SYNTHESIS AND PROPERTIES OF PYRROLO[1,2-*a*]PYRAZINES (REVIEW)

V. I. Terenin, E. V. Kabanova, and E. S. Feoktistova

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The synthesis and properties of pyrrolo[1,2-a]pyrazines are reviewed.

Some derivatives of pyrrolo[1,2-*a*]pyrazine possess neuroleptic, cardiovascular [1], and antidepressant [2] activity. Alkylated pyrrolo[1,2-*a*]pyrazines have been identified as ingredients of the smell of roasted meat [3]. Interest for this class of compounds is determined mainly by the wide range of their physiological activities. Also, they are of interest in food chemistry. The aim of this review article is to give an overview and summary of the existing methods for the preparation of pyrrolo[1,2-*a*]pyrazines that should be useful in the development of new synthetic approaches. Two short reviews on the synthesis and properties of pyrrolo[1,2-*a*]pyrazines have been published earlier [4, 5], but a number of new original papers have appeared since then.

In the pyrrolo[1,2-*a*]pyrazine system, the condensed pyrrole and pyrazine rings share one nitrogen atom. The synthetic approaches to these compounds can be divided into three groups:

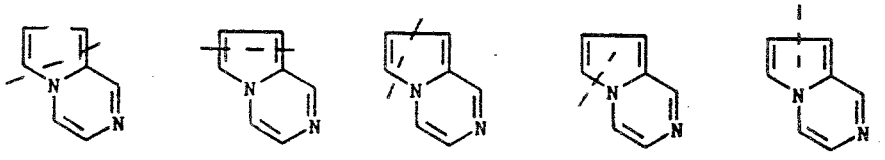
1. Construction of a pyrrole ring onto an existing pyrazine one.
2. Construction of a pyrazine ring onto an existing pyrrole one.
3. Consecutive formation of the pyrrole and pyrazine rings.

A number of derivatives of pyrrolo[1,2-*a*]pyrazine can also be prepared by dehydrogenation of the corresponding polyhydrogenated compounds. In this review, only a few methods for the preparation of polyhydrogenated derivatives of this class of compounds are presented, since their synthesis is itself an interesting and important topic of organic chemistry [5].

METHODS FOR THE SYNTHESIS OF PYRROLO[1,2-*a*]PYRAZINES

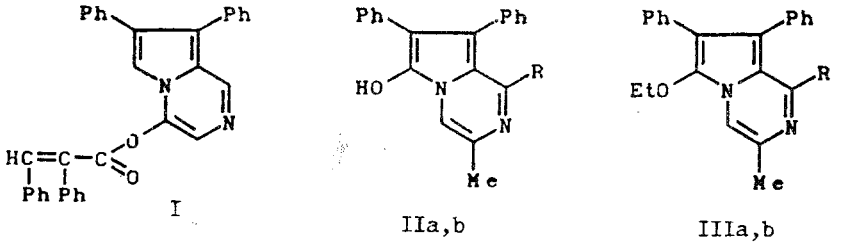
1. Construction of a Pyrrole Ring onto an Existing Pyrazine One

This is the most general group of synthetic approaches. The starting compounds used here are usually N- and 2-substituted pyrazines. A pyrrole ring can be formed by a number of different routes:



1 2 3 4 5

1.1. Unsubstituted pyrazine or its 2-methyl and 2,6-dimethyl derivatives react with diphenylcyclopropenone [6] and diphenylcyclopropenethione [7], producing a number of derivatives of pyrrolo[1,2-*a*]pyrazine. Compound



I IIa,b IIIa,b

II,III a R=H, b R=Me

M. V. Lomonosov Moscow State University, Moscow 119899. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1299-1311, October, 1991. Original article submitted April 7, 1991.

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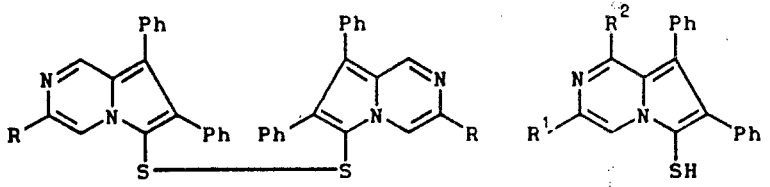
I (a 1:2 adduct) is obtained in 31% yield when unsubstituted pyrazine reacts with diphenylcyclopropenone in methanol. When 2-methyl and 2,6-dimethylpyrazine are used as the starting materials in the same reaction, 7,8-diphenyl-6-hydroxypyrrolo[1,2-*a*]pyrazines IIa and IIb (1:1 adducts) are formed in 45 and 80% yields, respectively. Treatment of the 1:1 adducts IIa and IIb with triethyloxonium tetrafluoroborate gives the corresponding ethers IIIa and IIIb in quantitative yields.

In the reaction with diphenylcyclopropenethione the unsubstituted pyrazine reacts differently than its 2-methyl- and 2,6-dimethyl-substituted derivatives. When pyrazine is reacted with diphenylcyclopropenethione in a methanol—chloroform solvent mixture without exclusion of atmospheric oxygen, compound IVa (a disulfide-bridged 1:1 adduct) is formed in 28% yield. When carried out under nitrogen, the same reaction gives a mixture of the monomeric 7,8-diphenylpyrrolo[1,2-*a*]pyrazine-6-thiol Va (1:1 adduct) and compound IVa in 25% yield.

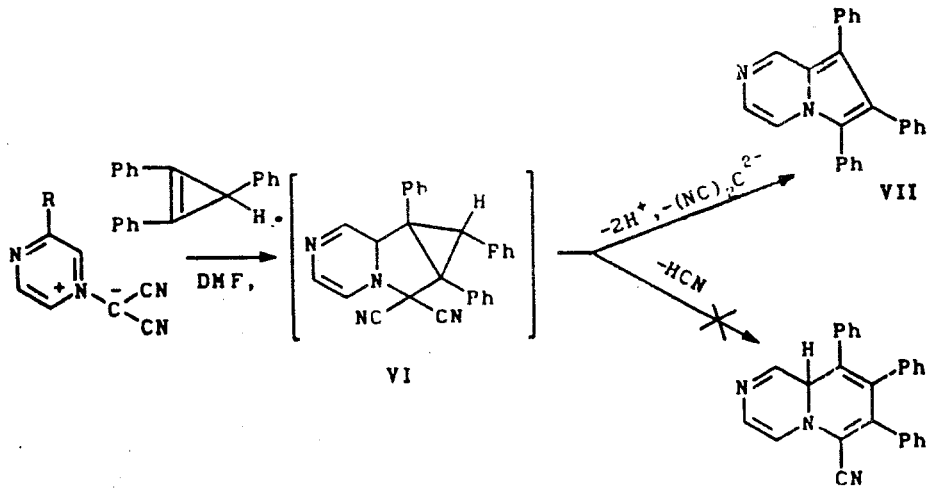


IVa,b Va-c

IV a R=H, b R=NH_2; V a $R^1=R^2=H$; b $R^1=Me$, $R^2=H$; c $R^1=R^2=Me$

The thiol Va can be quantitatively oxidized to IVa by refluxing in chloroform in the presence of air oxygen. Similarly, 2-aminopyrazine gives rise to IVa in 70% yield on refluxing in chloroform in the presence of air oxygen. Likewise, 2-aminopyrazine gives rise to IVa in 70% yield. The compounds 2-methylpyrazine and 2,6-dimethylpyrazine react with diphenylcyclopropenethione to give compounds Vb and Vc only, in 75 and 68% yields, respectively. With 2-methylpyrazine, only one of the possible isomers is formed. Compounds Va-c and the monomeric IVa and b are the sulfur analogs of compounds IIa and b. No sulfur analogs of compound I have been detected.

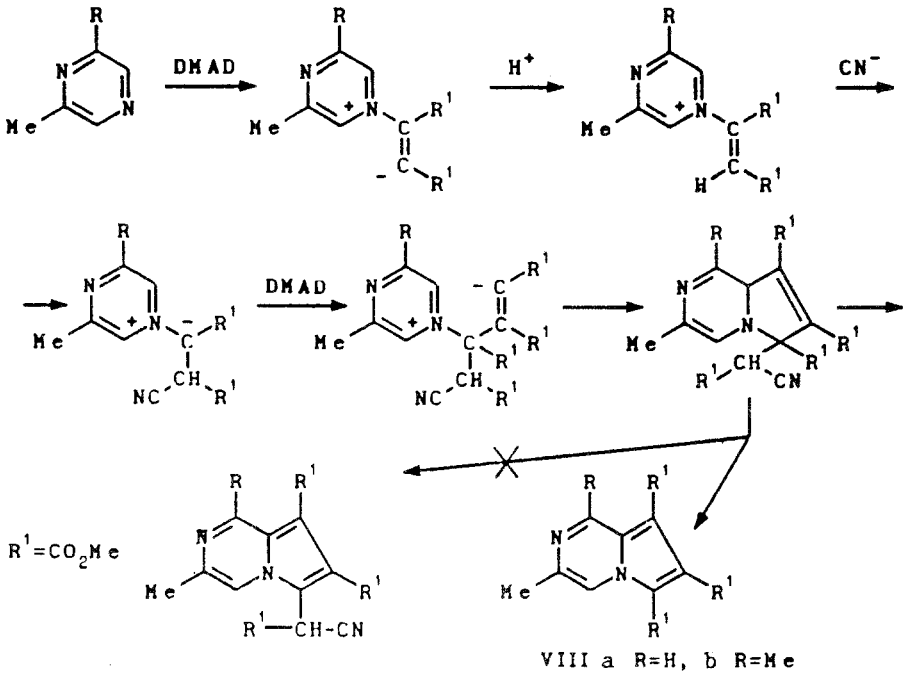
The cycloaddition of 1,2,3-triphenylcyclopropene with pyrazinium dicyanomethylide products 6,7,8-triphenylpyrrolo[1,2-*a*]pyrazine in 47% yield [8]. Most probably, the reaction proceeds as a 1,3-dipolar cycloaddition of the ylide to 1,2,3-triphenylcyclopropene with the formation of the adduct VI, followed by opening of the cyclopropane ring and a formal cleavage of malonic dinitrile:



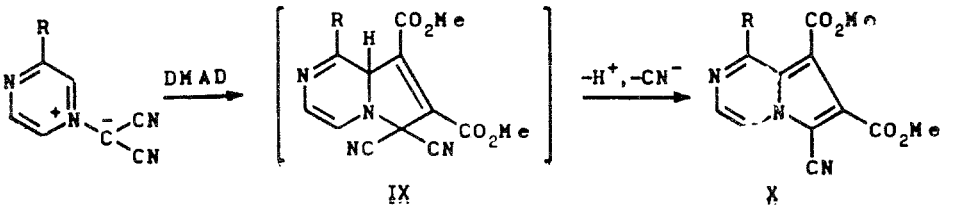
VI VII

The alternative pathway involves cleavage of HCN and is the main route of this reaction in the case of pyridazine and other heterocycles. This pathway is not observed with pyrazine.

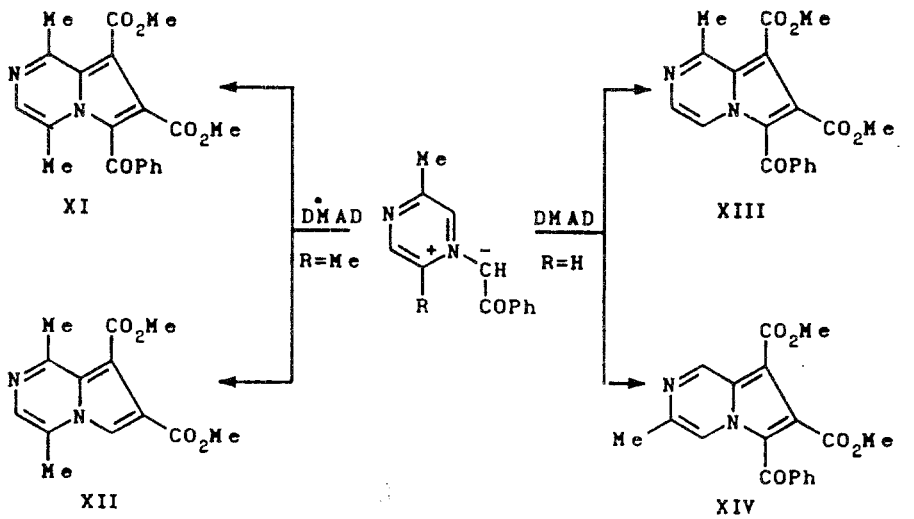
An interesting area of heterocyclic chemistry is the interaction of nitrogen-containing heterocycles with dimethyl acetylenedicarboxylate (DMAD). When a solution of 2-methyl or 2,6-dimethylpyrazine is refluxed in acetonitrile in the presence of DMAD, the pyrrolo[1,2-*a*]pyrazines VIIIa and b are obtained in 5 and 6% yields, respectively [9]. The most likely mechanism of this reaction is as follows [10]:



1.2. Pyrazinium dicyanomethylide undergoes a 1,3-dipolar cycloaddition with the acetylenedicarboxylate to give the adduct IX, which is then converted to 6-cyano-7,8-dimethoxycarbonylpyrrolo[1,2-*a*]pyrazine X {11]:

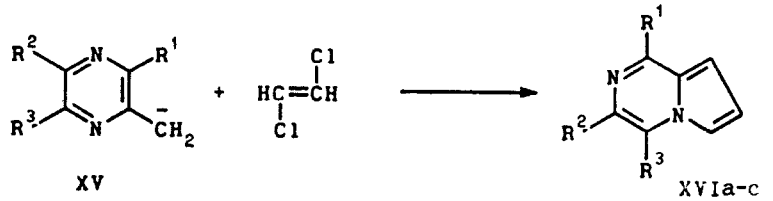


When 1-phenacyl-2,5-dimethylpyrazinium bromide is treated with an aqueous solution of sodium carbonate, 2,5-dimethylpyrazinium 1-phenacylid is formed. The latter reacts with acetylenedicarboxylate in chloroform in the presence of Pd on carbon to give a mixture of the two pyrrolo[1,2-*a*]pyrazines XI and XII [10]. The analogous reaction of 3-methylpyrazinium 1-phenacylid in acetonitrile (at about 20°C) gives rise only to compound XIII, one of the possible isomers, in 4% yield, whereas a 2:1 mixture of the two isomers XIII and XIV is obtained when the same reaction is carried out in refluxing chloroform (8% total yield) [12].



1.3. An unusual route to pyrrolo[1,2-*a*]pyrazines is the reaction of 2-methylpyrazine anions with trans-1,2-dichloroethylene [13]. Alkylpyrazine anions are easily obtained by treatment of alkylpyrazines with lithium

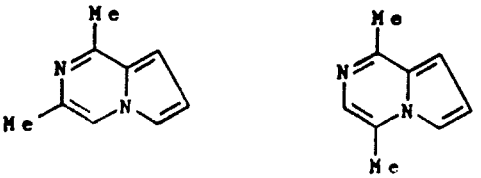
diisopropylamide. The reaction of the anions XVa-c with one equivalent of trans-1,2-dichloroethylene at 0°C in ether gives the corresponding pyrrolo[1,2-*a*]pyrazines XVIa and b in 29 and 15% yields, respectively, and XVIc in less than 1% yield:



XV XVIa-c

XV, XVI a $R^1=CH_3$, $R^2=R^3=H$, b $R^1=R^2=H$, $R^3=CH_3$, c $R^1=R^2=R^3=CH_3$

In the case of 2,3,5-trimethylpyrazine, a 2:1 mixture of only two of the possible isomers XVId and XVIe, is formed in 8% yield.

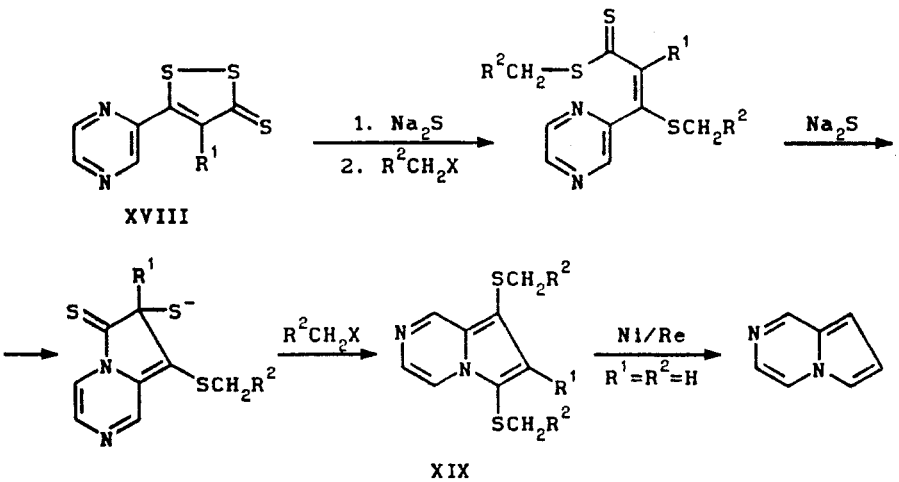


XVI d XVI e

Remarkably, under the same conditions 1,2-dibromoethylene gives a completely different product, namely 1,2-bis(3-methyl-2-pyrazyl)ethane (XVII) in 55% yield:

XVII

1.4. During studies on the mechanism of physiological action of 4-methyl-5-(2-pyrazinyl)-1,2-dithiol-3-thione (XVIIIa) (a drug known as OLTIPPAZ), a method for the synthesis of derivatives of pyrrolo[1,2-*a*]pyrazine was found, whereby this ring system is formed either by reaction of XVIIIa with nucleophiles or by its electrochemical reduction [14-18]. Thus, the pyrrolo[1,2-*a*]pyrazine derivatives XIXa-d were obtained in 23-62% yield upon reduction of compounds XVIIIIa and b with sodium sulfide, followed by alkylation of the intermediates [14]. The acidic hydrolysis of compound XIXd gives compound XIXe. The following reaction mechanism has been proposed in [14]:

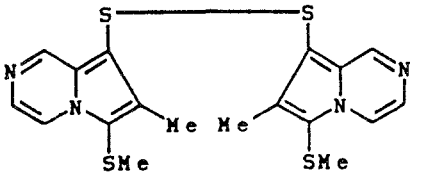


XVIII XIX

XVIII a $R^1=CH_3$, b $R^1=H$; XIX a $R^1=CH_3$, $R^2=H$; b $R^1=R^2=H$; c $R^1=CH_3$, $R^2=$ $=(CH_2)_2N(CH_3)_2$; d $R^1=CH_3$, $R^2=CO_2C_2H_5$; e $R^1=CH_3$, $R^2=CO_2H$

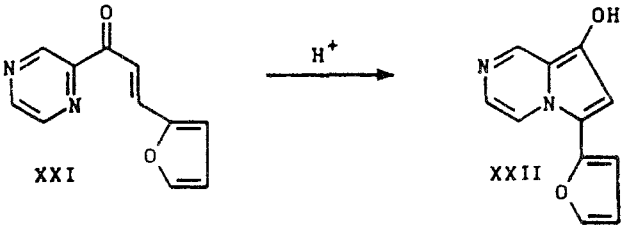
The desulfurization of the compounds thus obtained using Raney nickel products the unsubstituted pyrrolo[1,2-*a*]pyrazine or its alkylated derivative.

The electrochemical reduction of compound XVIIIa followed by alkylation with methyl iodide has also been reported [15, 16, 18]. Compounds XIXa and XX were thereby formed in 40 and 30% yields, respectively.



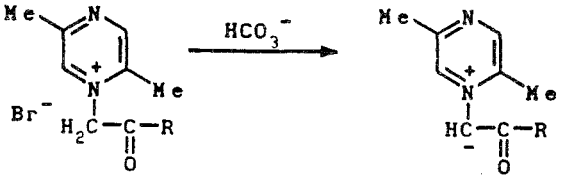
XX

A pyrrole ring can also be formed by a nucleophilic attack of the N-atom in position 1 of the pyrazine ring on the γ-carbon atom of the substituent in position 2 of the compound 2-(2-furfurylidene)acetylpyrazine (XXI). The reaction takes place upon treatment with hydrochloric acid and easily produces 6-(2-furyl)-8-hydroxypyrrolo[1,2-*a*]pyrazine (XXII) [19]:



XXI XXII

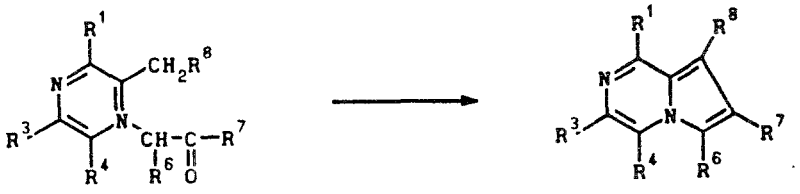
1.5. A classic approach to 5-, 6-, and 8-azaindolizines is based on the Chichibabin reaction, which utilizes the CH-acidity of the hydrogens of the methyl groups in the α and γ positions with respect to the pyridine nitrogen [20]. This method has, however, only recently been used for the synthesis of 7-azaindolizines, i.e., pyrrolo[1,2-*a*]pyrazines, from 2-methylpyrazines [21]. An earlier attempt to synthesize 3-methyl-7-phenylpyrrolo[1,2-*a*]pyrazine by heating 1-phenacyl-2,5-dimethylpyrazinium bromide (XXIIIa) with aqueous sodium hydrogen carbonate has produced only the zwitterion instead of the desired product of ring cyclization [22]. An analogous outcome was reported in the attempted cyclization of 1-acetonyl-2,5-dimethylpyrazinium bromide (XXIIIb) [21].



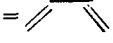
XXIIIa,b

XXIII a R=Ph, b R=Me

The salts XXIVa-*l* of alkyl-substituted pyrazines with α-halo ketones have been successfully cyclized under the classic conditions of the Chichibabin reaction, giving the corresponding pyrrolo[1,2-*a*]pyrazines XXVa-*l* in 2-63% yields [21]:



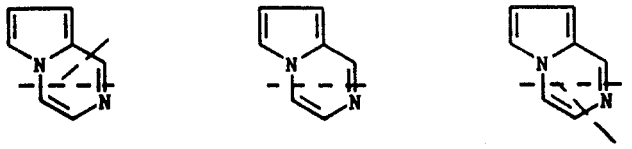
XXIV*a-l* XXV*a-l*

XXIV, XXV a $R^3=R^6=R^7=CH_3$; b $R^1=R^7=CH_3$; c $R^1=CH_3$, $R^7=C_6H_5$; d $R^1=R^6=R^7=CH_3$; e $R^1=R^3=R^7=CH_3$; f $R^1=R^3=R^6=R^7=CH_3$; g $R^1=R^3=CH_3$, $R^7=C_6H_5$; h $R^1=R^3=R^4=R^7=CH_3$; i $R^1=OCH_3$, $R^3=R^7=CH_3$; j $R^1=OCH_3$, $R^3=CH_3$, $R^7=C_6H_5$; k $R^1=Cl$, $R^3=R^7=CH_3$; l $R^1=R^7=CH_3$, $R^3+R^4=$  . Unspecified R=H

We have shown that the yields of the pyrrolo[1,2-*a*]pyrazines can be substantially increased by using triethylamine as the cyclizing reagent and acetonitrile as the solvent. This improved method also allowed the preparation of the earlier unavailable 3-methyl-7-phenyl- and 3,7-dimethylpyrrolo[1,2-*a*]pyrazines in 37 and 16% yields, respectively.

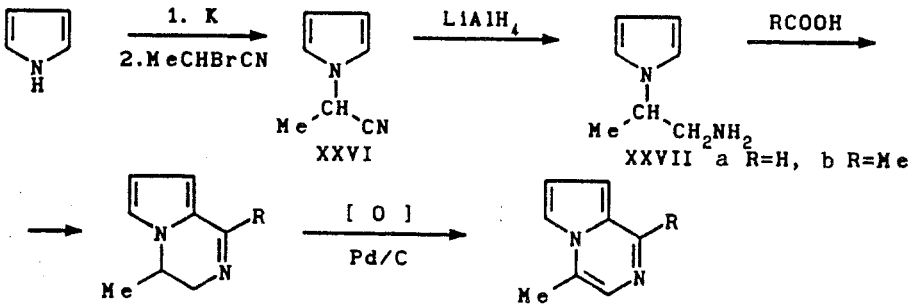
2. Construction of a Pyrazine Ring onto an Existing Pyrrole Ring

A smaller number of methods falls into this category. The starting materials are generally 2-substituted pyrroles. A pyrazine ring can be formed by several routes:

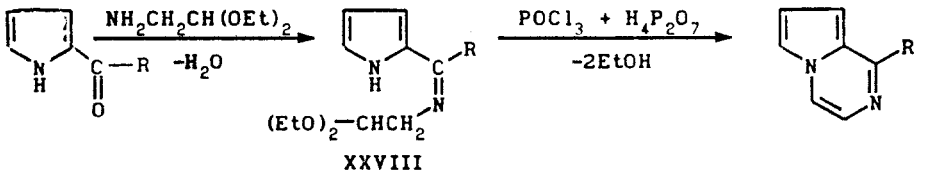


1 2 3

2.1. The preparation of 4-methyl- and 1,4-dimethylpyrrolo[1,2-*a*]pyrazines, as described in [3], involves the following steps: a) preparation of 2-(1-pyrrolyl)propionitrile (XXVI) from pyrrole and 2-bromopropionitrile; b) its reduction with $LiAlH_4$ to 2-(1-pyrrolyl)-1-propylamine (XXVII); c) cyclization of XXVII into 3,4-dihydropyrrolo[1,2-*a*]pyrazines with inclusion of an acid molecules; and d) aromatization of the latter compounds using Pd on carbon:



2.2, 2.3. The methods of these two routes allow the preparation of both pyrrolo[1,2-*a*]pyrazines and their oxo derivatives, depending on the structure of the starting 2-substituted pyrroles. Pyrrolo[1,2-*a*]pyrazines can be prepared starting with 2-acylpyrroles. Thus, the condensation of pyrrole-2-carboxaldehyde or 2-acetylpyrrole with 2,2-diethoxyethylamine, followed by cyclization of the resulting intermediate XXVIII using a mixture of $POCl_3$ and polyphosphoric acid gives the unsubstituted pyrrolo[1,2-*a*]pyrazine or its 1-methyl derivative in about 20% yield [23, 24]:



a R=H, b R=Me

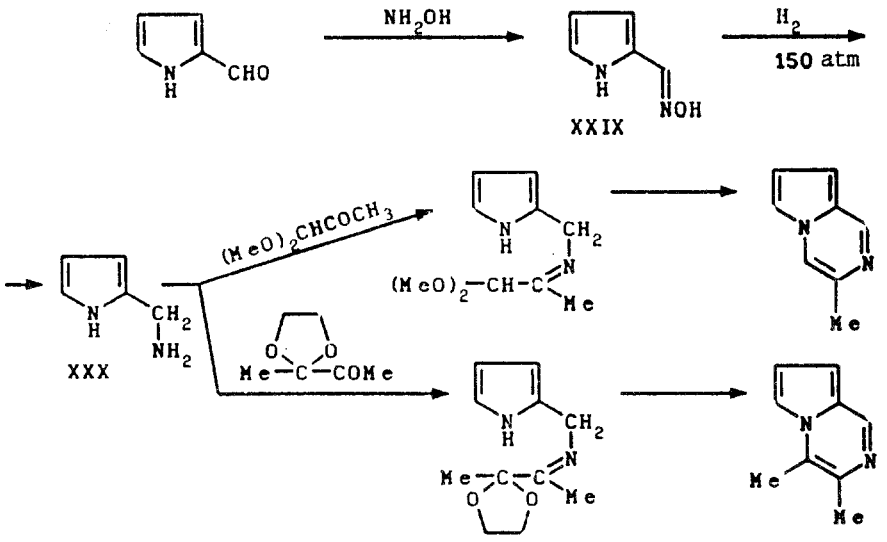
In the above reaction, the corresponding pyrrolo[1,2-*a*]pyrazines are also formed (in lower yields), along with the pyrrolo[2,3-*c*]pyrazines.

Starting with pyrrole-2-carboxaldehyde, 3-methyl- and 3,4-dimethylpyrrolo[1,2-*a*]pyrazines can also be prepared as outlined in Scheme 1 [3] (see below).

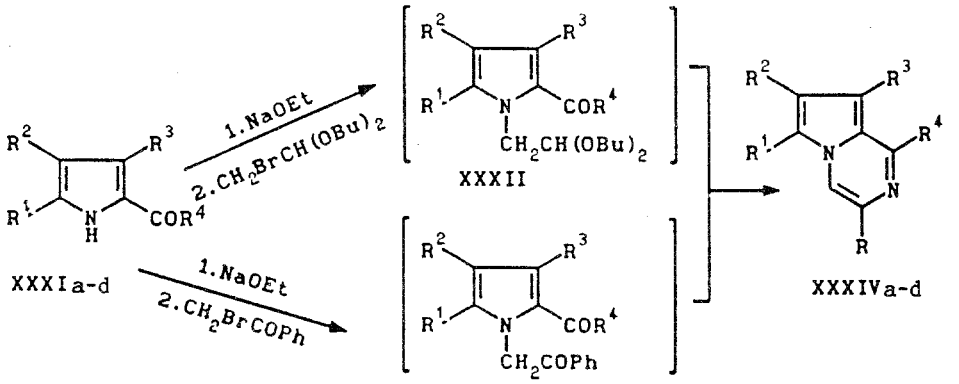
This method consists of reduction of pyrrole-2-carboxaldehyde oxime XXIX to 2-aminomethylpyrrole XXX, followed by condensation of the latter with 1,1-dimethoxy-2-propanone or 2,3-butanedione monoethylene acetal using a mixture of $POCl_3$ and polyphosphoric acid.

The search for improved methods for the preparation of pyrrolo[1,2-*a*]pyrazines from 2-acylpyrroles led to the development of a new approach for their synthesis [25]. In this method, 2-acylpyrroles XXXI are treated with sodium alkoxide and alkylated by α-bromoacetaldehyde dibutyl acetal or bromoacetophenone. The resulting intermediates XXXII and XXXIII are then refluxed without prior isolation in a solution of ammonium acetate in acetic acid, and the pyrrolo[1,2-*a*]pyrazines XXXIVa-d formed thereby are precipitated as their hydrochloride salts.

Scheme 1

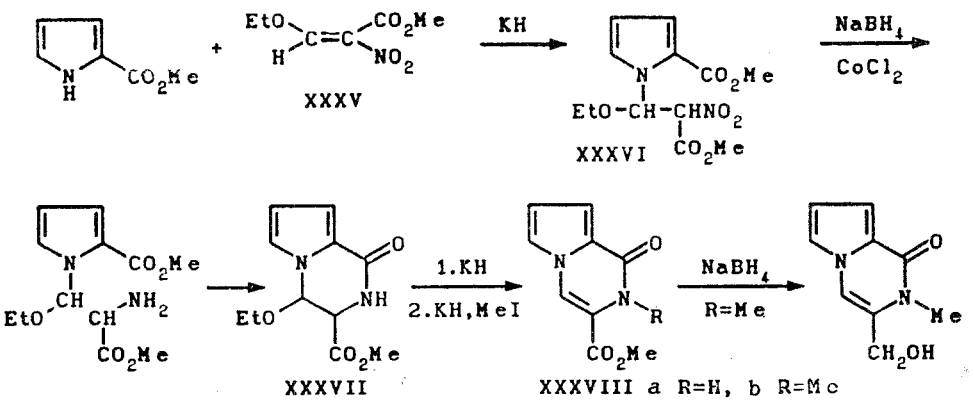


The yields are 25-50%. This approach circumvents the problems associated with the separation of the mixtures of pyrrolo[1,2-*a*]pyrazines and pyrrolo[2,3-*c*]pyridines, and also the use of some not easily available reagents that are required in some of the above-mentioned methods [3, 23].



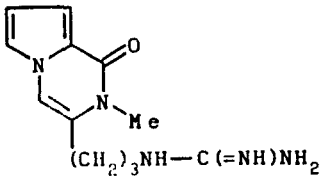
XXXI—XXXIV a $R=R^1=R^2=R^3=R^4=H$; b $R=H$, $R^1=R^2=R^3=R^4=CH_3$; c $R=R^1=R^2=R^3=H$, $R^4=C_6H_5$; d $R=R^4=C_6H_5$, $R^1=R^2=R^3=H$

When a carboxyl group is substituted for the carbonyl group in position 2 of the starting 2-substituted pyrroles, 1-oxo derivatives of pyrrolo[1,2-*a*]pyrazines can be synthesized. For example, the reaction of the methyl ester of pyrrole-2-carboxylic acid with the nitroalkene XXXV gives the adduct XXXVI [26], which upon reduction with $NaBH_4$ in the presence of $CoCl_2$ followed by cyclization and elimination of the ethoxy group leads to the formation of the lactam XXXVII. The reduction of the latter compound with KH in THF and its N-alkylation of



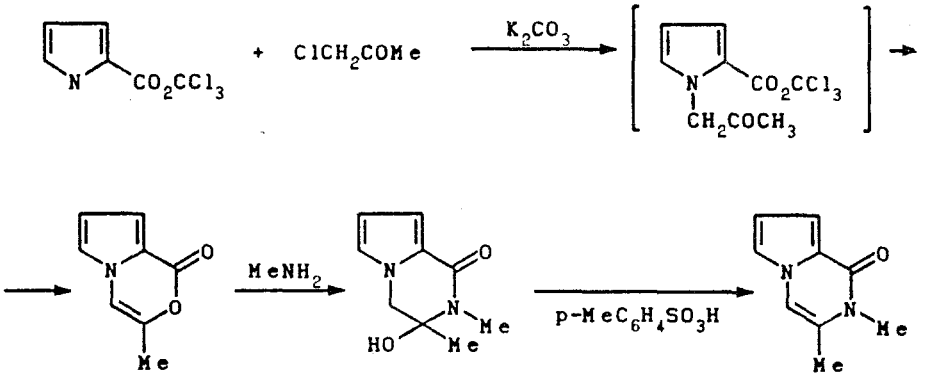
methyl iodide gives compounds XXXVIIIa and b, respectively. The reduction of the α,β-unsaturated ester XXXVIIIb with $NaBH_4$ in methanol gives 1-oxo-3-hydroxymethyl-2-methylpyrrolo[1,2-*a*]pyrazine. The yields at all stages exceed 60-70% [27].

Considerable efforts have been devoted to the development of a convenient synthesis of 1-oxo-2,3-disubstituted pyrrolo[1,2-*a*]pyrazines, since these compounds are intermediates in the preparation of the important biologically active peramine XXXIX and its derivatives [27, 28].



XXXIX

2-(Trichloroacetyl)pyrrole has been used as the starting material for the preparation of 1-oxo-2,3-disubstituted pyrrolo[1,2-*a*]pyrazines. The alkylation of 2-(trichloroacetyl)pyrrole with chloroacetone gives 3-methyl-1H-pyrrolo[2,1-*c*][1,4]oxazine-1-one (XL), which upon treatment with methylamine in THF followed by p-toluenesulfonic acid in benzene is converted to 1-oxo-2,3-dimethylpyrrolo[1,2-*a*]pyrazine (XLI), which is finally converted to the peramine XXXIX:



XL XLI

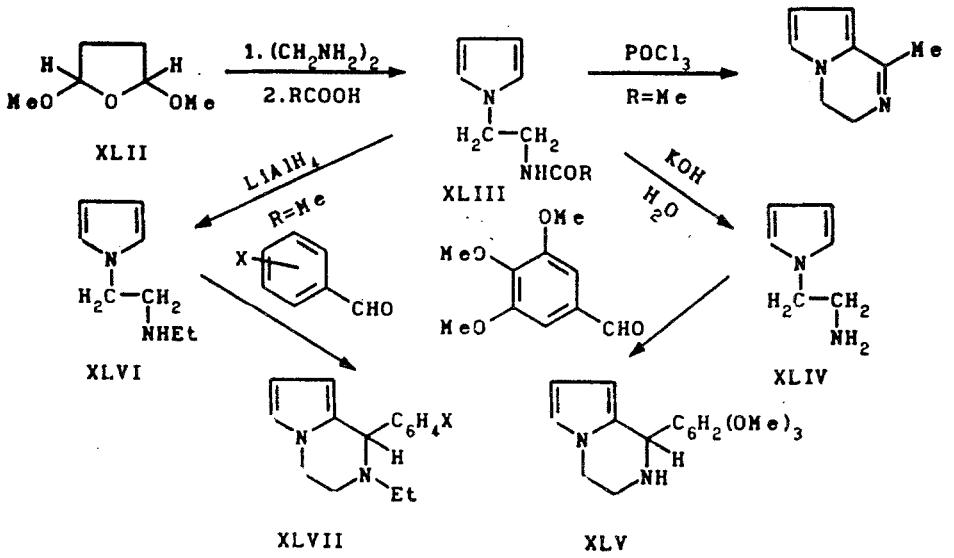
3. Consecutive Formation of the Pyrrole and Pyrazine Rings

Derivatives of furan are used as the starting materials for this group of methods. The formation of the pyrrolo[1,2-*a*]pyrazine ring system is possible by two routes:

1 2

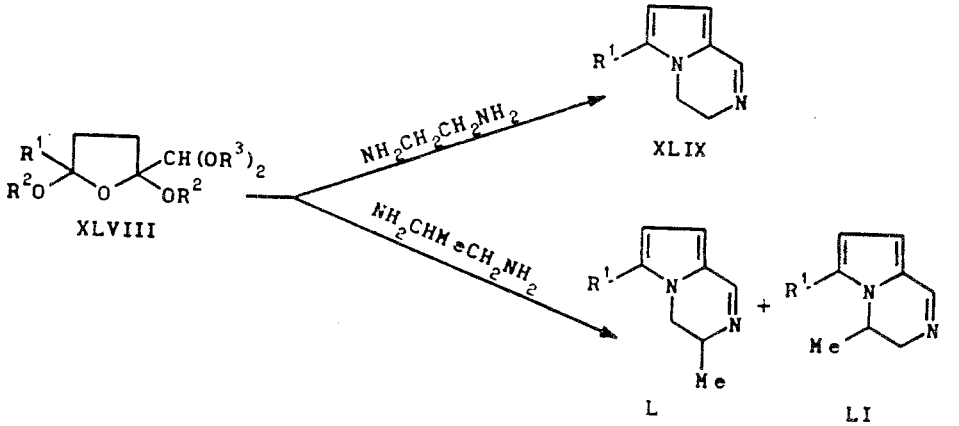
3.1. Pyrrolo[1,2-*a*]pyrazines are easily obtained from 1-(2-aminoethyl)pyrrole, which in turn can be prepared from 2,5-disubstituted tetrahydrofurans. Thus [29], the easily available 2,5-dimethoxytetrahydrofuran (XLII) can be converted in two steps into 1-(2-aminoethyl)pyrrole, the first step being reaction with 1,2-ethylenediamine in an acetic acid—dioxane mixture, followed by alkaline hydrolysis of the resulting amide (XLIIIa) as the second step. The use of formic or 2-methylpropanoic acid allows the preparation of the amides XLIIIb and c, respectively, which can be reduced to the amines XLIV and XLVI. The condensation of the amines thus obtained with aromatic aldehydes produces the 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines XLV and XLVII. The highly efficient (95% yield) cyclization of the amide XLIIIa into 1-methyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine by treatment with $POCl_3$ has also been described (see below).

3.2. The reaction of 2,5-disubstituted tetrahydrofurans with aliphatic 1,2-diamines can be used to prepare pyrazine rings. Thereby, a substituent in position 2 of the starting furan is retained in the same position of the final product. The starting materials for this reaction are the 2,5-dialkoxymethyltetrahydrofurans XLVIIIa-d, which are



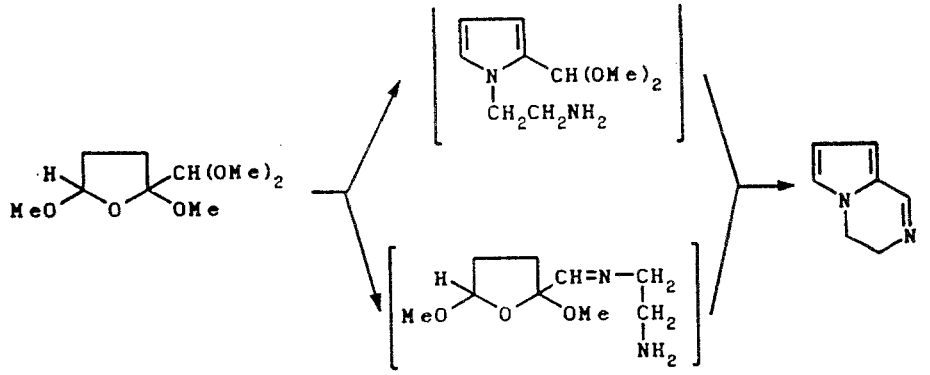
XLIII a R=Me, b R=H, c R=$CHMe_2$

condensed in acetic acid with aliphatic diamines to give the corresponding 3,4-dihydropyrrolo[1,2-*a*]pyrazines [30].



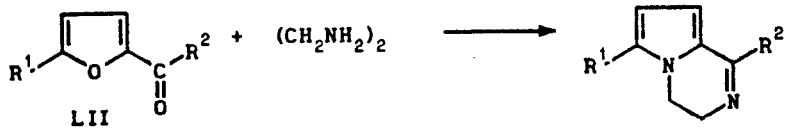
XLVIII a R^1=H, R^2=R^3=CH_3, b R^1=H, R^2=R^3=C_2H_5, c R^1=H, R^2=CH_3; R^3=C_2H_5, d R^1=R^2=R^3=CH_3; L, LI a R^1=H, b R^1=CH_3

The bicyclic final product can be formed by two alternative reaction pathways, involving either a pyrrole intermediate or an azomethine intermediate.



Best results (about 80% yield) are obtained on heating the acetal, ethylenediamine, water, and acetic acid in a ratio of 1:1.2:2:15. Two isomers can be formed when unsymmetrical 1,2-diamines are condensed with acetals. Thus, the reaction of the acetals XLVIIIa-c with 1,2-diaminopropane gives a 4:1 mixture of the 3- and 4-methyl-3,4-dihydropyrrolo[1,2-*a*]pyrazines in 83% overall yield. The regiospecificity of the reaction is increased when an alkyl substituent is present in position 5 of the starting tetrahydrofuran. Thus, the ratio of the isomers Lb and LIb is 16:1.

Pyrrolo[1,2-*a*]pyrazines can also be obtained from the more easily accessible acylfurans. Although the conversion of furan into pyrrole by the Yur'ev reaction requires very harsh conditions (400°C, aluminum oxide) [31], it was later shown that 2-acylfurans can be condensed with aliphatic 1,2-diamines in mild conditions (reflux in an 85% aqueous solution of the diamine) to produce 3,4-dihydropyrrolopyrazines [32]. The reaction of 2-acetylfuran with 1,2-diaminopropane afforded 1,3- and 1,4-dimethylpyrrolo[1,2-*a*]pyrazine [3]. A general method for 1-substituted 3,4-dihydropyrrolo[1,2-*a*]pyrazines by the reaction of 2-acylfurans with ethylenediamine has been described in [33].



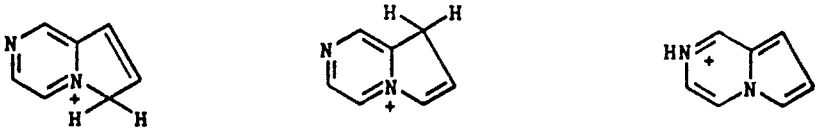
LII

LII a $R^2=CH_3$; b $R^2=C_3H_7$; c $R^2=CH_2C_6H_5$; d $R^2=c\text{-}C_6H_{11}$; e $R^1=CH_3$, $R^2=C_3H_7$; f $R^2=C_6H_5$; g $R^2=p\text{-}FC_6H_4$; h $R^2=p\text{-}ClC_6H_4$; i $R^2=p\text{-}CH_3OC_6H_4$. unspecified $R^1=H$

The reactions with ethylenediamine can proceed with either opening or preservation of the furan ring [33]. The optimal conditions for the preparation of 3,4-dihydropyrrolo[1,2-*a*]pyrazines involve 3 h refluxing of the starting 2-acylfurans with a 90% aqueous solution of ethylenediamine, in a molar ratio of 1:3. Under these conditions the yields of the pyrrolepyrazines are about 60%. However, numerous attempts to prepare the unsubstituted 3,4-dihydropyrrolo[1,2-*a*]pyrazine from furfurol by this reaction have been unsuccessful. In that case the amination reaction proceeds with formation of the mono- and bisazomethines [34], i.e., without cleavage of the furan ring. When aryl-2-furyl ketones are used as the starting materials in this reaction, the yields of 1-aryl-3,4-dihydropyrrolo[1,2-*a*]pyrazines are higher (70-80%) than those obtained with alkyl ketones as starting materials [35].

PROPERTIES OF PYRROLO[1,2-*a*]PYRAZINES

A very limited number of studies on the reactivity of pyrrolo[1,2-*a*]pyrazines have been published. In the pyrrolo[1,2-*a*]pyrazine ring system, an electron-deficient pyrazine ring is condensed to an electron-rich pyrrole ring. Thus, both electrophilic (involving the pyrrole ring) and nucleophilic substitution reactions (involving the pyrazine ring) can be expected to take place. Theoretical calculations [24, 36] show that the highest electron density is located at the C6 and C8 atoms of the pyrrole ring, whereas the Cl atom of the pyrazine ring is the most electron-deficient. The observed bromination of pyrrolo[1,2-*a*]pyrazine at positions 6 and 8 is in agreement with this [24], as is the reaction with phenyllithium, which gives 1-phenylpyrrolo[1,2-*a*]pyrazine. However, pyrrolo[1,2-*a*]pyrazine is relatively unreactive in both electrophilic and nucleophilic substitution reactions. The protonation of pyrrolo[1,2-*a*]pyrazine has been shown to take place only at N2 [37], the other two possible structures of the conjugated acid have not been observed.



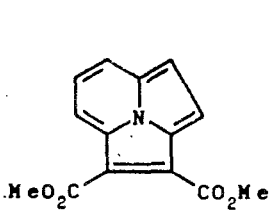
1 2 3

No deuterium exchange takes place in positions C6 and C8. Upon reaction with methyl iodide, pyrrolo[1,2-*a*]pyrazine is quaternized to the corresponding 2-methyl iodide. These results show that the excess electron density is concentrated mainly at the nonbridgehead nitrogen, and to a lesser extent at the C6 and C8 atoms. Weakly electrophilic reagents do not react with pyrrolo[1,2-*a*]pyrazine, e.g., no Vilsmeier formylation takes place, no nitroso or diazo derivatives can be obtained. However, upon refluxing in acetic anhydride the 6-monoacetyl derivatives is formed in low yield [38].

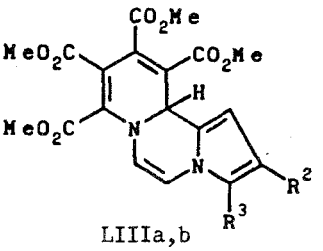
A similar behavior is seen in nucleophilic substitution reactions. Thus, pyrrolo[1,2-*a*]pyrazine reacts with phenyllithium [39], but cannot be aminated by the Chichibabin reaction, although it is possible to replace the chlorine atom located at the electron-deficient C atom in 1-chloro-7-methylpyrrolo[1,2-*a*]pyrazine by an amino or methoxy group.

In the reaction with dimethyl acetylenedicarboxylate, pyrrolo[1,2-*a*]pyrazines give rise to 1:2 adducts, e.g., compound LIII, where two molecules of the acetylenedicarboxylate have reacted at the N2 and C1 positions of the

pyrrolo[1,2-*a*]pyrazine molecule. This is in contrast with the similar reaction of indolizine, where 1,2-dimethyoxycarbonylcyclo[3,2,2]azine LII, an 1:1 adduct, is formed.



LIIa,b



LIIIa,b

LIII a $R^2=R^3=R^6=H$, b $R^2=R^3=R^6=Me$

In summary, the data presented in this review show that pyrrolo[1,2-*a*]pyrazines are not easily accessible compounds, whose chemical properties are insufficiently studied.

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