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Δ^3-PIPERIDEINES

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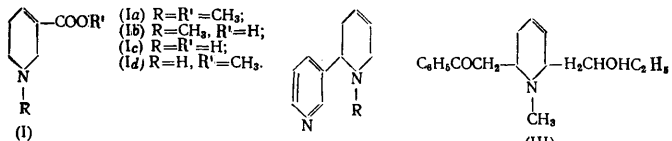
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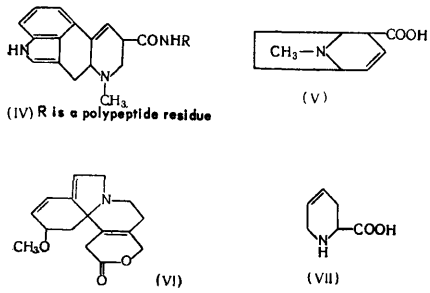
INTRODUCTION

Interest in the chemistry of 1,2,5,6-tetrahydropyridines (Δ^3-piperideines) is mainly due to the existence of a number of alkaloids which contain this structure. The fruit of the palm *Areca catechu*, which grows in India, Ceylon, and the Malay and Philippine Islands, is the source of a considerable number of alkaloids[1]. Jahns[2-5] obtained arecoline (*Ia*) and arecaidine (*Ib*) in a pure form from this fruit, and showed that they are both tetrahydropyridines methylated on the nitrogen and containing a carboxymethyl and a carboxy group respectively. Jahns believed that the double bond was in the 2,3-position, but Meyer[6,7] established that it is actually in the 3,4-position, and this has been confirmed synthetically by Wohl and Johnson[8]. Arecoline has been shown to be the methyl ester of 1-methyl--1,2,5,6-tetrahydronicotinic acid. Jahns also obtained guvacine and arecaine from the areca palm fruit; it was later shown[9-12] that guvacine is norarecaidine, i.e. 1,2,5,6--tetrahydronicotinic acid (*Ic*), and that arecaine is a mixture of arecaidine and guvacine. Hess[13] found another alkaloid related to arecoline, which has been named guvacoline (*Id*) and is norarecoline, i.e. 1,2,5,6-tetrahydronicotinic acid methyl ester.

The tobacco (*Nicotiana*) alkaloids anatabine (*IIa*)[14,15] and *N*-methyl anatabine (*IIb*)[16] are also Δ^3-piperideine derivatives; the secondary alkaloids from *Lobelia inflata* lobinine[17] and isolobinine[18-20] are stereoisomers of structure (III).[21]

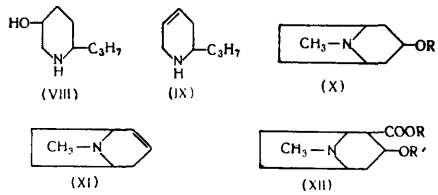


The Δ^3-piperideine nucleus is found in the ergot (*Secale cornutum*) alkaloids ergotoxine, ergotamine, ergometrine, etc. of general formula (IV)[22,23], and in anhydroecgonine (V), of which the ethyl ester has been found in waste materials from the production of minor alkaloids of the leaves of *Erythroxylon coca*[24] and the methyl ester separated from Peruvian and Javanese coca seeds[25]. The *Erythrina* alkaloid β-erythroidine, to which Boekelheide and coworkers[26,27] give the formula (VI), also contain the Δ^3-piperideine nucleus. The amino-acid baikiain[28] (L-1,2,3,6-tetrahydropyridine-2-carboxylic acid) (VII) has been separated from Rhodesian teak (*Baikiaea plurijuga*).



The structure of certain alkaloids contains a piperidine ring substituted in the 3- or 4-position by a hydroxyl group, which is often esterified; dehydrating agents convert these compounds into the corresponding Δ^3-piperideines. Thus pseudoconiceine (IX) is obtained by the action of phosphorus

pentoxide on pseudoconhydrine (VIII) from hemlock[29-31]. Dehydration of tropine (X*a*), obtained by the hydrolysis of atropine and hyoscyamine (X*b*)[32-34], produces tropidine (XI)[35-38], whose structure was largely elucidated by Willstätter[39].



(VIII) (IX) (X)

(XI) (XII)

(X*a*) R=H; (X*b*) R=COCHCH$_2$OH; (XII*a*) R=R′=H;
|
C$_6$H$_5$

(XII*b*) R=CH$_3$, R′=C$_6$H$_5$CO.

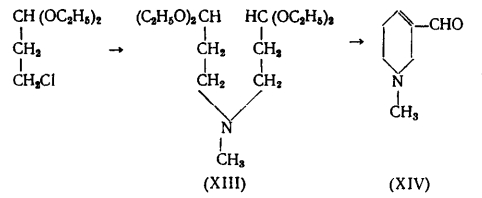
Anhydroecgonine (ecgonidine) (V) has been synthesised by the action of PCl_5 [40] or $POCl_3$ [41] on ecgonine (XII*a*) or directly from cocaine (XII*b*).[42] A number of studies[43-45] have been devoted to the structure of anhydroecgonine, but it has not yet been settled whether the carboxyl group is in the 3- or the 5-position of the piperideine nucleus. Decarboxylation of ecgonidine produces tropidine (XI)[46]; this transformation relates the alkaloids of the cocaine group to atropine.

Arecoline, the main areca palm alkaloid, has a physiological action similar to those of muscarine, acetylcholine, pilocarpine, and eserine, showing parasympathetic stimulation and acting on the majority of parasympathetically innervated organs. Arecoline reduces the blood pressure, increases salivation, and causes myosis of the eye[47]. It is used as a myotic preparation, but its main application is in veterinary practice as a purgative and anthelmintic[48]. Isolobinine exhibits a weak nicotine-like action; it stimulates breathing and raises the blood pressure (in large doses it paralyses the central nervous system and causes cessation of breathing)[49]. The ergot alkaloids are widely used in medicine, mainly in obstetrics and gynaecology[50,51]. β-Erythroidine has a considerable curare-like action[52]. Because of the great practical value of compounds containing the Δ^3-piperideine ring, many publications have dealt with the synthesis of systems of this type.

SYNTHESIS FROM HALOGENO- OR HYDROXY-PIPERIDINES

1,2,5,6-Tetrahydropyridines have generally been synthesised by preparing the corresponding 3- or 4-substituted piperidines followed by dehydration or dehydrohalogenation (certain syntheses of this type have already been mentioned). The elegant methods used for such syntheses have only achieved practical application in individual cases, but most of these syntheses have independent scientific interest.

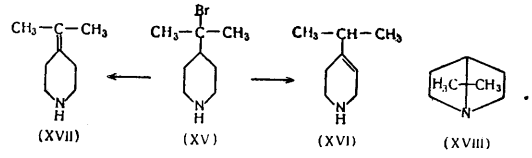
Arecaidine was first synthesised by Wohl and Johnson[8,53], who utilised the easy cyclisation of certain aminoacetals in an acid medium. The acetal of β-chloropropionaldehyde, prepared from acrolein, condenses with methylamine to form the diacetal of β-methyliminodipropionaldehyde (XIII), which is converted by the action of acid into 1-methyl-Δ^3-piperideine-3-aldehyde (XIV) and then to arecaidine by way of the oxime and nitrile. The same method has been used to prepare guvacine, 1-ethylguvacine, and a number of analogous compounds[54-61].



(XIII) (XIV)

Hess and Leibbrandt[11] described a preparation of arecaidine by bromination of 1-methylnipecotinic acid methyl ester, removal of hydrogen bromide from the resulting 3-bromo derivative, and hydrolysis of the arecoline formed. However, Preobrazhenskii and Fisher[62] repeated this procedure and showed that the ester obtained after bromination and treatment with alkoxide is not arecoline, but the unchanged ester of 1-methylhexahydronicotinic acid.

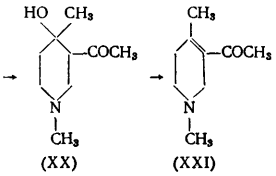
The synthesis of a number of substituted Δ^3-piperideines by the removal of hydrogen halide with reagents, mainly basic, has been described[63-69]. Pauly and Harries[70] treated 2,4,6-trimethyl-4-iodopiperidine with silver mandelate to obtain the salt of the corresponding piperideine with mandelic acid. Removal of hydrogen bromide from 2-bromo-2-(4′-piperidyl)propane (XV) produced not the expected 7,7-dimethyl-1-azabicyclo[2,2,1]heptane (XVIII), but 4-isopropyl-Δ^3-piperideine (XVI) and 4-isopropylidenepiperidine (XVII).[71]



(XVII) (XV) (XVI) (XVIII)

By condensing acetone, formaldehyde, and methylamine hydrochloride, Mannich and Ball[72] obtained the aminoketone (XIX). Dilute hydrochloric acid induced this to undergo an aldol condensation to produce the compound (XX) (the conditions for this reaction — a comparatively low temperature and a weakly acid medium — are very reminiscent of biological conditions); the latter is easily dehydrated to 4-methylarecolone (XXI) (see also Mannich and Ritsert[73]). Other arecolones have been prepared similarly[74,75]. The barium hypobromite oxidation of (XX) gives the corresponding acid, which was converted to 4-methylarecoline by dehydration and methylation[76].

$$CH_3COCH_3 + CH_2O + CH_3NH_2\cdot HCl \rightarrow CH_3N(CH_2CH_2COCH_3)_2 \rightarrow$$
(XIX)

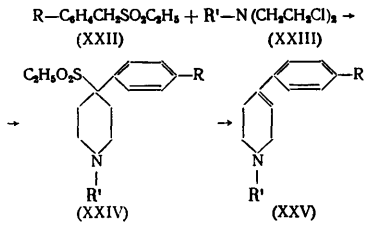


(XX) (XXI)

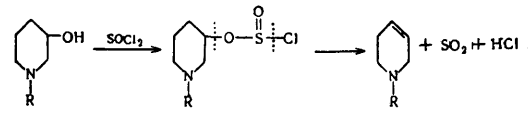
Starting from formaldehyde, acetaldehyde, and methylamine hydrochloride, and using the same method, has given arecaidine aldehyde in ~ 20% yield; in this case dehydration of the intermediate piperidine takes place spontaneously[77]. Similar methods for the synthesis of other Δ^3-piperideines have been described[78,79].

The condensation of sulphones containing an active methylene group (XXII) with β,β′-dichlorodiethylamines (XXIII)

gives compounds (XXIV), which on hydrolysis and dehydration afford alkyl derivatives of 4-phenyl-1,2,5,6-tetrahydropyridine (XXV).[80,81]



Paul and Tchelitcheff[82] found that thionyl chloride partially dehydrates 3-piperidols, leading to the formation of 1,2,5,6-tetrahydropyridines; in certain cases this reaction may be used preparatively. They suggest that a chlorosulphinic ester is formed as an intermediate rather than a chloropiperidine, since removal of hydrogen chloride from the latter takes place under completely different conditions.



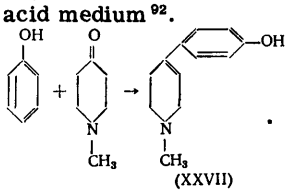
On analogous treatment, 1-ethyl-4-piperidol is converted directly to the chloro derivative, which gives up hydrogen chloride only by the action of sodium methoxide, forming the corresponding Δ^3-piperideine in low yield[68].

The organo-metallic synthesis with piperidones gives tertiary alcohols, which can be easily dehydrated to Δ^3-piperideines. Thus 1-methyl-4-(2'-thienyl)-Δ^3-piperideine (XXVI) has been prepared by the action of thienyl lithium on 1-methyl-4-piperidone and subsequent dehydration[83,84-91].

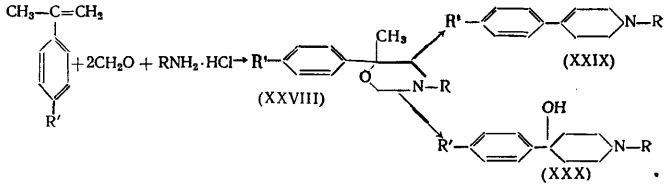


(XXVI)

1-Methyl-4-(4'-hydroxyphenyl)-Δ^3-piperideine (XXVII) has been prepared by the reaction of 1-methyl-4-piperidone with phenol in an acid medium[92].

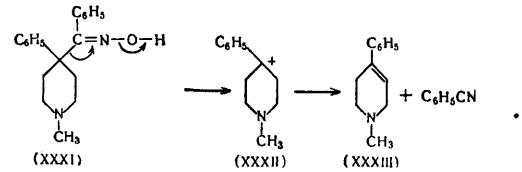


Schmidle and Mansfield[93,94] have shown that 3-alkyl-6-methyl-6-aryltetrahydro-1,3-oxazines (XXVIII) (the condensation products of a substituted α-methylstyrene, formaldehyde, and a salt of a primary alkylamine) are converted by the action of acid to 1-alkyl-4-aryl-1,2,5,6-tetrahydropyridines (XXIX) in yields up to 82%.



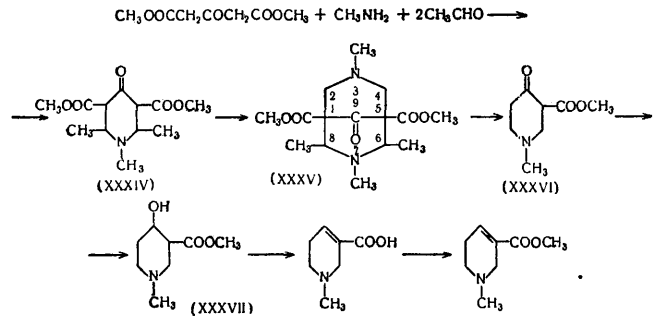
If an excess of acid is not used in this reaction, the corresponding piperidols (XXX) are formed; these may be dehydrated to the piperideines.

Under the conditions of the Beckmann rearrangement, 1-methyl-4-phenyl-4-piperidyl phenyl ketoxime (XXXI) decomposes to form benzonitrile and 1-methyl-4-phenyl-Δ^3-piperideine (XXXIII); this reaction apparently proceeds by way of the carbonium ion (XXXII), which becomes stabilised by the loss of a proton[95].



A number of other syntheses of Δ^3-piperideines by dehydration of the piperidols have been described[96-101].

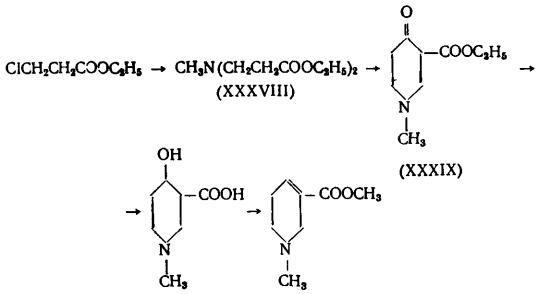
The preparation of arecaidine by the dehydration of 1-methyl-4-hydroxypiperidine-3-carboxylic acid has been reported[102]. Ugryumov has developed a method for the synthesis of this acid[103], and has used it to prepare arecaidine and arecoline. In this method, dimethyl acetone dicarboxylate is condensed with acetaldehyde and methylamine to give dimethyl 1,2,6-trimethyl-4-piperidone-3,5-dicarboxylate (XXXIV), which reacts with methylamine and formaldehyde to form dimethyl 3,6,7,8-tetramethyl-9-oxobispidine-1,5-dicarboxylate (XXXV). On heating with hydrochloric acid, methyl 1-methyl-4-piperidone-3-carboxylate (XXXVI) is formed, which, on catalytic reduction, gives methyl 1-methyl-4-hydroxypiperidine-3-carboxylate (XXXVII). Arecaidine is then obtained by the action of acid, and esterification produces arecoline.



Recently Maurit and Preobrazhenskii[104] studied various methods of reduction of the keto-ester (XXXVI) and the configurations of the resulting piperidols.

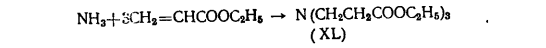
Dankova, Sidorova, and Preobrazhenskii[105] devised a preparative synthesis of arecoline, based on McElvain's method[105]. Ethyl β-chloropropionate reacts with methylamine to form β,β'-diethoxycarbonyldiethylmethylamine (XXXVIII), which is cyclised by sodium isoamylate. The resulting 1-methyl-3-ethoxycarbonyl-4-piperidone (XXXIX) is reduced with Raney nickel or with sodium amalgam in an

acid medium; subsequent dehydration and esterification give arecoline.

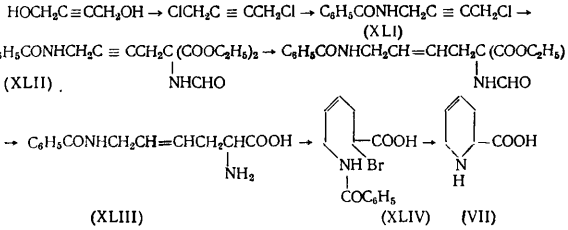


Dobrowsky[107] published an analogous synthesis of arecoline, compound (XXXVIII) being obtained by the condensation of ethyl acrylate with methylamine; the procedure was altered slightly and slightly higher yields were obtained. The method (starting from methyl acrylate) has recently been further improved and applied to the synthesis of a number of homologues of arecoline[108]. Acrylonitrile may be used in place of the acrylic esters in this and similar syntheses[109,110].

A similar method has been described for the preparation of guvacine[111]. Three molecules of ethyl acrylate are reacted with one of ammonia, the resulting β, β', β''-triethoxycarbonyltriethylamine (XL) is cyclised to piperidone, and the latter is reduced, hydrolysed, dehydrated, and esterified in a process similar to that described above. This method had already been used by Ugryumov to prepare 2,6-dimethylarecoline[112].



In 1958 racemic baikiain (VII) was synthesised[113]. The starting material was 1,4-dichloro-2-butyne, which was converted by the action of urotropine and then benzoyl chloride into 1-benzamido-4-chloro-2-butyne (XLI). This reacted with the sodium derivative of formylaminomalonic ester to give compound (XLII). Further steps in the reaction sequence comprised the partial hydrogenation of (XLII), hydrolysis, and decarboxylation, and produced the amino-acid (XLIII) of the *cis*-configuration. Replacing the amino group by bromine by the action of nitrosyl bromide gave *cis*-1-bromo-5-benzamido-3-pentene-1-carboxylic acid (XLIV), which was cyclised by $Ba(OH)_2$ to *dl*-baikiain (VII).



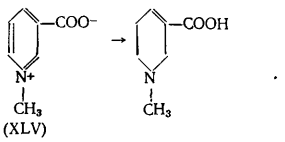
The main disadvantages of these syntheses are, as already mentioned above, their complexity and the large number of steps involved, which cause low yields of the final products.

SYNTHESIS BY THE REDUCTION OF PYRIDINE DERIVATIVES

The preparation of Δ^3-piperideine derivatives by the partial reduction of the corresponding pyridine derivatives is of considerable interest. It is known that reduction of the pyridine ring produces not only the completely hydrogenated derivatives, but also partially reduced compounds, including Δ^3-piperideines. Many methods exist for the hydrogenation of the pyridine nucleus, but only a few are of preparative value.

Catalytic Reduction

It is practically impossible with this reduction method to stop the reaction at the required stage; hydrogenation proceeds to the hexahydropyridine stage, the yields of 1,2,5,6-tetrahydropyridines being insignificant. Thus the yield of arecaidine by the reduction of trigonelline (XLV) over platinum black[114] does not exceed 1%.



Mumm[115-117] obtained similar results for pyridines but showed that substituted pyridinium salts are reduced in the presence of platinum to Δ^2-piperideines, which on distillation in vacuum isomerise to Δ^3-piperideines. Catalytic hydrogenation of 1,2-dihydropyridines over platinum black gives tetrahydro-derivatives in which the double bond is probably in the 3,4-position[118,119]. The hydrogenation of methyl isonicotinate methiodide over platinum oxide is said to produce methyl 1,2,5,6-tetrahydroisonicotinate[120].

Electrolytic Reduction

This method of reduction gives somewhat better results. Davies and McGee[121] separated 10% of Δ^3-piperideine and a small quantity of tetrahydropicoline from commercial piperidine; they suggest that these compounds are formed in the electrolytic reduction of pyridine containing homologues as impurities. The electrolytic reduction of pyridine and its quaternary salts in an acid medium has given ~ 20% of tetrahydro derivatives[122,123]. Šorm[124] and Ferles[125] reduced α-, β-, and γ-picolines, 2,6-lutidine, and picolinic, nicotinic, and isonicotinic acids electrolytically, obtaining the 1,2,5,6-tetrahydro-derivatives in yields of 10–58%; trigonelline was reduced to arecaidine in satisfactory yield. In the course of this reaction, decarboxylation products appear and hexahydro-derivatives are also formed[126].

Reduction by Sodium and Alcohols

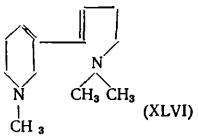
In 1902 Chichibabin reported[127] that the reduction of 4-benzylpyridine with sodium in alcohol produced a small amount of the tetrahydropyridine as well as the corresponding piperidine. The same phenomenon occurs, but to a lesser extent, in the reduction of 2-benzylpyridine. Similar results were later reported for the reduction of 4-methyl-3-ethylpyridine and certain other compounds[128-130]. In 1950 Lukeš and Ernest[131], attempting to prepare *s*-butylpiperidine by reducing the corresponding pyridine with sodium in amyl alcohol, obtained a mixture of the hexa- and tetrahydro-compounds. Wawžonek and coworkers[132] generalised the earlier results and developed the reduction of pyridines with sodium in butyl alcohol as a preparative method for Δ^3-piperideines (see also Lukeš and Ferles[133]). The yields

are high (57–87%), but only when the pyridine contains a 4-alkyl substituent, which considerably limits the applicability of the method.

Reduction by Mixed Metal Hydrides

Panouse[134-137] studied the reduction of alkyl pyridine halides with potassium borohydride, and found that pyridine methiodide is converted to 1-methyl-Δ^3-piperideine in 65% yield. Increasing the chain length of the *N*-alkyl radical favours side reactions, leading to the formation of various boron complexes, dihydropyridine dimers, etc.; however, the yields of Δ^3-piperideines are usually satisfactory (40–74%). Ferles[138] obtained similar results with sodium borohydride. Lyle and coworkers[139] described the preparation of 1-methyl-4-benzyloxy-Δ^3-piperideine from the corresponding quaternary salt in a yield of 86%. Panouse also reduced the methiodides of nicotinic acid, methyl nicotinate, and nicotinamide to arecaidine, arecoline, and arecaidine amide respectively, with yields of the order of 30% (see also Ferles[126]).

Nicotine methiodide is easily reduced to the tetrahydro-derivative; in this case there is a side reaction involving the opening of the pyrrolidine ring with the formation of the compound (XLVI). It should be noted that the reduction of pyridinium salts with potassium borohydride produces 1,2-dihydro-derivatives in a number of cases, particularly if the radical attached to the nitrogen is glycosidic in nature[137].

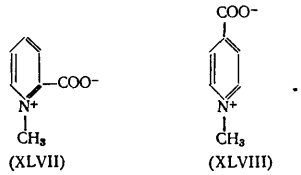

(XLVI)

Pyridinium salts can also be reduced to Δ^3-piperideines with lithium aluminium hydride. Panouse[137] showed that considerable amounts of the 1,2-dihydro-derivatives are usually formed, but this can be avoided by carrying out the reaction in tetrahydrofuran. The yields of Δ^3-piperideines are always lower than when using potassium borohydride. However, Ferles[126] succeeded in obtaining high yields of Δ^3-piperideines (up to 56%) by carrying out the reaction under conditions normal for lithium aluminium hydride reductions.

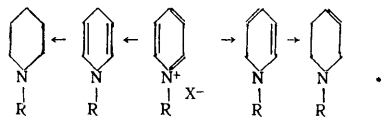
Reduction by Formic Acid

In 1936 Mayo[140] obtained a mixture of 1,1-dimethylpiperidinium formate and partially hydrogenated pyridines by the reaction of pyridine with formic acid and methyl alcohol under forcing conditions. Lukeš[141] showed that pyridine itself is not reduced by formic acid, but that reaction of pyridine methobromide with formic acid in the presence of potassium formate gives a mixture of 1-methylpiperidine and 1-methyl-Δ^3-piperideine, the first being predominant. It is assumed that in Mayo's work[140] it is not pyridine itself which is reduced, but the 1-methylpyridinium ion. It is interesting that, unlike pyridine, quinoline is reduced by formic acid (advantageously in the presence of sodium formate[142] or triethylamine[143]), forming 1-formyl-1,2,3,4-tetrahydroquinoline in good yield. Lukeš and coworkers have applied their method for the reduction of pyridinium salts[141,144] to the preparation of a number of alkyl- and aryl-substituted Δ^3-piperideines[145-149]. Kost, Yudin, and Shipov[150] applied this method to other alkylpyridinium halides.

Interesting attempts were made to reduce the pyridine carboxylic acids by this method, so as to obtain arecaidine and its isomers directly. However, in reducing homarin (XLVII) and trigonelline (XLV) (the methyl-betaines of picolinic and nicotinic acids) under forcing conditions, Lukeš[151] obtained only a mixture of decarboxylation products, i.e. 1-methyl-Δ^3-piperideine and 1-methylpiperidine. The reduction of the methyl-betaine of isonicotinic acid (XLVIII) gave 1-methylisonipecotinic acid, i.e. the pyridine ring had been completely hydrogenated. Reduction of *N*-carboxyalkylpyridinium halides gave only decarboxylation products[152].


(XLVII) (XLVIII)

Yields of the mixture of reduced pyridines obtained by Lukeš' method are usually high (~80%), but the Δ^3-piperideine content does not exceed 10% in the majority of cases; a very high yield (82%) of the Δ^3-piperideine was obtained only in the reduction of 1,4-dimethylpyridinium bromide[147]. According to Lukeš, the reduction of the pyridinium salts proceeds in two ways:



As a rule, hydrogen first adds on predominantly in the 1,4-position, and since the 2,3-double bond is easily reduced by formic acid, considerably more of the hexahydro-derivative is formed in these experiments than of the tetrahydro-derivative. Kost and coworkers[153] have shown that when potassium formate is replaced by triethylamine in the reduction of pyridinium salts by formic acid, more hydrogen adds initially in the 1,2-position. This enables alkyl-substituted Δ^3-piperideines to be obtained in yields of ~35%.

Other Methods of Reduction

Jahns[5] reduced trigonelline (XLV) with tin and hydrochloric acid, but the separation of arecaidine from the reaction mixture was complex and yields were low. Meyer[6] used sodium amalgam to prepare arecaidine, but it was later shown[114] that the yield by this method does not exceed 1%.

PROPERTIES OF Δ^3-PIPERIDEINES

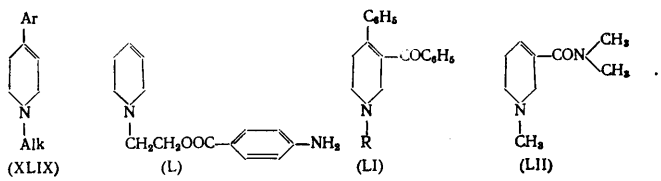
Δ^3-Piperideines possess all the normal properties of aliphatic amines and ethylenic compounds. They are fairly strong bases which easily form salts with various acids, can be acylated, alkylated, and nitrosated on the nitrogen, and form *N*-oxides (for the preparation of arecoline *N*-oxide see Shchukina and coworkers[154]). 1-Methyl-Δ^3-piperideine can be demethylated without rupture of the ring by the reaction with cyanogen bromide and hydrolysis of the resulting *N*-cyanide[155]. The Hofmann degradation of the quaternary ammonium bases formed by Δ^3-piperideines gives the

corresponding des-bases, and has been used for proving the structure of the original compounds[145,146,156]. Although the double bond of the Δ^3-piperideines is markedly more stable to reduction than the Δ^2 double bond, they are nevertheless easily hydrogenated in the presence of metal catalysts[11,65,66,75,86,124,132,157]; the content of Δ^3-piperideines in mixtures with piperidines can be determined by this method.

Δ^3-Piperideines easily add bromine to the double bond. The resulting dibromopiperidines are commonly used for separating piperideines from the corresponding piperidines; treatment of the dibromides with zinc quantitatively regenerates the Δ^3-piperideines[144-148,150,153]. The double bond of Δ^3-piperideines also adds malonic acid (usually in the 4-position)[59,61]; this method was used to synthesise cincholoiponic acid (3-carboxy-4-piperidylacetic acid)[58], obtained by the degradation of quinine. Treatment of arecoline with ammonia under pressure gives the amide of 1-methyl-4-aminopiperidine-3-carboxylic acid[158]. The hydration of Δ^3-piperideines to 4-piperidols[94] and the addition of hydrogen halides across the double bond to form 4-halopiperidines[96,129] have been described; the latter reaction was used to effect a series of conversions in a number of tropane alkaloids[38,159]. By the oxidation of guvacine under mild conditions with permanganate, Freudenberg[10] obtained a compound presumed to be 3,4-dihydroxypiperidine-3-carboxylic acid.

The double bond of Δ^3-piperideines is easily ozonolysed[145]; this reaction also can be used for the proof of structure. For this purpose, rather than the piperideines themselves, the corresponding des-bases (the Hofmann degradation products) are usually ozonolysed[146,156]. Δ^3-Piperideines can be dehydrogenated in the presence of zinc[5], selenium[78,160], or palladium[78] to the corresponding pyridines.

Certain synthetic analogues of arecoline and other natural Δ^3-piperideines are physiologically active. Thus 1-alkyl-4-aryl-Δ^3-piperideines (XLIX) possess analgesic activity, and some are as effective as codeine[91,161]. The Δ^3-piperideine derivative (L) and its analogues have been used as local anaesthetics[162]; compound (L) also has a nicotine-like action. Compounds of the type (LI) were found to be quite effective spasmolytics[88]. Studies of a number of close analogues of natural Δ^3-piperideines have led to certain conclusions about the way in which physiological activity depends on structure; one of the compounds studied was 1-methyl-1,2,5,6-tetrahydronicotinic acid dimethylamide (LII)[163].



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INVESTIGATION OF COMPLEX FORMATION IN SOLUTION BY THE DISTRIBUTION METHOD

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Extraction with non-aqueous solvents is very widely employed in solving various problems in chemistry and chemical technology. The separation of elements with closely similar properties, the concentration and isolation of micro- and ultramicro-concentrations of metals, the clear separation and identification of difficultly separable organic substances, show why many investigators have evinced interest, especially in recent years, in the study of extraction processes[1-5]. The solubility of internal complexes and of a number of complexes of metals with inorganic ligands in organic solvents makes it possible to utilise the distribution method as a reliable means of studying the composition and many other physicochemical characteristics of complex compounds.

The principles of the distribution (or extraction) method were laid down by Nernst (1891). In the first paper on the constancy of the partition coefficient for species of the same molecular composition distributed between two immiscible solvents, Nernst established[6] the possibility of using his distribution law to study the dissociation equilibria of a number of substances in aqueous solution. Shortly afterwards Hendrixson[7] studied the distribution of benzoic and salicylic acids between water and benzene or chloroform and determined the dissociation constants K_{diss} of these acids in the aqueous phase, their dimerisation constants K_{dim} in the organic phase, and their distribution constants (partition coefficients) K_{part} between organic and aqueous phases*:

$$[H^+][A^-] = K_{diss}[HA]_{aq} , \quad (1)$$

$$[HA]_{org} = K_{part}[HA]_{aq} , \quad (2)$$

$$[H_2A_2]_{org} = K_{dim}[HA]^2_{org} . \quad (3)$$

* HA = molecule of acid, A^- = anion of acid, and H_2A_2 = = dimer molecule. We shall use the symbolic formula HA to denote reagents which dissociate as monobasic acids.

At about the same time similar investigations were carried out with inorganic compounds, e.g. thiocyanates of iron and halides of mercury[8]. In this work, however, the authors do not consider the possible formation of charged complex species. As far as we know, the first attempt to explain the experimental results by a stepwise mechanism of complex formation was published by Morse in 1902.[9] After studying the distribution of mercury complexes between toluene and an aqueous phase containing halide ions (A^-), Morse came to the conclusion that the aqueous phase contains, apart from Hg^{2+} and uncharged HgA_2 molecules, positively charged HgA^+. Assuming the impossibility of extracting charged particles with an organic solvent, Morse calculated from his results the distribution constant λ_N for HgA_2 between the phases and the successive formation constants k_1 and k_2:

$$[MA_{n-1}^{N-n+1}][A^-]k_n = [MA_n^{N-n}] , \quad (4)$$

$$[MA_N]_{org} = \lambda_N[MA_N]_{aq} . , \quad (5)$$

where $M^{N+} = Hg^{2+}$ and A^- is the halide ion.

Although the possibility of using the distribution method to study complex compounds in solution has been demonstrated so long ago, no attempt was made before 1941 to formulate quantitatively the relation between the partition coefficients for a metal in a given system and the parameters of the latter (concentration of metal ions, pH of aqueous phase, concentration of reagent, etc.). In 1941 Kolthoff and Sandell[10], studying the dithizone derivatives of certain metals, attempted to establish such a relationship on the basis of the distribution law and the law of mass action. Assuming that only free (hydrated) metal ions M^{2+} are present in the aqueous phase and excluding the possibility of association of the molecules of dithizone and the complex MA_2 in either phase, these authors accepted the following equations as correct:

$$K'_{part\ HA} = \frac{[HA]_{aq}}{[HA]_{org}} , \quad (6)$$

$$K'_{part\ MA_2} = \frac{[MA_2]_{aq}}{[MA_2]_{org}} \quad (7)$$

(according to the conventions which are now generally adopted these quantities are the reciprocals of the distribution constants of HA and the complex MA_2).

$$M^{2+} + 2HA \rightleftarrows MA_2 + 2H^+ , \quad (8)$$

(in the aqueous phase)

$$\frac{[MA_2]_{aq}}{[M^{2+}]_{aq}}\frac{[H^+]^2_{aq}}{[HA]^2_{aq}} = K_{eq} . \quad (9)$$

Substituting the concentrations of MA_2 and HA in the aqueous phase from Eqns. (6) and (7), they established the expression

$$\frac{[MA_2]_{org}}{[M^{2+}]_{aq}}\frac{[H^+]^2_{aq}}{[HA]^2_{org}} = K_{eq}\frac{K'^2_{part\ HA}}{K'_{part\ MA_2}} = K, \quad (10)$$

by means of which they arrived at Eqn. (12) linking the partition coefficient of the metal q with the characteristics of the system:

$$q = \frac{[MA_N]_{org}}{\sum_{n=0}^{n=N}[MA_n]_{aq}} , \quad (11)$$

$$q = \frac{[MA_2]_{org}}{[M^{2+}]_{aq}} = K\frac{[HA]^2_{org}}{[H^+]^2_{aq}} . \quad (12)$$

As can be seen from Eqn. (12), the partition coefficient of a bivalent metal increases proportionally to the square of the concentration of the reagent in the organic phase and