamines to the corresponding hydroxamic acids.[158] N-hydroxyindoles are said to give a green color with ferric chloride solution and also a stronger color with sodium 2-naphthol-4-sulfonate than do the corresponding indoles.[28]

A more specific spot test for hydroxylamines, including cyclic compounds, is provided by reaction with triphenyltetrazolium chloride (TTC) which, in the presence of alkali, gives a characteristic purple-red color. This seems to be a specific reaction[159] and by its means the presence or absence of hydroxylamines can usually be safely deduced.[141,161] Other investigators[23,24,37] have used this test to follow the progress of reactions which involve hydroxylamines. Feigl,[156] however, considers hydroxylamine to be completely

inactive towards this reagent. It should also be remembered that other substances, such as sugars and ascorbic acid give a positive test with TTC.[156]

The separation of some cyclic hydroxylamines from their corresponding amines as well as from some related nitroxides can be achieved by means of thin-layer chromatography. Weil[160] developed some useful solvent systems for this purpose. Iodine vapor or potassium permanganate solution were used for detection and were found to be more useful than TTC which gave only very faint pink spots.

Although a number of methods have been developed for quantitative estimation of aryl hydroxylamines[162] and hydroxamic acids,[163,164] there is as yet no general method for analysis of cyclic hydroxylamines. However, it is possible that these compounds could be determined quantitatively by gas-liquid chromatography, after conversion into suitably volatile ethers.

(C) Molecular Spectroscopy and Mass Spectrometry:

Ultraviolet spectroscopy: This technique was used by several investigators[102,165,166] to study the tautomerism of cyclic N-hydroxy compounds. In such cases, the position of maxima as well as their intensities were compared with "fixed" models in which tautomerism was not possible. Kawana et al[28] also used the bathochromic shift (5-10 mμ) showed by N-hydroxyindole derivatives on addition of alkali, as a method for confirming the presence of the N-hydroxy function.

Infrared spectorscopy: This has proved to be more useful than u.v. spectorscopy for both identification purposes and tautomeric studies. The i.r. spectra of some 1-hydroxyindoles were studied and found to

provide evidence for the existence of intermolecular hydrogen bonding.[28,167] The simple compounds, N-methyl and N,N-dimethylhydroxylamine were also strongly hydrogen bonded.[168]

The presence of either or both the N-hydroxy and N-oxy tautomers in any compound could be readily deduced from its infrared spectrum and this was used to assign tautomeric equilibria in different systems.[167,169,170] Distinction between the N-OH and C-OH functions is probably more difficult since both absorptions seem to be affected similarly by the same parameters (table 1). Their acetates or benzoates, however, are of particular advantage for identification purposes since electronegative groups attached to the oxygen atom of carboxylic acids are known to raise the stretching frequency of the carbonyl group by 15-70 cm^{-1} depending on the group.[171] The most pronounced shifts were observed with hydroxamic acids but also all compounds where the oxygen substituent was attached to nitrogen showed abnormally high frequency carbonyl absorptions. As expected, the N-benzoate esters absorb at a lower frequency (~1770 cm^{-1}) than the N-acetates (~1800 cm^{-1}) but still much higher than the ordinary benzoates (~1720 cm^{-1}) (see table 1).

Nuclear magnetic resonance spectroscopy: This technique has been employed more frequently for detecting the N-hydroxy function as well as for studying the tautomerism of cyclic N-hydroxy compounds.[116,155,167,172,173] With few exceptions, studies showed that the N-hydroxy proton resonance is detected at low field even in the absence of intramolecular hydrogen bonding (table 1). Acheson et al[155] detected the N-hydroxy proton in 1-hydroxy-2-methylindole near δ9.00 and reassigned the resonance near δ6.00, attributed

Table 1. Infrared absorption maxima and n.m.r. chemical shifts (relative to TMS) of some cyclic hydroxylamines and their methyl and acyl derivatives.

Compound	ν_{max} (cm^{-1})[a]	δ (N-O<u>H</u>)	Ref.
N-Hydroxydimethylamine[b]	OH 3600-3000		168
, benzoate	CO 1740		171
N-Benzoyloxypiperidine (XXIVb)	CO 1762 (f)		171
	CO 1766 (s)		171
1,2-Dihydro-1-hydroxy-2-phenylpyridine (LVa, R=Ph)[c]	OH 3400-2400	8.72, 9.20	84,56
, benzoate	CO 1759, 1755		174,84
1-Hydroxyphenmetrazine (XII)	OH 3600	3.30	32
1-Hydroxy-2-methylindole (VIIa, R=Me)	OH 3510-3498 (s)	6.0	167
	OH 3450 (k)		167
		8.30-8.94	173
		9.75	173
, p-chlorobenzoate	CO 1775		155
1-Hydroxy-2-phenylindole (VIIa, R=Ph)	OH 3250, 2400 br	8.85	28
	OH 2430 br		66
, acetate	CO 1772		28
, benzoate	CO 1760		149
1-Hydroxyindole-2-carboxylic acid (VIIa, R=COOH)	OH 3225		28
, acetate	CO 1800		28
, benzoate	CO 1783		28
Methyl 1-hydroxyindole-2-carboxylate (VIIa, R=COOMe)	OH 3180		28
, acetate	CO 1802		64
, benzoate	CO 1778		28
Ethyl 3-cyano-1-hydroxyindole-2-carboxylate (CVI)	OH 3260	9.50-10.50	173
Ethyl 3-carbamoyl-1-hydroxyindole-2-carboxylate (CVIII)	OH 3350, 3150		88
, acetate	CO 1800		88

2,3-Diphenyl-1-hydroxypyrrole (CXXVII, R=Ph)	OH 3320	absent	116
, acetate	CO 1700		116
, benzoate	CO 1760		116
Ethyl 1-hydroxy-3-phenylpyrrole-2-carboxylate (CXXVII, R=COOEt)	OH 3370	10.2	116
1-Hydroxy-3-phenylpyrrole (CXXVII, R=H)		10.1	116
4,5-Dimethyl-1-hydroxyimidazoles (CXXXIII, R=Me)		13.33	119
, benzoate	CO 1730		120
4,5-Dimethyl-1-hydroxypyrazoles (CLXIV, R=R'=CH_3)		8.5	94
, p-nitrobenzoate	CO 1790		48
3,4,5-Trimethyl-1-hydroxypyrazole 2-oxide (CLXIII, R=R'=R"=CH_3)		15.8	95
2,6-Diphenyl-1-hydroxy-4-pyridone (CLXXVI)	OH 3636		148
1,2,3,4,2',3'-Hexahydro-1-hydroxy-4,1'-dimethyl-3,2'-dioxopyrazine-2-spiro-3'-indole (CLXXII)	OH 3320		29

	δ (N-OCH_3)	
1-Methoxy-2-substituted-benzimidazoles (CLXXX)	4.1-4.2	175
1-Methoxy-3-(2-dimethylaminoethyl)indole (XIX)	4.09	17
1,5-Dimethoxy-3-(dimethylaminomethyl)indole (XX)	3.99	18

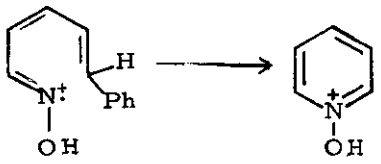
[a] OH stretching of N-OH group; C=O stretching of N-OCOR carbonyl; (f) = film ; (s) = solution; (k) = KBr; br = broad.

[b] included for comparison

[c] structure has been revised[56a]

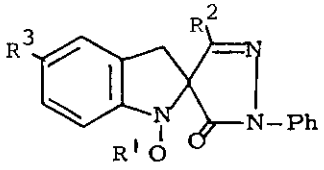
earlier[167] to this proton, to the 3-hydrogen atom of the indole. The N-methoxy function might also be detected with n.m.r. spectroscopy since the methoxy group is attached to an electronegative atom. In the few reported examples (table 1), the N-methoxy protons resonate at a lower field (δ4-4.2) than usually demonstrated by aromatic ethers (δ~3.8).

Mass spectrometry: No detailed study of the effect of electron-impact on cyclic N-hydroxy compounds has been reported. However, there are three isolated literature reports[32,116,155] in which the presence of an $(M-17)^+$ ion in a mass spectrum was considered evidence in support of a cyclic hydroxylamine structure. Additional information on the mass spectral behavior of other cyclic hydroxylamines is yet to published.[84] In this study, the mass spectra of some spiro-(N-hydroxyindoline)pyrazolones (CLXXXIII, R'=H) were recorded and interpreted. Although these spectra were complex,



CLXXXI

CLXXXII



CLXXXIII

	R^1	R^2	R^3
a,	H	CH_3	H
b,	H	Ph	H
c,	H	CH_3	Cl
d,	CH_3	CH_3	H

initial fragmentation pathways could be deduced. Abundant $(M-16)^+$ and $(M-17)^+$ ions were present in each of the spectra corresponding to the loss of an oxygen atom and a hydroxyl radical from the

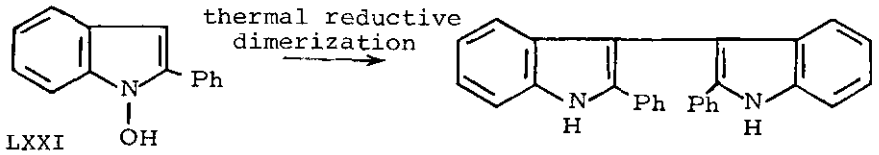
molecular ions. Strong metastable ions in the spectra of (CLXXXIII a-c) indicated that the $M^+ \rightarrow (M-17)^+$ transition was a direct one. These findings are comparable to those of Coutts and Mukherjee[176] who observed that aromatic hydroxylamines fragment by expelling an oxygen atom and a hydroxyl radical from their molecular ions.

It is of interest that an examination of the mass spectrum of 5-phenyl-2(cis),4(trans)-pentadienal (syn)-oxime (LVb, R=Ph) previously claimed[56] to be 1,2-dihydro-1-hydroxy-2-phenylpyridine (LVa, R=Ph), revealed[56a,84] that the molecular ion (CLXXXI) expelled a phenyl radical and gave the cyclic N-hydroxy ion (CLXXXII) which subsequently lost the OH radical.

The mass spectra of two cyclic N-methoxy compounds (XX)[18] and (CLXXXIIId)[84] have been examined. In the former, a methoxyl radical is expelled from the $(M-NMe_2)^+$ ion. In the latter, the methoxyl group is lost from the molecular ion as a formaldehyde molecule and as a methoxyl group.

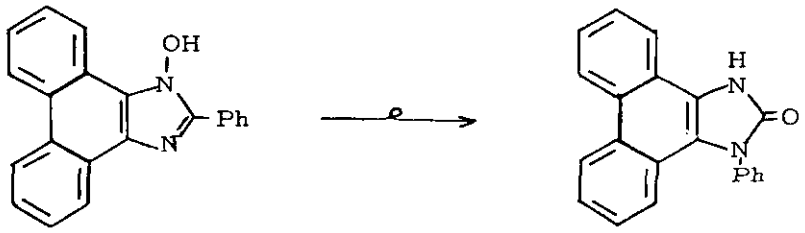
(D) Stability:

Cyclic hydroxylamines and their alkyl and acyl derivatives vary greatly in their stability. Some show surprising stability and are isolated readily while others are very difficult to isolate and undergo oxidation, dehydration or rearrangement. Many of these compounds also dimerize, dehydrate or rearrange when heated with or without solvent. Thus, in refluxing cymene, 1-hydroxy-2-phenylindole (LXXI) was converted to the dimeric indole (CLXXXIV),[66] and the N-hydroxyimidazole (CLXXXV) is claimed to rearrange to the imidazolone (CLXXXVI) upon heating to 235°.[177]



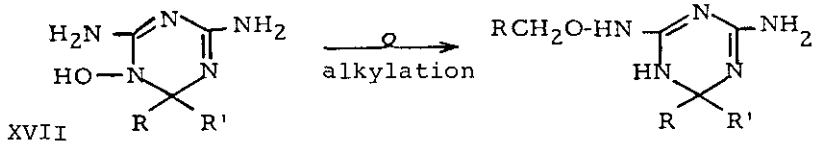
LXXI CLXXXIV

On alkylation, some N-hydroxydihydrotriazines (XVII) yielded rearrangement products (CLXXXVII). When the N-alkoxy derivatives



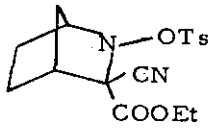
CLXXXV CLXXXVI

(XVII, OCH_2R for OH) were isolated, they converted smoothly into (CLXXXVII) by heating with or without solvent. The N-hydroxy compounds did not rearrange on heating.[15]

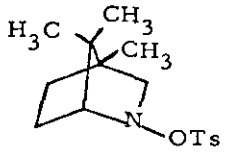


XVII CLXXXVII

Acyl and sulfonyl derivatives of N-hydroxy compounds are generally less stable than their parent compounds. Some, such as (CLXXXVIII), are stable at room temperature in non-aqueous media.[178] In contrast, the related tosylate (CLXXXIX) which lacks the pre-



CLXXXVIII

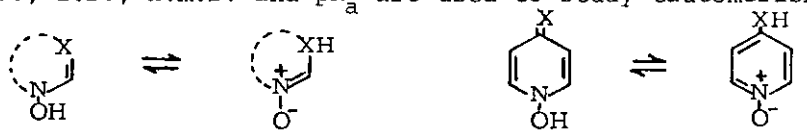


CLXXXIX

sence of electron withdrawing groups is extremely unstable even at very low temperatures in relatively non-polar solvents.[179]

(E) Tautomerism:

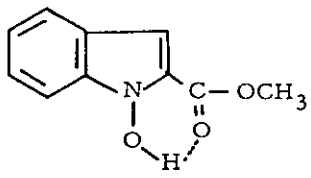
A tautomeric relationship between N-hydroxy and N-oxide forms is possible in some systems. This tautomerism might involve transfer of the N-OH hydrogen atom to a ring carbon or another nitrogen atom (CXCa⇌CXCb, X=CH or N) or to a ring carbonyl or imine function (CXCIa⇌CXCIb, X=O or NH). Generally, physical methods such as u.v., i.r., n.m.r. and pK_a are used to study tautomerism in



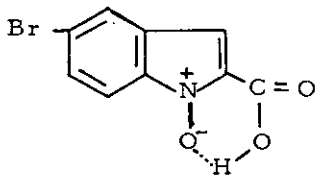
CXCa CXCb CXCIa CXCIb

different systems. Sometimes, chemical means are also employed for this purpose. The tautomeric equilibrium in most cases, is dependent on both the over-all nature of the molecule and the solvent system used.

The tautomeric behavior of some N-hydroxyindoles (VII) was studied by Mousseron-Canet and Boca.[167] N-Hydroxyindole (VIIa, R=H) itself was found to exist solely as 3H-indole N-oxide (VIIb) whereas the 2-substituted derivatives (VIIa, R=CH_3 or Ph) were tautomeric mixtures. The N-oxide form (VIIb) is favored in solvents which are capable of strong hydrogen bonding. For 1-hydroxy-2-methylindole (VIIa, R=CH_3), the proportion of each tautomer has been quantitatively estimated from the n.m.r. methyl integral. In deuterochloroform, methyl 1-hydroxyindole-2-carboxylate (CXCII) exists as such while 5-bromo-1-hydroxyindole-2-carboxylic acid is present entirely in the 1-oxide form (CXCIII) in the same solvent.



CXCII

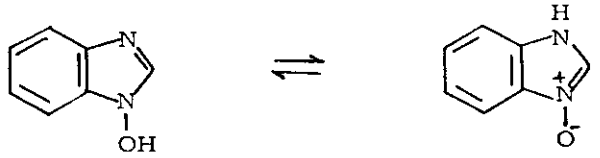


CXCIII

These results were attributed to intramolecular hydrogen bonding.[173]

Similar studies have been reported on the tautomerism of 1-hydroxypyrroles,[116,172] 1-hydroxyimidazoles,[120] tetrahydropyridine 1-oxides and dihydro-1,4-oxazine 4-oxides.[158] Two tautomers of certain triaryl-1-hydroxyimidazoles (CXXXIII) were claimed to be isolated under controlled conditions.

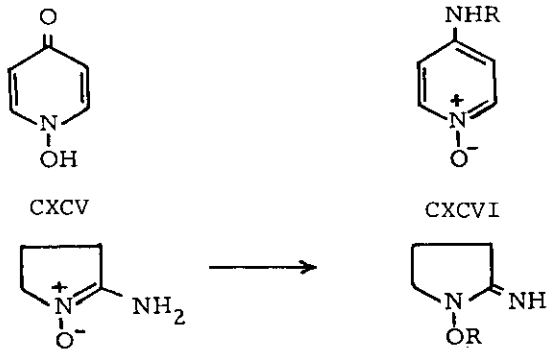
The structure of 1-hydroxybenzimidazole (CXCIVa) evoked some controversy. Kew and Nelson[180] suggested the N-oxide form (CXCIVb)



CXCIVa CXCIVb

for this compound but Takahashi and Kano[166] showed, using u.v. spectroscopy, that a solvent-dependent tautomeric equilibrium existed between the two forms. Further evidence supports tautomerism; reaction of 1-hydroxybenzimidazole with diazomethane yield-a mixture of O- and N-alkyl derivatives.[181] A solvent-dependent tautomerism was also observed with 1-hydroxy-6-nitrobenzimidazole,[104] whereas 1-hydroxy-2-phenylbenzimidazole was shown to exist entirely as the N-hydroxy form even in aqueous solution.[102] 1-Hydroxybenzotriazole derivatives also behaved similarly; some are tautomeric mixtures while others exist only as the N-hydroxy structure.[165]

Studies using physical methods indicated that both tautomers of 1-hydroxy-4-pyridone (CXCV) are of comparable importance.[92] Similarly, 10-hydroxyacridone exists in equilibrium with equal amounts of 9-hydroxyacridine 10-oxide.[182] In contrast, amino N-oxides exist predominantly in the amino form (CXCVI).[92] In certain in-



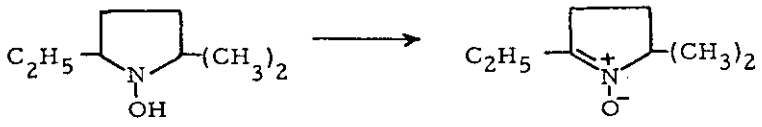
CXCV CXCVI

CXCVII CXCVIII

stances, however, chemical reactions gave products derived from the N-hydroxy tautomer of amino N-oxides. Alkylation and benzoylation of 2-aminopyrroline 1-oxide (CXCVII) occurred at the oxygen atom giving products of the type (CXCVIII) while acetylation gave only the N-acetyl derivative.[183]

(F) Oxidation:

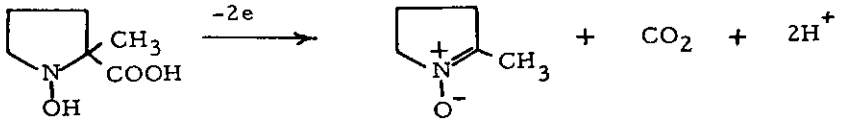
Cyclic hydroxylamines are readily oxidized by a wide variety of oxidizing agents. When an α-hydrogen is available, the products are mostly cyclic nitrones. The passage of oxygen (or air) into a solution of the N-hydroxy compound, in the presence of a catalyst such as copper/ammonia complex, is commonly employed, but sometimes fails to oxidize these compounds. This method was used for the oxidation of 1-hydroxypyrrolidines such as (CXCIX) to the corresponding nitrones (CC).[38] Similar results were obtained when



CXCIX CC

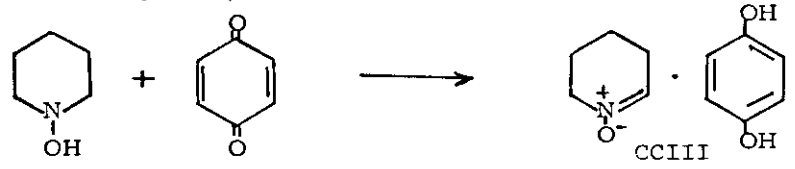
alkaline potassium ferricyanide[37] or yellow mercuric oxide[24] were used as oxidizing agents. The latter reagent was also employed for the oxidation of N-hydroxypiperidine, N-hydroxymorpholine,[158] 2-hydroxy-1,2,3,4-tetrahydroisoquinoline,[43] and 1-hydroxybenzodiazepines[11,41,42] to the corresponding nitrones.

Other ring substituents can also be affected during the oxidation of the N-hydroxy function. 1-Hydroxy-2-methylpyrrolidine-2-carboxylic acid (CCI) undergoes oxidative decarboxylation during the nitrone (CCII) formation.[37]

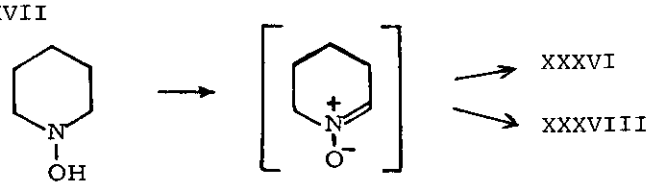


CCI CCII

1-Hydroxypiperidine (XXXVII) reacted with p-benzoquinone to yield an adduct (CCIII).[184] Aerial oxidation of the same N-hydroxy



XXXVII CCIII

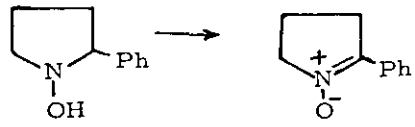


XXXVII CCIV

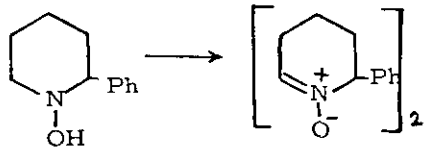
compound in the presence of cupric acetate yielded 3,4,5,6-tetra-

hydropyridine 1-oxide (CCIV) which dimerized immediately to the cyclic dimer (XXXVI).[43] A trimer formulated as (XXXVIII) was formed by the oxidation of (XXXVII) using potassium ferricyanide.[43] Related polymers were obtained by the oxidation of N-hydroxyhexaethyleneamine[44] and N-hydroxymorpholine.[185]

In some cases, the course of oxidation was found to depend on subtle steric effects. Oxidation of 1-hydroxy-2-phenylpyrrolidine (LII) with mercuric oxide gave the nitrone (CCV) in which the nitrone double bond was conjugated with the phenyl group.[43,186] In contrast, the same reagent oxidized 1-hydroxy-2-phenylpiperidine (CCVI) to a dimer of the nitrone (CCVII) in which the nitrone group and the phenyl group are not conjugated.[43] This difference in the behavior of these analogous N-hydroxy compounds was explained in terms of their stereochemistry.[24]

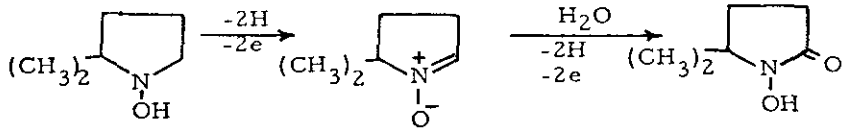


LII CCV

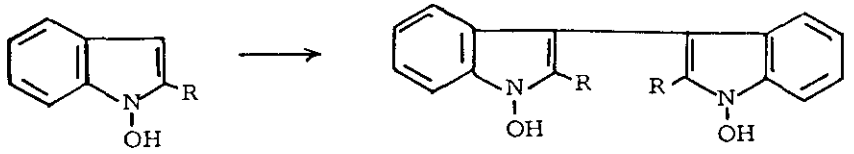


CCVI CCVII

Ferric chloride is reported to oxidize 2,2-dimethyl-1-hydroxypyrrolidine (CCVIII) to the corresponding hydroxamic acid (CCIX) via the nitrone (XLIX) intermediate.[158] The same reagent oxidized ethyl 1-hydroxyindole-2-carboxylate (VIIa, R=COOEt) to the bis N-hydroxy compound (CCX, R=COOEt).[98] A related product (CCX, R=Ph) was obtained by the oxidation of 1-hydroxy-2-phenylindole (VIIa, R=Ph) with nitrobenzene or diethyl azodicarboxylate.[187] The diradical (CCXI) was formed when (VIIa, R=Ph) was treated with t-butyl hydroperoxide or diethyl azodicarboxylate. Oxidation

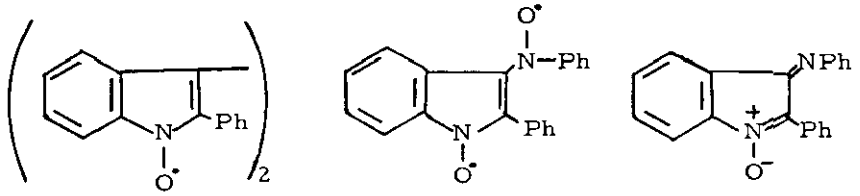


CCVIII XLIX CCIX



VIIa CCX

with excess nitrobenzene gave in addition to (CCXI) another diradical (CCXII) and a nitrone (CCXIII).[188-190]



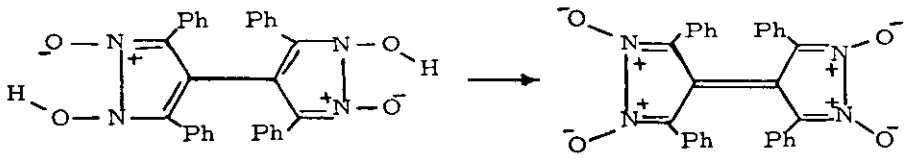
CCXI CCXII CCXIII

Other cyclic hydroxylamines are also reported to yield free radicals on oxidation. 1-Hydroxyimidazole was converted to the radical (CCXIV) on treatment with halogens in polar solvents or with lead dioxide.[191,192] The stable free radicals (CCXV) and (CLXVII) were also obtained by the silver oxide[193] and catalyzed (Na_2WO_2) hydrogen peroxide oxidation of the corresponding hydrox-

CCXIV CCXV

ylamines. Oxidation of the N-hydroxypyrazole dimer (CCXVI) with iodine yielded a compound (CCXVII) for which preliminary electron

spin resonance studies suggested biradical character.[194]



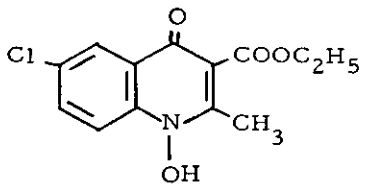
CCXVI CCXVII

(G) Reduction:

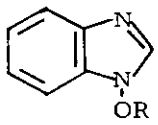
The N-hydroxy function as well as its O-substituted derivatives can be reduced by chemical reagents or by catalytic hydrogenation. Zinc and acetic acid is used very frequently for this purpose. N-Hydroxypyrazoles,[95] N-hydroxyindole[88] and N-hydroxypyrroles,[49] for example, were reduced to the corresponding amines by the use of this reagent. Phosphorus and hydriodic acid were also used for the reduction of 1-hydroxybenzotriazole[195] and 1,5-dihydroxy-3,3-dimethylpiperidine (XXXII).[37]

N-Hydroxyphenmetrazine (XII) is said to reduce quantitatively to phenmetrazine (XI) by means of titanous chloride or lithium aluminum hydride.[32] The latter reducing agent was also used for the reduction of some substituted 1-hydroxyimidazole derivatives.[177] Other chemical reagents which have been used for the reduction of cyclic hydroxylamines include sodium hydrosulfite,[125] tin or tin chloride and hydrochloric acid,[107,112] and dimethylformamide.[106]

The N-hydroxy function is, in most cases, susceptible to catalytic hydrogenation. N-Hydroxybenzimidazoles[107,166] and N-hydroxyimidazole[191] were readily hydrogenated over suitable catalysts. In contrast, hydrogenation of the N-hydroxyquinolone (CCXVIII) over Pd-C replaced only the chlorine atom with hydrogen without



CCXVIII

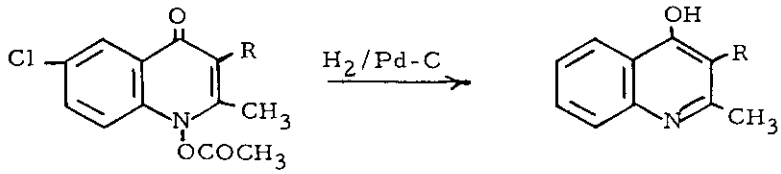


CCXIX

affecting the N-hydroxy function.[88] Also, catalytic hydrogenation of tetrahydropyridine 1-oxide dimer (XXXVI) in dilute hydrochloric acid resulted only in partial reduction and gave 1-hydroxypiperidine hydrochloride.[43]

Reduction of cyclic N-alkoxy compounds generally results in elimination of the alkoxy group. The N-methoxy compound (XIX) was successfully hydrogenated over Pd-C or reduced with lithium aluminum hydride to the corresponding indole.[17] N-Alkoxybenzimidazoles (CCXIX) also eliminated the alkoxy group when catalytically reduced.[74] In certain cases, however, reduction does not affect the N-alkoxy function. 1-Methoxyindole-2-carboxylic acid, for example, was reduced with lithium aluminum hydride and yielded 1-methoxy-2-hydroxymethylindole and 1-methoxy-2-formylindole; the N-methoxy function was not eliminated.[28]

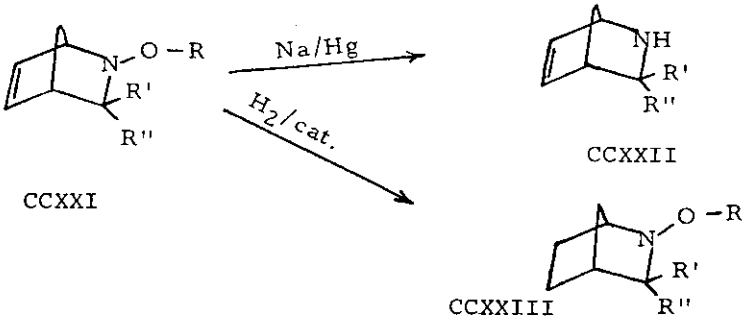
Hydrogenation of acetates of structure (CCXX) over Pd-C caused replacement of both the acetate group and the chlorine atom by hydrogen and 4-hydroxyquinolines (CCXXa) resulted.[88] Sodium-



CCXX

CCXXa

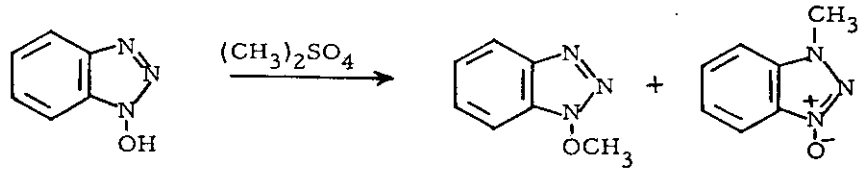
amalgam also reduced the benzoate and sulfonate derivatives of 2-azanorbornenes (CCXXI) to (CCXXII), but when catalytic hydrogenation was carried out, only the double bond was reduced (CCXXIII).[178]



CCXXI CCXXII CCXXIII

(H) Alkylation Reactions:

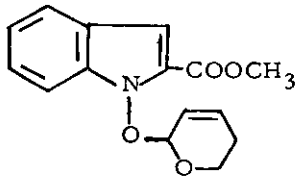
Many N-hydroxy compounds are sufficiently acidic to be O-methylated with diazomethane.[64,173,181] Dimethyl sulfate[106,195,196] and alkyl halides[74,112,151] are used more frequently for this purpose. 1-Hydroxybenzotriazole (CXXIV) reacted with dimethyl sulfate to give a mixture of O-methyl (CCXXIV) and N-methyl (CCXXV) derivatives, the ratio of which was found to alkali-dependent.[197,198] In the absence of alkali and solvent, (CXXIV) was converted only to the N-methyl compound. A better yield of the O-methyl derivative was obtained when the silver salt of (CXXIV) was methylated with methyl iodide.[195]



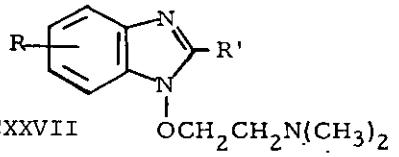
CXXIV CCXXIV CCXXV

2,3-Dihydropyran reacted with methyl 1-hydroxyindole-2-carboxylate to yield an addition product (CCXXVI).[28] Similarly, the 1-alkoxy derivative (CCXXVII) formed when dimethylaminoethyl chloride

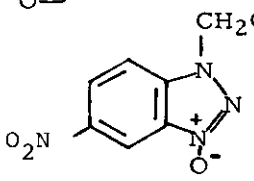
was reacted with 1-hydroxybenzimidazole in the presence of sodium hydride and dimethylformamide.[13] In contrast, the reaction of 6-



CCXXVI



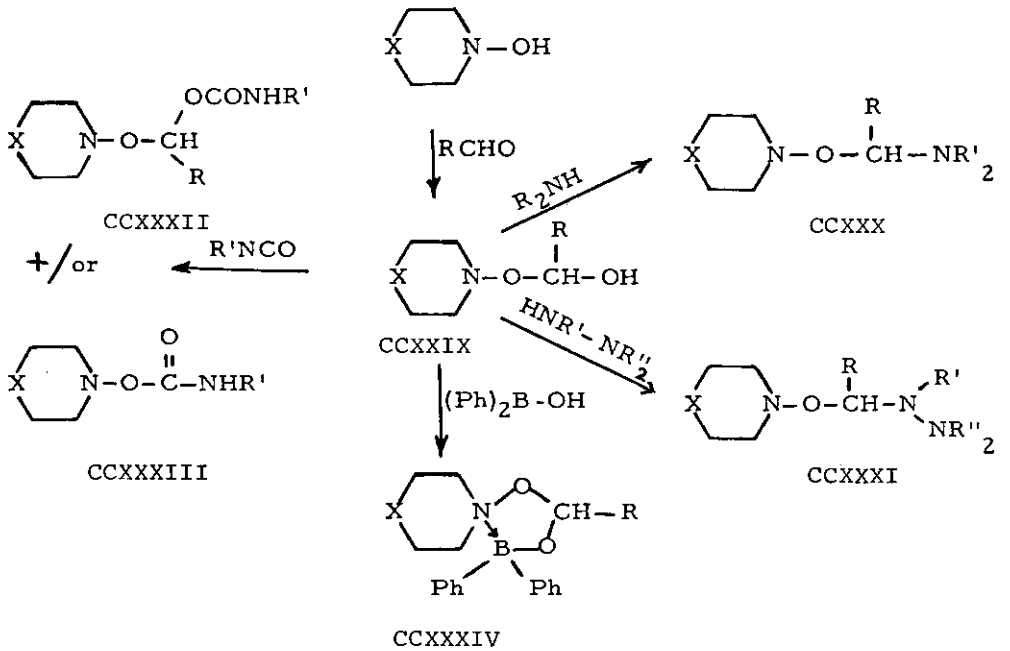
CCXXVII



CCXXVIII

nitro-1-hydroxybenzotriazole with 1-chloropentane-3-one yielded only the N-substituted product (CCXXVIII).[199]

Several aldehydes react with cyclic N-hydroxy compounds to give O-semiacetals (CCXXIX) which are converted to the so-called "mixed



CCXXXII

CCXXXIII

CCXXIX

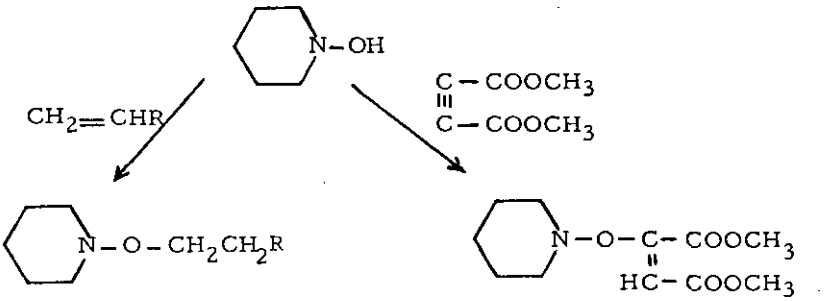
CCXXX

CCXXXI

CCXXXIV

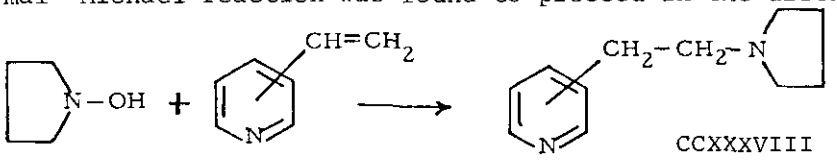
N,O-acetals" (CCXXX) and (CCXXXI) when reacted with amines, or hydrazines.[23] Treatment of the semiacetal (CCXXIX) with aryliso-cyanates yielded a mixture of (CCXXXII) and (CCXXXIII)[200] while reaction of (CCXXIX) with diphenylboric acid gave dihydro-5-bora-1,3,4-dioxazole derivatives (CCXXXIV).[23,134]

1-Hydroxypiperidine has been successfully condensed in a Michael-type reaction with various electron deficient alkenes ($RCH=CH_2$; $R=COCH_3$, COOR, CN) to produce adducts of structure (CCXXXV).[199] The N-hydroxy group also added across the triple bond of acetylene dicarboxylic esters and the adduct (CCXXXVI) was formed.[201] On the other hand, the reaction of 1-hydroxypyrrolidine with 2- or



CCXXXV CCXXXVI

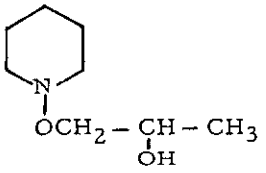
4-vinylpyridines (CCXXXVII) resulted in the loss of the oxygen atom and gave pyridylethylpyrrolidines (CCXXXVIII).[24] This "abnormal" Michael reaction was found to proceed in the absence



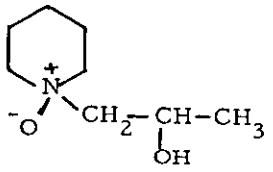
CCXXXVII CCXXXVIII

as well as in the presence of acidic or basic catalysts.[142]

Treatment of N-hydroxypiperidine with propylene oxide was originally claimed[202] to give 1-piperidinoxy-2-propanol (CCXXXIX). This report was discounted by Cannon et al[203] who showed that the product was, in fact, the amine oxide (CCXL). Based on this, the products obtained by the reaction of other N-hydroxy compounds with alkylene oxides[200] would be worthy of reinvestigation.



CCXXXIX



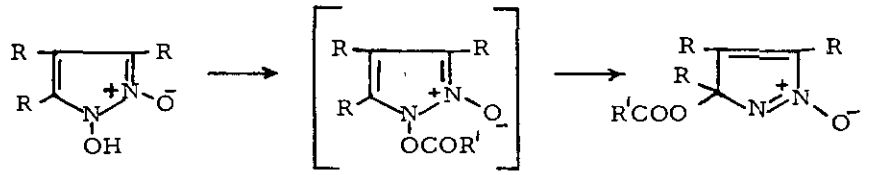
CCXL

(I) Acylation and Sulfonation Reactions:

Acetyl, benzoyl and sulfonyl chlorides react readily with cyclic N-hydroxy compounds to form acetate, benzoate and sulfonate derivatives. Acetic anhydride, benzoic anhydride as well as ketene are also used for this purpose. Alternatively, cyclic acetoxy and benzoyloxy derivatives are obtained by the action of acetyl or benzoyl peroxide on the corresponding cyclic amines or by condensation reactions in which the acyloxy function is already present in one of the reacting components.

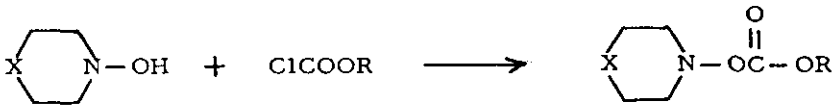
1-Acetoxypiperidine was prepared by the action of acetyl chloride, acetic anhydride or ketene on 1-hydroxypiperidine.[157] Similarly, treatment with benzoyl chloride yielded 1-benzoyloxypiperidine. Both these acyloxy derivatives were also prepared by reacting piperidine with the corresponding acyl peroxide.[36,204,205] Similar preparations of N-acetoxy and N-benzoyloxy derivatives of morpholine, indoles, imidazoles, pyrazoles, benzimidazoles and benzotriazoles are known; examples of these compounds are presented

in table 1. There are cases, however, where dehydrated or rearranged products were obtained. For example, when various 1-hydroxypyrazole 2-oxides of general structure (CLXIII) were treated with acetic anhydride or benzoyl chloride, the acetyl and benzoyl derivatives (CCXLI, R'=CH_3 or Ph) formed initially then rearranged to (CCXLII). In the absence of the N-oxide function, however, O-benzoyl derivatives could be isolated.[95]



CLXIII CCXLI CCXLII

Esters (CCXLIII) of cyclic hydroxylamines can be prepared by the action of alkyl chloroformates on N-hydroxy compounds.[23,157] Isocyanates can also react with cyclic hydroxylamines and give N-

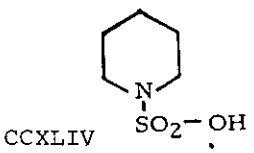


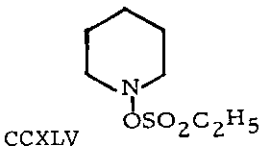
X=CH_2 or O

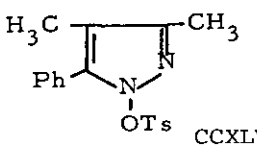
CCXLIII

carbamoyloxy derivatives.[23,120]

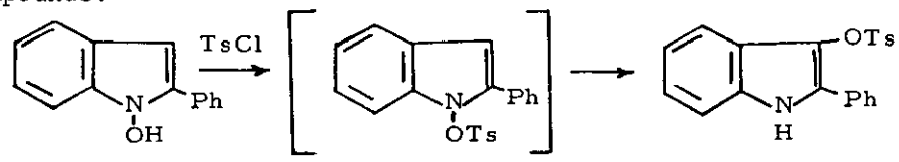
Sulfonate derivatives of N-hydroxy compounds are less stable than the corresponding acetates or benzoates and only a few O-sulfonates have been isolated. Zinner[157,204,206] described the formation of piperidine N-sulfonic acid (CCXLIV) and the piperidine N-oxysulfinic ester (CCXLV) by the interaction of 1-hydroxypiperidine with sulfur dioxide and chlorosulfinic ester respectively. The stable tosylate (CCXLVI, Ts=p-$CH_3C_6H_4SO_2$) was also isolated.[95]


CCXLIV


CCXLV


CCXLVI

On the other hand, attempts to prepare the O-sulfonate derivative (CCXLVII) by reacting 1-hydroxy-2-phenylindole (LXXI) with p-toluenesulfonyl chloride gave a rearrangement product which was formulated as (CCXLVIII).[66] Similar rearrangements were also observed[179,207] during attempted sulfonylation of other N-hydroxy compounds.


LXXI CCXLVII CCXLVIII

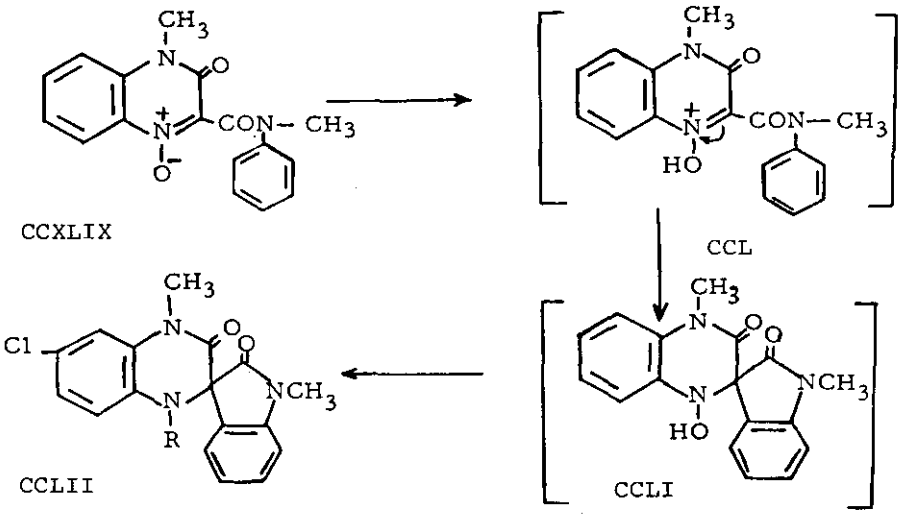
The possibility of employing N-acyloxy derivatives of cyclic hydroxylamines as acylating agents was studied by Sammes.[205] N-Benzoyloxypiperidine was found to react with benzylamine and with ethyl aminoacetate to give N-benzylbenzamide and hippuric acid respectively. 1-Acetoxypiperidine was also shown to be a reactive acylating agent. Other studies[208,209] have demonstrated the usefulness of these esters and other esters of N-hydroxypiperidine in peptide sythesis and as selective acylating agents.

(J) Reactions with Nucleophilic Reagents:

The reactions of arylhydroxylamines and hydroxamic acids with different nucleophilic reagents including tissue nucleophiles (amino acids, proteins and nucleic acids) have been studied in great detail. However, only few of these reactions have been attempted with cyclic hydroxylamines or their alkyl, acyl or

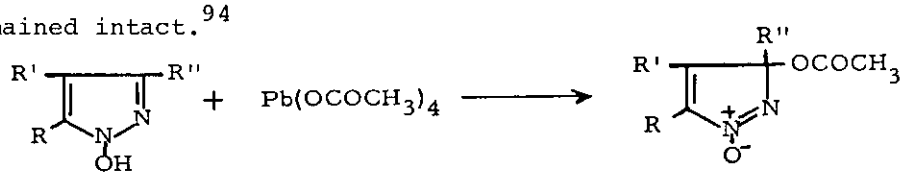
sulfonyl derivatives. The importance of these studies is to provide information on any interactions which might occur between cellular macromolecules and N-hydroxy compounds if the latter are metabolically formed in the body.

Ethanolic hydrogen chloride is known[210] to convert the N-oxide (CCXLIX) to the spiro-quinoxaline derivative (CCLII, R=H). When hydrogen chloride is replaced with acetyl chloride, the 1-acetyl derivative (CCLII, R=$COCH_3$) is formed. In view of the work on the interaction of phenylhydroxylamine with chloride ions[211,212]



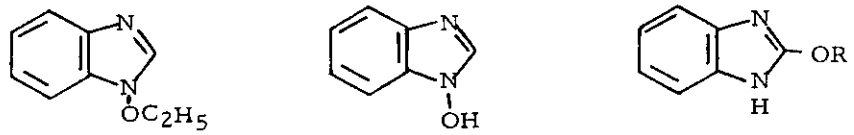
it was proposed that the formation of (CCLII) proceeded via N-hydroxy intermediates (CCL, CCLI). Attempts to prepare the latter compound failed,[29] although, as described earlier, it proved possible to prepare the structurally related N-hydroxypyrazine (CLXXII). Treatment of 1-hydroxyindole-2-carboxylic acid with methanolic hydrogen chloride results in the formation of its methyl ester without elimination of the N-hydroxy function.[64]

Also, treatment of the 1-hydroxypyrazoles (CCLIII) with lead tetracetate yielded acetate derivatives (CCLIV) in which the N-O bond remained intact.[94]



CCLIII CCLIV

Heating 1-ethoxybenzimidazole (CCLV) with hydrochloric or hydrobromic acids in a sealed tube, caused cleavage of the C-O bond of the ethoxy group giving N-hydroxyimidazole (CXCIVa).[74] On the other hand, the 2-alkoxy derivatives (CCLVI) were obtained when (CCLV) was heated with sodium alkoxide. The same N-ethoxy compound

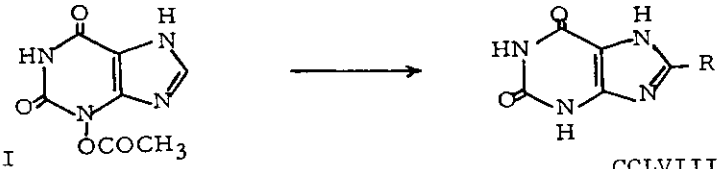


CCLV CXCIVa CCLVI

(CCLV) reacted with nucleophilic reagents such as hydrazine hydrate and sodium hydrogen sulfite to give 2-hydrazinobenzimidazole and sodium 2-benzimidazolesulfonate respectively, but it did not react with potassium cyanide except at elevated temperature to give a poor yield of 2-benzimidazolecarbamic acid. In these reactions, it was assumed that a nucleophilic reagent attacked the electron deficient 2-position of the 1-alkoxybenzimidazoles, then elimination of alcohol occurred to give 2-substituted benzimidazoles.[74]

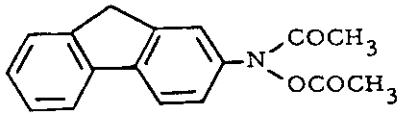
Glucuronide, sulfonate and acetate esters were found to be more reactive biochemically with tissue nucleophiles than their parent N-hydroxy compounds. Although enzymatic O-acetylation of foreign compounds containing N-OH groups has not been demonstrated, O-acetate derivatives such as (CCLVII) have been used as models of glucuronide

or sulfonate conjugates. Compound (CCLVII) reacted *in vitro* with chloride ion and with methionine to give 8-chloroxanthine (CCLVIII, R=Cl) and 8-methylmercaptoxanthine (CCLVIII, R=SCH_3), respectively. These products were identical to two urinary metabolites of 3-



CCLVII CCLVIII

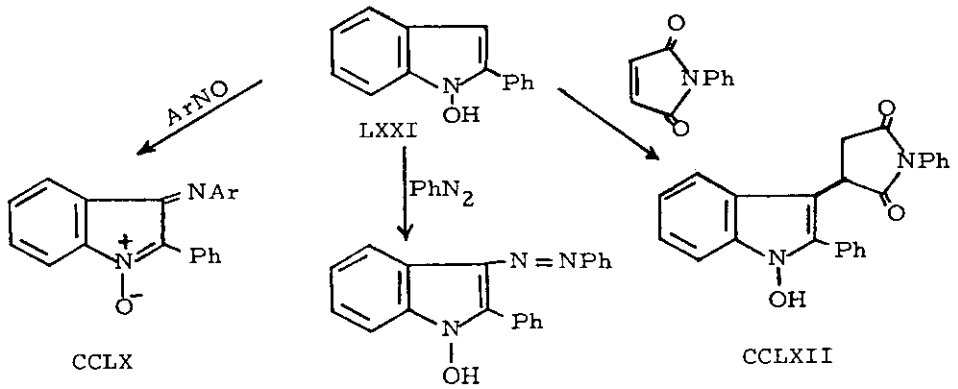
hydroxyxanthine.[213] This reaction with methionine is reminiscent of the well studied[5,214,215] interaction of the carcinogenic model compound N-acetoxy-N-acetyl-2-aminofluorene (CCLIX) with tissue nucleophiles.



CCLIX

(K) Reactions with Electrophilic Reagents:

The reactions of 1-hydroxy-2-phenylindole (LXXI) with a number of electrophilic reagents were studied by Colonna and co-workers.[187,189,216,217] Treatment of (LXXI) with aromatic nitroso

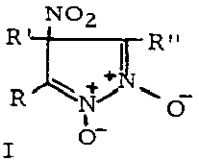


CCLX LXXI CCLXII

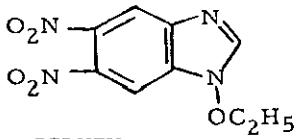
CCLXI

compounds gave 2-phenyl-3-aryliminoindole 1-oxide (CCLX). An adduct of 1-hydroxy-2-phenyl-3-(phenylazo)indole (CCLXI) with (LXXI) was formed when the latter was treated with phenyldiazonium chloride. The same N-hydroxy compound (LXXI) reacted with some dienophiles such as N-phenylmaleimide to yield 1-hydroxy-2-phenyl-3-(N-phenylsuccinimidyl)indole (CCLXII).

1-Hydroxypyrazole 2-oxides (CLXIII) reacted with nitrous acid to yield nitropyrazolenine 1,2-dioxides (CCLXIII).[95] In a similar reaction, 1-ethoxybenzimidazole was converted to a 5- or 6-mono-



CCLXIII



CCLXIV

nitro derivative when treated with a mixture of fuming nitric acid and sulfuric acid at room temperature, and a dinitro derivative (CCLXIV) on heating.[74]

REFERENCES

1. R. T. Coutts, Canad. J. Pharm. Sci., 1967, 2, 27.

2. J. B. Bapat, D. St.C. Black, and R. F. C. Brown, in 'Advances in Heterocyclic Chemistry', vol. 10, ed. by A. R. Katritzky and A. J. Boulton, Academic Press Inc., New York, 1969, p. 199.

3. B. Zeeh and H. Metzger in 'Houben-Weyl Methoden der Organischen Chemie', vol. X/1, ed. by E. Muller, Georg Thieme, Stuttgart, 1971, p. 1091.

4. J. H. Weisburger and E. K. Weisburger, Pharmacol. Rev., 1973, 25, 1.

5. C. C. Irving in 'Metabolic Conjugation and Metabolic Hydrolysis', vol. I, ed. by W. H. Fishman, Academic Press, New York, 1970, p. 53.

6. A. H. Beckett and S. Al-Sarraj, J. Pharm. Pharmacol., 1972, 24, 174.

7. L. W. Jones and R. T. Major, J. Amer. Chem. Soc., 1927, 49, 1527.

8. P. Mamalis, Xenobiotica, 1971, 1, 569.

9. R. T. Major and F. Dürsch, J. Org. Chem., 1961, 26, 1867.

10. French Patent 1,482,641 (1967); Chem. Abstr., 1968, 68, 105261t.

11. Netherlands Patent 6,515,759 (1966); Chem. Abstr., 1966, 65, 15406f.

12. F. J. Petracek, United States Patent 3,296,277 (1967); Chem. Abstr., 1967, 66, 55386y.

13. Netherlands Patent 6,515,833 (1966); Chem. Abstr., 1966, 65, 15388h.

14. G. DeStevens, A. B. Brown, D. Rose, H. I. Chernov, and A. J. Plummer, J. Medicin. Chem., 1967, 10, 211.

15. P. Mamalis, J. Green, D. J. Outred, and M. J. Rix, J. Chem. Soc., 1965, 1829.

16. R. Gmelin and A. I. Virtanen, Acta Chem. Scand., 1962, 16, 1378.

17. H. Morimoto and H. Oshio, Annalen, 1965, 682, 212.

18. S. R. Johns, J. A. Lamberton, and J. L. Occolowitz, Austral. J. Chem., 1967, 20, 1737.

19. Y. Hirata, O. Shimomura, and S. Eguchi, Tetrahedron Letters, 1959, No. 5, 4; O. Shimomura, J. Chem. Soc. Japan, 1960, 81, 179.

20. Y. Kishi, T. Goto, Y. Hirata, O. Shimomura and F. H. Johnson, Tetrahedron Letters, 1966, 3427.

21. R. A. Henry and W. M. Dehn, J. Amer. Chem. Soc. 1950, 72, 2280.

22. E. R. Blout, S. G. Cohen, and M. Green, United States Patent 2,843,481 (1958); Chem. Abstr., 1958, 52, 18044h.

23. G. Zinner, and W. Kliegel, Chem. Ber., 1966, 99, 895.

24. J. Thesing and W. Sirrenberg, Chem. Ber., 1959, 92, 1748.

25. W. Ruppert, German Patent 1,004,191 (1957); Chem. Abstr., 1960, 54, 584c.

26. T. Kawaguchi, T. Matsubara, and H. Kato, Japanese Patent 19,495 (1966); Chem. Abstr., 1967, 66, 85529.

27. F. Ingraffia, Gazzetta, 1933, 63, 175.

28. M. Kawana, M. Yoshioka, S. Miyaji, H. Kataoka, Y. Omote, and N. Sugiyama, J. Chem. Soc. Japan, 1965, 86, 526.

29. M. S. Habib and C. W. Rees, J. Chem. Soc., 1962, 123.

30. H. vonDobeneck and W. Lehnerer, Chem. Ber., 1957, 90, 161.

31. W. H. Houff, O. N. Hinsvark, L. E. Weller, S. H. Wittwer, and H. M. Sell, J. Amer. Chem. Soc., 1954, 76, 5654.

32. A. H. Beckett and M. A. Salami, J. Pharm. Pharmacol., 1972, 24, 900.

33. G. W. Stacy, B. V. Ettling, and A. J. Papa, J. Org. Chem., 1964, 29, 1537.

34. S. Niementowski, Chem. Ber., 1892, 25, 860.

35. S. Gambarian and L. Kazarian, J. Gen. Chem. (U.S.S.R.), 1933, 3, 222; S. Gambarian, Chem Ber., 1925, 58, 1775.

36. A. M. Feldman, A. K. Hoffmann, French Patent 1,360,030 (1964); Chem. Abstr., 1964, 61, 13289d.

37. R. F. C. Brown, V. M. Clark, and Sir A. Todd, J. Chem. Soc., 1959, 2105.

38. R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland, and Sir A. Todd, J. Chem. Soc., 1959, 2094.

39. G. F. Field, W. J. Zally, and L. H. Sternbach, Tetrahedron Letters, 1966, 2609.

40. O. Exner, Coll. Czech. Chem. Comm., 1955, 20, 202.

41. T. S. Sulkowski and S. J. Childress, J. Org. Chem., 1963, 28, 2150.

42. L. H. Sternbach and E. Reeder, J. Org. Chem., 1961, 26, 1111.

43. J. Thesing and H. Meyer, Chem. Ber., 1956, 89, 2159; Annalen, 1957, 609, 46.

44. E. J. Alford, J. A. Hall, and M. A. T. Rogers, J. Chem. Soc. (C), 1966, 1103.

45. M. A. T. Rogers, Nature, 1956, 177, 128.

46. E. P. Kohler and G. R. Barrett, J. Amer. Chem. Soc., 1926, 48, 1770.

47. E. C. Taylor and N. W. Kalenda, J. Org. Chem., 1953, 18, 1755.

48. J. P. Freeman, J. J. Gannon, and D. L. Surbey, J. Org. Chem., 1969, 34, 187.

49. A. H. Blatt, J. Amer. Chem. Soc., 1934, 56, 2774.

50. V. M. Clark, B. Sklarz, and Sir. A. Todd, J. Chem. Soc., 1959, 2123.

51. G. R. Delpierre and M. Lamchen, J. Chem. Soc., 1963, 4693.

52. P. Ruggli, B. Hegedüs, and E. Caspar, Helv. Chim. Acta., 1939, 22, 411.

53. M. Colonna, and A. Risaliti, Gazzetta, 1953, 83, 58.

54. E. Ochiai, and K. Arima, J. Pharm. Soc. Japan, 1949, 69, 51.

55. M. Colonna and A. Risaliti, Ann. Chim. (Italy), 1954, 44, 1029.

56. T. Kato, and H. Yamanaka, J. Org. Chem., 1965, 30, 910.

56a. T. J. van Bergen and R. M. Kellogg, J. Org. Chem., 1971, 36, 1705.

57. W. D. S. Bowering, V. M. Clark, R. S. Thakur, and Lord Todd, Annalen, 1963, 669, 106.

58. R. F. C. Brown, V. M. Clark, I. O. Sutherland, and Sir A. Todd, J. Chem. Soc., 1959, 2109.

59. R. F. C. Brown, V. M. Clark, and Sir A. Todd, J. Chem. Soc., 1965, 2337.

60. J. D. Loudon and G. Tennant, Quart. Rev., 1964, 18, 389.

61. M. Mousseron-Canet and J.-P. Boca, Bull. Soc. Chim. France, 1965, 2704.

62. A. Reissert, Chem. Ber., 1897, 30, 1030.

63. R. T. Coutts and D. G. Wibberley, J. Chem. Soc., 1963, 4610.

64. I. Baxter and G. A. Swan, J. Chem. Soc., (C), 1967, 2446.

65. M. Krajcinovic and D. Vranjican, Bull. Soc. Chim. France, 1933, 53, 145.

66. R. J. Sundberg, J. Org. Chem., 1965, 30, 3604.

67. S. Gabriel and W. Gerhard, Chem. Ber., 1921, 54, 1067.

68. K. L. McCluskey, J. Amer. Chem. Soc., 1922, 44, 1573.

69. S. Niementowski, Chem. Ber., 1910, 43, 3012.

70. R. Kuhn and W. Blau, Annalen, 1958, 615, 99.

71. S. Niementowski, Chem. Ber., 1899, 32, 1456.

72. W. Baczynski and S. Niementowski, Chem. Zentr., 1902, 73, 940.

73. Z. Bankiewicz, Chem. Ber., 1889, 22, 1396.

74. S. Takahashi and H. Kano, Chem. and Pharm. Bull. Japan , 1964, 12, 282.

75. K. Fries and H. Reitz, Annalen, 1937, 527, 38.

76. M. Kamel, M. A. Allam, and N. Y. Abou-Zeid, Tetrahedron , 1967, 23, 1863.

77. A. Harden and J. Okell, Chem. News, 1901, 45; A. Harden, Annalen, 1889, 255, 159.

78. F. L. Scott and F. J. Lalor, Chem. and Ind., 1966, 420.

79. G. Heller and P. Wunderlich, Chem. Ber., 1914, 47, 2889.

80. I. J. Pachter and M. C. Kloetzel, J. Amer. Chem. Soc., 1951, 73, 4958.

81. J. M. Tyler, J. Chem. Soc., 1955, 203.

82. K. S. Narang, J. N. Ray, and A. Singh, J. Indian Chem. Soc., 1934, 11, 427.

83. R. T. Coutts, and J. B. Edwards, Canad. J. Chem., 1966, 44, 2009.

84. R. T. Coutts, and A.-M. M. K. El-hawari, unpublished results.

85. H. C. Brown, 'Hydroboration', W. A. Benjamin Inc., New York. 1962, p. 242.

86. R. T. Coutts, J. Chem. Soc. (C), 1969, 713.

86a. J. P. Freeman, Chem. Rev., 1973, 73, 283.

87. E. Fischer and H. Hütz, Chem. Ber., 1895, 28, 585.

88. J. D. Loudon and I. Wellings, J. Chem. Soc., 1960, 3462 and 3470.

89. J. D. Loudon, and G. Tennant, J. Chem. Soc. , 1962, 3092.

90. K. Lehmstedt, Chem. Ber., 1932, 65, 999.

91. A. Kliegl and A. Brösamle, Chem. Ber., 1936, 69, 197.

92. A. R. Katritzky and J. M. Lagowski, 'Chemistry of the Heterocyclic N-Oxides', Academic Press, London, 1971.

93. C. Harries and H. Tietz, Annalen, 1904, 330, 237.

94. J. P. Freeman and J. J. Gannon, J. Heterocyclic Chem., 1966, 3, 544.

95. J. P. Freeman and J. J. Gannon, J. Org. Chem., 1969, 34, 194.

96. J. P. Freeman and J. F. Hansen, Chem. Comm., 1972, 961.

97. A. Reissert, Chem. Ber., 1896, 29, 639.

98. S. Gabriel, W. Gerhard, and R. Wolter, Chem. Ber., 1923, 56, 1024.

99. J. D. Loudon and G. Tennant, J. Chem. Soc., 1963, 4268.

100. A. E. Luetzow, N. E. Hoffman, and J. R. Vercellotti, Chem. Comm., 1966, 301.

101. A. E. Luetzow and J. R. Vercellotti, J. Chem. Soc. (C), 1967, 1750.

101a. D. B. Livingstone and G. Tennant, J. Chem. Soc. Chem. Comm., 1973,96

102. G. W. Stacy, T. E. Wollner, and T. R. Oakes, J. Heterocyclic Chem., 1966, 3, 51.

103. R. J. Pollitt, Chem. Comm., 1965, 262.

104. D. J. Neadle and R. J. Pollitt, J. Chem. Soc. (C), 1967, 1764.

105. D. W. Russell, Chem. Comm., 1965, 498.

106. E. C. Taylor and E. E. Garcia, J. Amer. Chem. Soc., 1964, 86, 4721.

107. F. Minisci, R. Galli, and A. Quilico, Tetrahedron Letters, 1963, 785.

108. A. J. Boulton, A. C. Gripper Gray, and A. R. Katritzky, J. Chem. Soc. (B), 1967, 911; Chem. Comm., 1966, 741.

109. S. Secareanu and I. Lupas, Bull. Soc. Chim. France, 1933, 53, 1436.

110. R. Nietzki, and E. Braunschweig, Chem. Ber., 1894, 27, 3381.

111. T. Zincke and P. Schwarz, Annalen, 1900, 311, 329.

112. T. Curtius and M. Mayer, J. Prakt. Chem., 1907, 76, 369.

113. E. Müller, and G. Zimmermann, J. Prakt. Chem., 1925, 111, 277.

114. B. Vis, Rec. Trav. Chim., 1939, 58, 847.

115. A. K. Macbeth and J. R. Price, J. Chem. Soc., 1934, 1637.

116. E. E. Schweizer and C. M. Kopay, J. Org. Chem., 1972, 37, 1561.

117. V. Sprio and G. C. Vaccaro, Ann. Chim. (Italy), 1959, 49, 2075.

118. C. Harries and F. Lehmann, Chem. Ber., 1897, 30, 2726.

119. F. J. Allan and G. G. Allan, Chem. and Ind., 1964, 1837.

120. K. Akagane, F. J. Allan, G. G. Allan, T. Friberg, S. O. Muircheartaigh, and J. B. Thomson, Bull. Chem. Soc. Japan, 1969, 42, 3204.

121. O. Diels, Chem. Ber., 1918, 51, 965.

122. O. Diels and C. Salomon, Chem. Ber., 1919, 52, 43.

123. M. Busch and R. Kämmerer, Chem. Ber., 1930, 63, 649.

124. M. Busch, Chem. Ber., 1931, 64, 1816.

125. J. B. Wright, J. Org. Chem., 1964, 29, 1620.

126. K. Bodendorf and H. Towliati, Arch. Pharm., 1965, 298, 293.

127. G. LaParola, Gazzetta, 1945, 75, 216.

128. L. B. Volodarsky, A. N. Lisack, and V. A. Koptyug, Tetrahedron Letters, 1965, 1565.

129. R. Stollé and K. Thomä, J. Prakt. Chem., 1906, 73, 288.

130. R. Huisgen, R. Grashey, E. Aufderhaar, and R. Kunz, Chem. Ber., 1965, 98, 642.

131. F. Eloy, J. Org. Chem., 1961, 26, 952.

132. H. Wieland, Chem. Ber., 1909, 42, 803.

133. S. Maffei, and G. F. Bettinetti, Ann. Chim. (Italy), 1956, 46, 812.

134. G. Zinner and R. Moll, Chem. Ber., 1966, 99, 1292.

135. V. A. Tartakovskii, O. A. Luk'yanov, and S. S. Novikov, Doklady Akad. Nauk S.S.S.R., 1968, 178, 123.

136. P. Mamalis, J. Green, D. J. Outred, and M. J. Rix, J. Chem. Soc., 1962, 3915.

137. J.-M. Biehler and J.-P. Fleury, Tetrahedron Letters, 1968, 4227.

138. W. Wernick and R. Wolffenstein, Chem. Ber., 1898, 31, 1553.

139. L. Mamlock and R. Wolffenstein, Chem. Ber., 1900, 33, 159.

140. A. C. Cope and E. R. Trumbull, in 'Organic Reactions', vol. 11, ed. by A. C. Cope, Wiley, New York, 1960, p. 317.

141. M. A. T. Rogers, J. Chem. Soc., 1955, 769.

142. L. A. Paquette, J. Org. Chem., 1962, 27, 2870.

142a. R. A. Abramovitch and B. W. Cue, J. Org. Chem., 1973, 38, 173.

143. G. Zinner and E. Duerkop, Arch. Pharm., 1968, 301, 776.

144. E. Hayashi and C. Iijima, J. Pharm. Soc., Japan, 1962, 82, 1093.

145. E. G. Rozantsev and A. B. Shapiro, Izvest. Akad. Nauk S.S.S.R., Ser. khim., 1964, 1123.

146. I. L. Knunyants and E. G. Bykhovskaya, Doklady Akad. Nauk S.S.S.R., 1960, 131, 1338.

147. R. M. Acheson, B. Adcock, G. M. Glover, and L. E. Sutton, J. Chem. Soc., 1960, 3367.

148. I. E. S. El-Kholy, F. K. Rafla, and G. Soliman, J. Chem. Soc., 1962, 1857.

149. J. D. Loudon and G. Tennant, J. Chem. Soc., 1960, 3466.

150. E. P. Kohler and G. R. Barrett, J. Amer. Chem. Soc., 1924, 46, 2105.

151. O. L. Brady and J. N. E. Day, J. Chem. Soc., 1923, 2258.

152. H. Singh and R. S. Kapil, J. Org. Chem., 1960, 25, 657.

153. H. L. Sharma and S. K. Mukerji, Bull. Chem. Soc. Japan, 1965, 38, 1086.

154. D. S. Deorha, and S. P. Sareen, J. Indian Chem. Soc., 1964, 41, 793.

155. R. M. Acheson, R. G. Bolton, and I. Hunter, J. Chem. Soc. (C), 1970, 1067.

156. F. Feigl, 'Spot Tests in Organic Analysis', translated by R. E. Oesper, 7th ed. (English), Elsevier, Amsterdam, 1966, p. 338.

157. G. Zinner, Arch. Pharm., 1956, 289, 714.

158. J. F. Elsworth and M. Lamchen, J. Chem. Soc. (C), 1966, 1477.

159. G. A. Snow, J. Chem. Soc., 1954, 2588.

160. J. T. Weil, J. Chromatog., 1968, 36, 381.

161. H. Maehr and M. Leach, J. Org. Chem., 1974, 39, 1166.

162. E. Boyland and R. Nery, Analyst, 1964, 89, 95 and 520.

163. R. Nery, Analyst, 1966, 91, 388.

164. R. Roncucci, M.-J. Simon, and G. Lambelin, J. Chromatog., 1971, 57, 410.

165. A. K. Macbeth and J. R. Price, J. Chem. Soc., 1936, 111.

166. S. Takahashi, and H. Kano, Chem. and Pharm. Bull. (Japan), 1963, 11, 1375.

167. M. Mousseron-Canet and J.-P. Boca, Bull. Soc. Chim. France, 1967, 1296.

168. M. Davies and N. A. Spiers, J. Chem. Soc., 1959, 3971.

169. A. R. Katritzky and R. A. Jones, J. Chem. Soc., 1960, 2947.

170. M. C. Kloetzel, J. L. Pinkus, and R. M. Washburn, J. Amer. Chem. Soc., 1957, 79, 4222.

171. J. P. Freeman, J. Amer. Chem. Soc., 1958, 80, 5954.

172. R. Bonnett and D. E. McGreer, Canad. J. Chem., 1962, 40, 177.

173. R. M. Acheson, C. J. Q. Brookes, D. P. Dearnaley, and B. Quest, J. Chem. Soc. (C), 1968, 504.

174. T. Kato, H. Yamanaka, T. Adachi, and H. Hiranuma, J. Org. Chem., 1967, 32, 3788.

175. S. Takahashi and H. Kano, Chem. and Pharm. Bull. (Japan), 1966, 14, 1219.

176. R. T. Coutts and G. Mukherjee, Org. Mass Spectrometry, 1970, 3, 63.

177. K. Volkamer and H. W. Zimmermann, Chem. Ber., 1969, 102, 4177.

178. J.-M. Biehler and J.-P. Fleury, Tetrahedron, 1971, 27, 3171.

179. P. G. Gassman and G. D. Hartman, Chem. Comm., 1972, 853.

180. D. J. Kew and P. F. Nelson, Aust. J. Chem., 1962, 15, 792.

181. E. Hayashi, E. Ishiguro, and M. Enomota, presented at the 80th Annual Meeting of Pharmaceutical Society of Japan (cited by ref. 166).

182. M. Ionescu, A. R. Katritzky, and B. Ternai, Tetrahedron, 1966, 22, 3227.

183. A. R. Forrester and R. H. Thomson, J. Chem. Soc., 1963, 5632.

184. C. W. Brown, and M. A. T. Rogers, British patent 850,418 (1960); Chem. Abstr., 1961, 55, 6498e.

185. J. F. Elsworth and M. Lamchen, J. Chem. Soc. (C), 1968, 2423.

186. J. Thesing and W. Sirrenberg, Chem. Ber., 1958, 91, 1978.

187. M. Colonna and A. Monti, Gazzetta, 1962, 92, 1401.

188. M. Colonna and U. De Martino, Gazzetta, 1963, 93, 1183.

189. M. Colonna, and P. Bruni, Ric. Sci., Rend. Sez. A., 1964, 4, 151; Chem. Abstr., 1964, 61, 633e.

190. M. Colonna and P. Bruni, Gazzetta, 1965, 95, 1172.

191. K. Volkamer, H. Baumgärtel, and H. Zimmermann, Angew. Chem. Internat. Edn., 1967, 6, 947.

192. K. Volkamer and H. W. Zimmermann, Chem. Ber., 1970, 103, 296.

193. E. G. Rozantzev and M. B. Neiman, Tetrahedron, 1964, 20, 131.

194. J. P. Freeman, Chem. Rev., 1973, 73, 283.

195. O. L. Brady and C. V. Reynolds, J. Chem. Soc., 1928, 193.

196. A. Kliegl and A. Fehrle, Chem. Ber., 1914, 47, 1629.

197. O. L. Brady and C. V. Reynolds, J. Chem. Soc., 1931, 1273.

198. O. L. Brady and J. Jakobovits, J. Chem. Soc., 1950, 767.

199. H. J. Shine, L.-T. Fang, H. E. Mallory, N. F. Chamberlain, and F. Stehling, J. Org. Chem., 1936, 28, 2326.

200. G. Zinner, W. Ritter, and W. Kliegel, Pharmazie, 1965, 20, 291.

201. E. Winterfeldt and W. Krohn, Chem. Ber., 1969, 102, 2336.

202. G. Zinner and W. Ritter, Angew. Chem., 1962, 74, 217.

203. J. G. Cannon, J. G. Rose, D. E. Nerland, and L. L. Darko, J. Heterocyclic Chem., 1969, 6, 747.

204. G. Zinner, Chem. Ber., 1958, 91, 302.

205. P. G. Sammes, J. Chem. Soc., 1965, 6608.

206. G. Zinner, Arch. Pharm., 1958, 291, 7.

207. H. Tanida, Chem. and Pharm. Bull. (Japan), 1959, 7, 887.

208. S. M. Beaumont, B. D. Handford, J. H. Jones, and G. T. Young, Chem. Comm., 1965, 53.

209. G. T. Young and B. O. Handford, British Patent 1,085,916 (1967); Chem. Abstr., 1968, 69, 27792w.

210. J. W. Clark-Lewis and G. F. Katekar, J. Chem. Soc., 1959, 2825.

211. H. E. Heller, E. D. Hughes, and C. K. Ingold, Nature, 1951, 168, 909.

212. C. K. Ingold, 'Structure and Mechanism in Organic Chemistry', Bell, London, 1953, p. 621.

213. G. Stöhrer and G. B. Brown, Science, 1970, 167, 1622.

214. P. D. Lotlikar, J. D. Scribner, J. A. Miller, and E. C. Miller, Life Sci., 1966, 5, 1263.

215. E. C. Miller, P. D. Lotikar, H. C. Pitot, T. L. Fletcher, and J. A. Miller, Cancer Research, 1966, 26, 2239.

216. M. Colonna and P. Bruni, Gazzetta, 1967, 97, 1569.

217. M. Colonna and P. Bruni, Gazzetta, 1967, 97, 1584.

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