SYNTHESIS OF PYRROLES FROM HETEROCYCLIC COMPOUNDS (REVIEW)

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Current information on methods of forming a pyrrole ring from heterocyclic compounds is systematized and generalized. Reaction schemes are discussed.

Over the past decade there has been a steady interest in the chemistry of pyrrole, one of the key heterocyclic systems [1, 2]. This has been fostered by the discovery of new reactions for forming the pyrrole ring [3] and introducing functional substituents into it [3], as well as by the appearance of new, practical vistas (pyrrole-based antibiotics and antiinflammatories, electrically conducting polypyrroles, catalytically active metal porphyrin complexes, etc.).

Ever more attention is being given to methods of synthesizing pyrroles from other heterocycles — approaches having their roots in the classical work of Yu. K. Yur'ev [4].

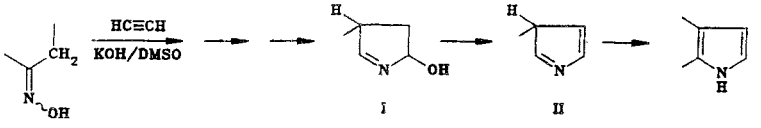
At the same time, despite the considerable amount of work in this area published at the present time, there has been no attempt to systematize and generalize it. Our purpose is to fill this gap. In order not to weigh down the review with material already covered in the basic monographs [1, 2], only publications from 1974-1986 were considered.

1. SYNTHESIS OF PYRROLES FROM FIVE-MEMBERED NITROGEN HETEROCYCLES

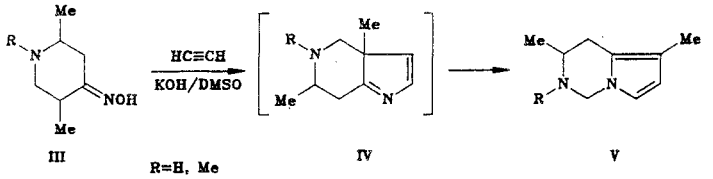
1.1. Pyrroles from 2H- and 3H-Pyrroles

To go from thermodynamically unstable (nonaromatic) 2H- and 3H-pyrroles to 1H-pyrroles (proper pyrroles) requires only the migration of a substituent from the 2 (3) position.

2H- and 3H-pyrroles not stabilized by two substituents in the 2 or 3 position, respectively, are known only as unisolable intermediates in some syntheses. For example, the Trofimov reaction [3, 5, 6] and its variants include steps in which 2-hydroxy-1-pyrrolines, I [7, 8], and 3H-pyrroles, II [9], are formed.



Recently [10-12], a new and promising approach to this reaction has been found in the case of oximes of 4-piperidones, III. It proceeds through the formation of 3H-pyrroles, IV, to tetrahydropyrrolo[1,2-c]pyrimidines, V,



The thermal rearrangement (benzene/pyridine, 170°C, 70 min) of 2-allyl-2-methyl-3,5-diphenyl-2H-pyrrole (VI) takes place via two, sequential [3, 3] and [1,3]-sigmatropic shifts [13].

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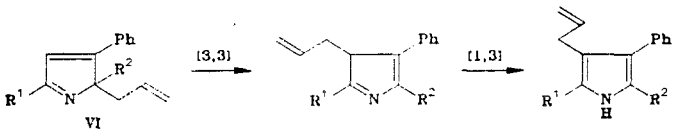
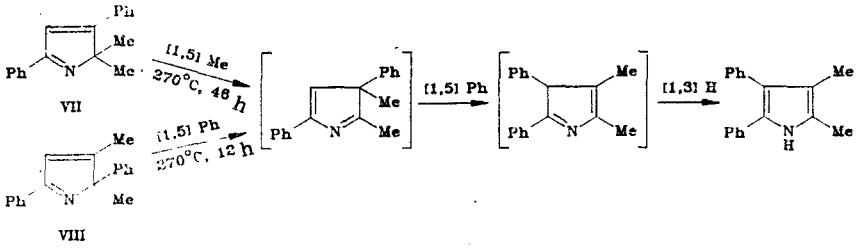


VI

R^1=Me, Ph; R^2=Me, Ph

2H-Pyrroles VII and VIII undergo two [1,5]-shifts on thermal rearrangement with migration of the Ph or Me and finishing with a [1,3]-shift of a hydrogen [14-16].



VII

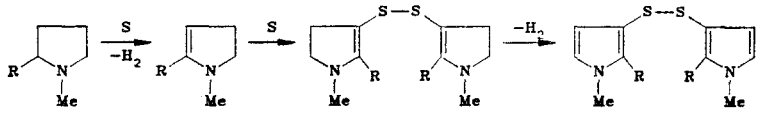
VIII

1.2. Pyrroles form Pyrrolidines and Pyrrolines

1.2.1. Dehydrogenation Reactions. One method of synthesizing pyrroles is the aromatization of its hydrogenated derivatives, pyrrolidines and pyrrolines. On the dehydrogenation of a mixture of cis- and trans-2,5-dimethylpyrrolines on a rhodium catalyst (Rh/Si, 320°C), 2,5-dimethyl-Δ^1-pyrroline and 2,5-dimethylpyrrole are formed (0.7% yield) [17]. Raising the temperature increases the yield of pyrrole up to ~40%. The use of Pd/Si as the catalyst allows one to obtain pyrrole selectively.

Palladium on carbon was used for the aromatization of 2-pyrrolidinylidine malonates to the corresponding 2-pyrrole acetates [18].

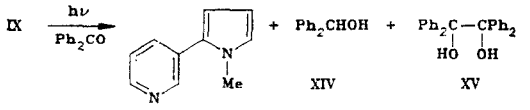
The reaction of nicotine, IX, with sulfur (toluene, 110°C, 72 h) gives bis[1-methyl-2-(3-pyridyl)pyrrole-3-yl] disulfide (XII) [19]. The dehydrogenation takes place in two steps: first pyrroline X is formed and then disulfide XI, the product of the reaction of pyrroline X with sulfur loses hydrogen.



IX X XI XII

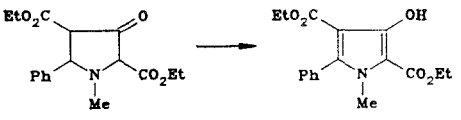
R=3- pyridyl

Nicotyrine, XIII, (40%), benzhydrol, XIV, and benzopinacone, XV, are obtained by irradiating (254 nm) a benzene solution of nicotine, IX, that contains benzophenone (photosensitizer [20].



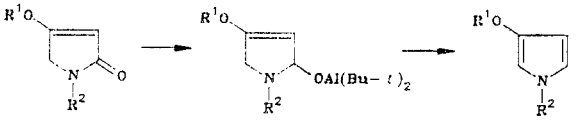
XIII XIV XV

3-Oxopyrrolidine XVI is oxidized to the pyrrole by oxygen in boiling benzene and also by chloranil or benzoquinone in the presence of Pd/C [21]. This process takes place most effectively, however, in the presence of N-bromosuccinimide in aqueous dioxane containing an excess of $NaHCO_3$ [21].



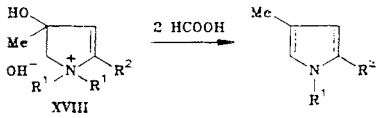
XVI

1.2.2. Elimination Reactions. 3-Alkoxypyrroles, XVII, are easily obtained from 4-alkoxy-3-pyrroline-2-ones by the action of excess $Al(t\text{-}Bu)_2H$ and aqueous NaOH (THF, 0°C, or hexane, 20°C, 12 h) [22].



R^1=Me, Et; R^2=Me, Et, Bz XVII

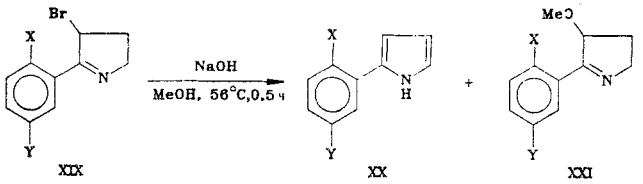
It has been shown possible to synthesize pyrroles from the hydroxides of N,N-dialkylpyrrolines, XVIII, by the action of formic or acetic acid [23]. The reaction involves two steps: a dealkylation and a dehydration.



XVIII

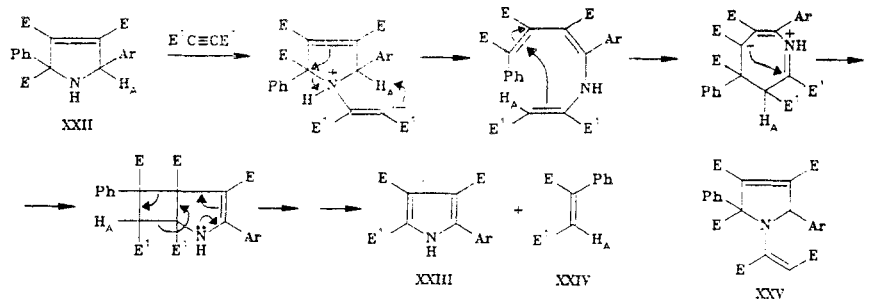
R^1=Me, Et; R^2=H, Me, Ph

Dehydrogenating agents such as quinone or selenium proved ineffective for the aromatization of 2-aryl-1-pyrrolines. The process is successfully accomplished by converting the compounds to the bromo derivatives, XIX, and dehydrobrominating them by boiling in methanol with alkalies [24]. At 20°C, 2-arylpyrrolines XXI are formed along with pyrroles XX as the result of a substitution reaction.



XIX XX XXI

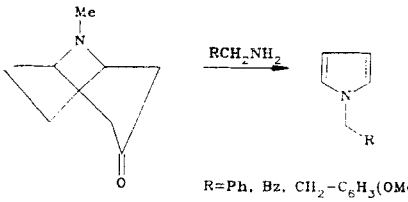
The corresponding pyrrole, XXIII, and olefin, XXIV, are formed from pyrrolines XXII (with Ar = a substituted phenyl) and an equimolar quantity of an acetylenedicarboxylic acid ester (toluene, 110°C). Under the same conditions, pyrroline XXII with Ar = Ph gives a mixture (1.4:1) of pyrroles XXIII and pyrrolines XXV [25].



XXII XXIII XXIV XXV

XXIV Ar = $CF_3C_6H_4$, CNC_6H_4, $NO_2C_6H_4$; E = CO_2Me; E' = CO_2Et; XXV Ar = Ph; E = E' = CO_2Me

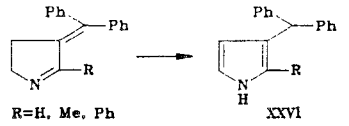
The reaction of 3-tropinone with amines in the presence of $TiCl_4$ (toluene, −5°C) forms N-substituted pyrroles in 3..5% yield [26].



R=Ph, Bz, CH_2-$C_6H_3(OMe)_2$

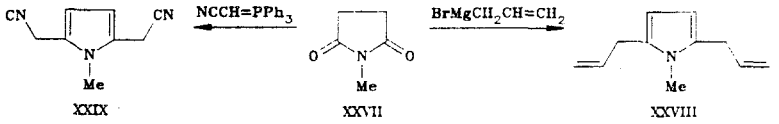
It is suggested [26] that the reaction takes place via an intermediate diene compound that enters into reaction with amines by a kind of C_4 + N condensation.

1.2.3. Transformations of Pyrrolidines and Pyrrolines by Isomerization. Under the action of sodium "dimsil," 3-diphenylmethylene-1-pyrroline, with an exocyclic double bond, isomerizes to pyrrole XXVI in 65% yield [27].



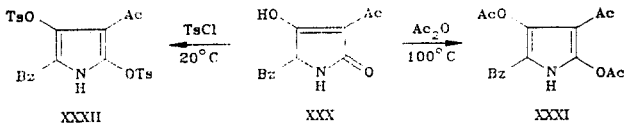
R=H, Me, Ph XXVI

The reaction of N-methylsuccinimide, XXVII, with allylmagnesium bromide (benzene, 80°C, 4 h) [28] or cyanomethinotriphenylphosphorane (xylene, 110°C, 4 h) [29] gives 2,5-substituted pyrroles XXVIII and XXIX.



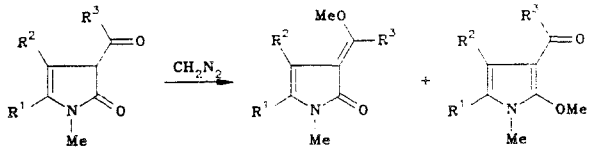
XXIX XXVII XXVIII

The reaction of pyrrolinone XXX with acetic anhydride or tosyl chloride in pyridine leads to pyrroles XXXI and XXXII [30].



XXXII XXX XXXI

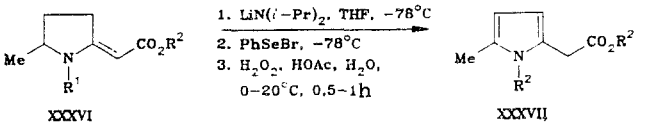
On reacting α-acyl-Δβ,γ-butenolides, XXXIII, with diazomethane (ether, −10°C), one obtains 2-methoxy-3-acylpyrroles, XXXV, in 43..63% yield along with 2,3-dihydro-2-pyrrolones, XXIV [31].



XXXIII XXXIV XXXV

R^1, R^2=CH=CHCH=CH; R^3=Me, Ph

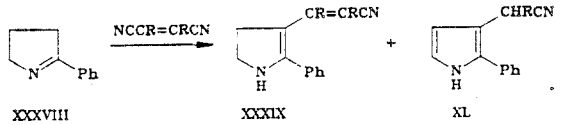
Enamine esters, XXXVI, are converted to substituted pyrroles, XXXVII, in 70...90% yield by the following sequence of reactions [32]:



XXXVI XXXVII

R^1 = $(CH_2)_2C_6H_3(OMe)_2$, $(CH_2)_3CO_2Me$; R^2=Me, Et

Pyrrolines XXXVIII condensing with cyano olefins form pyrrolines XXXIX and pyrroles XL [33].

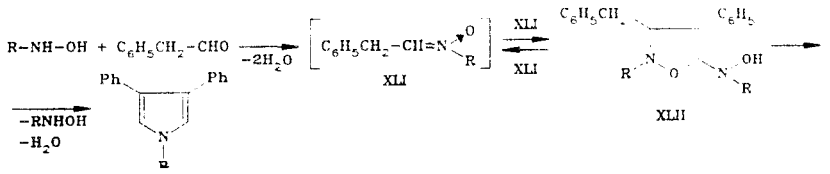


XXXVIII XXXIX XL

R=CN, CO_2Et

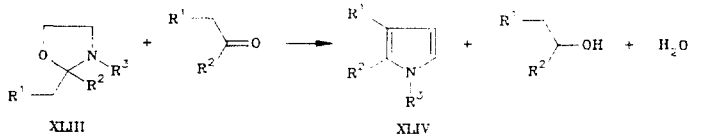
1.3. Pyrroles from 1,2- and 1,3-Oxazolidines

When N-substituted hydroxylamines react with phenylacetaldehyde, crystalline, cyclodimers of C-benzylnitrones, XLI, are formed. On storage in chloroform for several days, these isoxazolidines, XLII, change into 3,4-diphenylpyrroles in 30...47% yield [34].



Aliphatic aldehydes do not enter into this reaction.

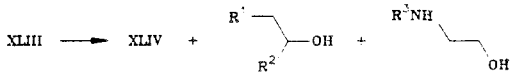
When 1,3-oxazolidines XLIII react with carbonyl compounds (150...200°C, 5...8 h) in the presence of alkalies, an oxidation-reduction takes place leading to pyrroles XLIV (25...57% yield) and the corresponding alcohols [35].



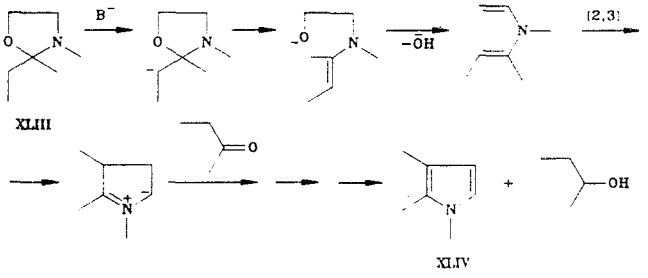
$R^1-R^2=(CH_2)_4$, $(CH_2)_5$; R^1=Et, *i*-Pr; R^2=H, *n*-Pr; $R^3=CH_2CH_2OH$. *i*-Pr, *n*-Bu

1-Alkyl-4,5,6,7-tetrahydroindoles form as the result of the condensation of cyclohexanone with diethanolamine or methylethanolamine in the presence of KOH [36]. The reaction proceeds via the formation of 1,3-oxazolidines.

Pyrroles XLIV are also formed (16...20% yield) when 1,3-oxazolidines XLIII are boiled with t-BuOK or alkali (NaOH, KOH) [37-39].



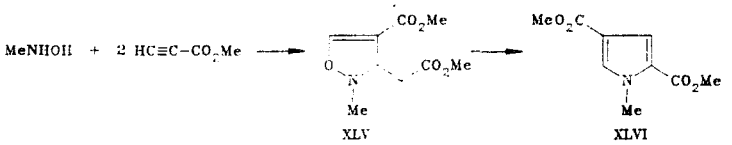
The reaction mechanism is not considered by the authors. It can be supposed, however, to involve the following steps:



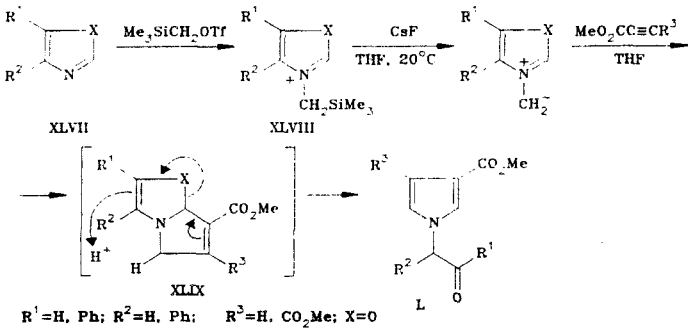
The elimination and redox steps are obviously facilitated by the conditions of super-high basicity (use of molten alkalies and the possibility of chelation of the alkali metal cation by the 2-aminoethanol being set free) [40]. In spite of the low yields of pyrroles (calculated from the starting oxazolidine, they are one-half those calculated by the authors on the basis of the disproportionation scheme) and the harsh reaction conditions and the limitations related to these, this method deserves attentive study in view of the availability of starting materials.

1.4. Pyrroles from Isoxazolines, Oxazoles, (Thiazoles), and Isoxazoles

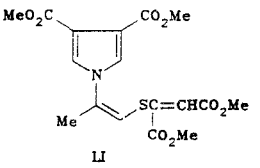
When heated, isoxazoline, XLV, forming from the reaction of N-methylhydroxylamine with methyl propiolate, rearranges to the corresponding pyrrole, XLVI [41].



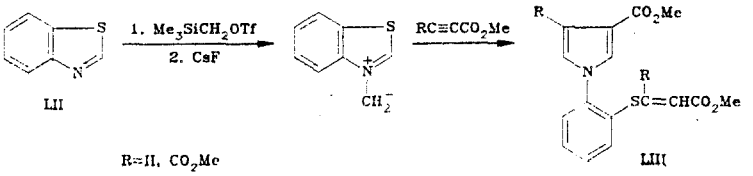
The reaction of 5- or 4-phenyloxazole, XLVII (X = 0), with trimethylsilylmethyl trifluoromethanesulfonate in methylene chloride leads to an oxazolium salt, XLVIII, which gives pyrrole L when treated with anhydrous cesium fluoride in the presence of an acetylenic dipolarophile [42]. Cycloadduct XLIX, forming in the first step, undergoes rapid 1,4-elimination, changing into pyrrole L with a yield of 80...90%.



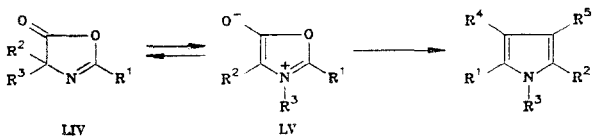
When a thiazolium salt, XLVIII (X=S), reacts with CsF in the presence of an acetylenic dipolarophile, diadduct XLIX (X = S) also forms, the further reaction of which with excess allkyne gives pyrrole LI.



The analogous reaction with benzothiazole, LII, leads to the formation of pyrroles LIII in good yield.



Azalactones LIV, which can be obtained by the alkylation of amino acids [43], containing a system of azomethinylide bonds through the mesoionic oxazolium-5-oxide, LV, react with dipolarophiles activated by alkenes [43, 44] or alkynes [45] in excess acetic anhydride at 20...100°C to form substituted pyrroles.

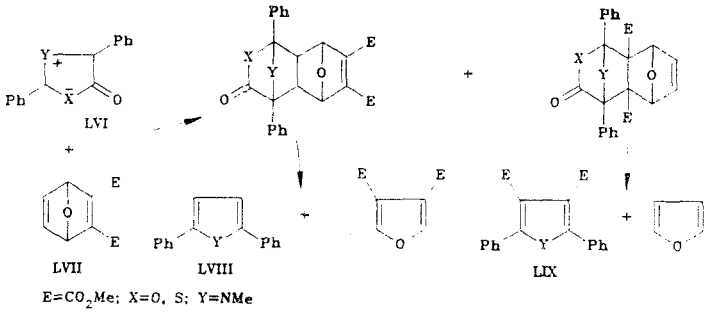


R^1=H, Me, *i*-Bu, Ph; R^2=H, Me, Ph; R^3=H, Me, COMe, Ph, 3-$CF_3C_6H_4$; R^4=H, Ph, CN; R^5=H, SO_2CF_3

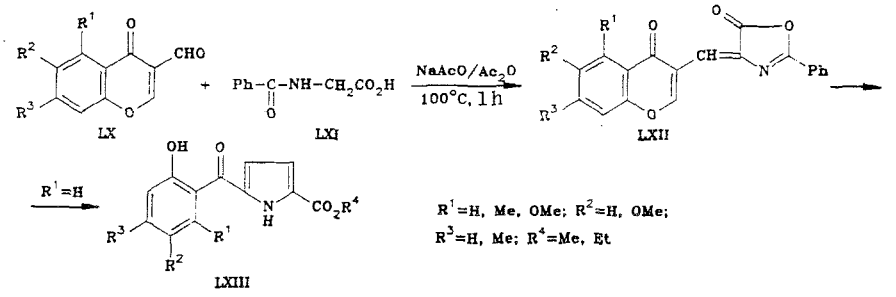
The cycloaddition of azalactones LIV is regiospecific and depends to a considerable extent on the substituents on both components. Thus in the reaction with chloracrylonitrile, the presence of a substituent in the 4 position of LIV is apparently necessary, because the

reaction does not go with N-formyl-, N-acylglycine and hippuric acid [38]. The reaction of oxazolone LIV with 1,2-dicyanostyrene gives pyrrole in 32% yield. With the replacement of one CN group by CO_2Me, it gives pyrroline in 85% yield [44].

The reaction of mesoionic oxazolone LVI (X = O, Y = NMe) with dimethyl-7-oxabicyclo-[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (LVII) in benzene at room temperature, leads to the formation of pyrroles LVIII (16%) and LIX (24%). With the less active thiazolone LVI (X = S, Y = NMe), the reaction becomes more selective; when this compound is boiled in benzene with compound LVII, (13 h), pyrroles LVIII (79%) and LIX (7%) are formed [46].

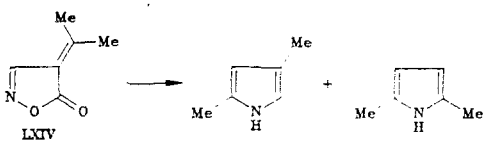


Azalactones LXII, readily formed by reaction of the corresponding chrome-3-aldehyde, LX, with hippuric acid, LXI, by the procedure in [47], give pyrroles LXIII when heated with a methanolic solution of sodium carbonate.



When $R^1 \neq H$, the pyrroles form via intermediate acrylic esters.

The vacuum pyrolysis of 4-alkylideneisoxazole-5-one, LXIV (500...700°C), $5 \cdot 10^{-4}$ mm Hg) gives a mixture of 2,4- and 2,5-dimethylpyrroles (45:55) [48].



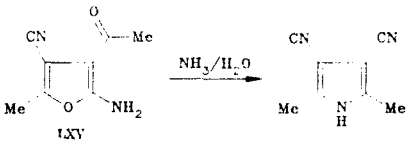
2. SYNTHESIS OF PYRROLES FROM OTHER HETEROCYCLES

2.1. Pyrroles from Furans and Thiophenes

The reaction of the reciprocal transformation of five-membered, aromatic heterocycles, discovered by Yu. K. Yur'ev in 1938, continues up to now to be used in the synthesis of pyrroles.

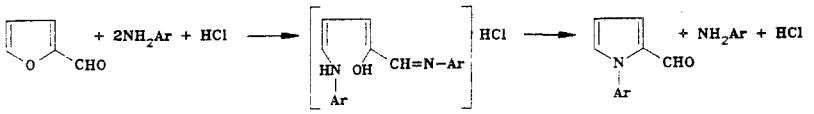
The gas-phase reaction of furan with ammonia is familiar [49-52]. Catalysts used are synthetic zeolites (330°C, 4...20% yield) [49], zeolites containing ions of divalent metals — Ca, Co, Cu, Ni, and Mn (400°C, 8...10 sec) [50]. Si/Al alloy containing 10....27% Al and various amounts of alkaline earth metal oxides —MgO, SiO, CdO, B_2O_3 (450°C, 8...10 sec, 73% yield) [51, 52].

Substituted furans are converted to pyrroles much more easily. Thus, 2,5-dimethyl-3,4-dicyanopyrrole is obtained in 60% yielded by boiling aminofuran LXV with a concentrated, aqueous ammonia solution for 14 h [53].



LXV

The reaction of furfurol with amines goes to form the Stenhaus salt, LXVI, which, depending on the reaction conditions and the structure of the amine, is converted into a pyridinium salt, pyrrole-2-aldehydes and their isomeric furfuralimines, or diaminocyclopentenones [54].



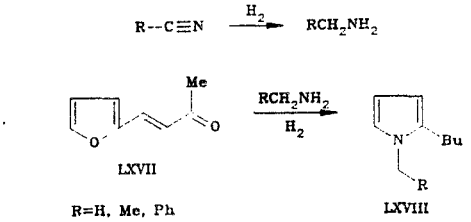
LXVI

Ar=4-$NH_2SO_2C_6H_4$, 3-$NH_2SO_2C_6H_4$, 4-$C_{10}H_6NO_2$, 4-$C_6H_4NO_2$

It was established [54] that pyridinium salts from weakly basic amines are unstable because of the presence of a strong electron-accepting substituent in the molecule, and the reaction occurs primarily with the formation of the pyrrole-2-aldehydes. In the case of the reaction of furfurol with 4-nitroaniline, the dependence of the yield of 1-arylpyrrole-2-aldehyde on the acidity of the solution was studied [54, 55], and the optimum acidity was established to be 0.2...0.45% HCl. At higher HCl concentrations, tar formation occurred, and the yield of pyrrole was reduced; at lower concentrations the reaction was complicated by the formation of by-products, 2- and 4-cyclopentenones [55]. At room temperature, furfurol forms Schiff bases with ortho-aminophenols [54].

The reaction of α-amino acids with 2-acetylfurans and furfurol leads to the N-alkyl-2-acylpyrroles [56].

The catalytic hydroamination of methyl-2-(2-furyl)vinyl ketone, LXVII, with nitriles in the presence of 15% Cu/Al_2O_3, or 15% Cu/MgO, or 15% Cu/ZnO under 15 atm pressure of H_2 leads to the formation of pyrrole LXVIII (17...22% yield) together with pyrrolidine and furan [57].



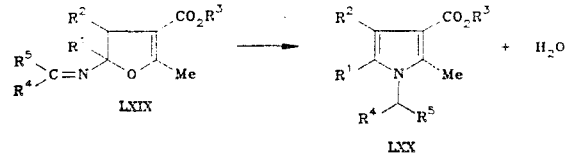
LXVII

R=H, Me, Ph

LXVIII

The pyrrole forms as the result of the direct replacement of the oxygen of the furan ring with an amine group with the simultaneous hydrogenation of the carbonyl group and the double bond in the side chain.

Catalytic hydrogenolysis (H_2, PtO_2 or Raney Ni, MeOH, 20°C) of 4,5-dihydro-5-(methyleneamino)-3-furancarboxylates, LXIX, leads to the substituted pyrroles, LXX, [58].



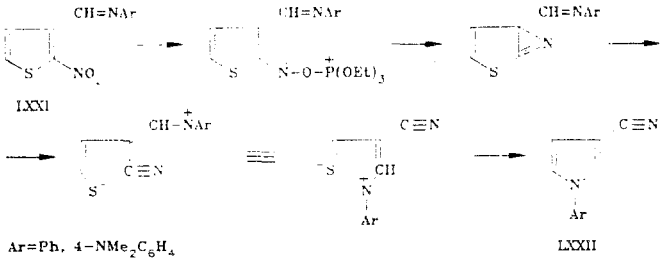
LXIX

LXX

R^1=Me, Et; R^2=Ar; R^3=Me, Et, *i*-Pr; R^4=CO_2Me, CO_2Et, CO_2Pr; R^5=CO_2Me

Obviously, the amine group is first reduced (to the R^4R^5CHNH radical), and recyclization with the splitting out of water then follows.

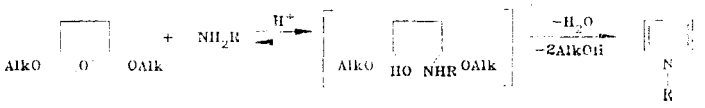
The reaction of anils LXXI with triethyl phosphite in tert-butylbenzene (1:3, 14 h) leads to 1-arylpyrrole-3-carbonitrile LXXII in 55...70% yield [59].



The formation of a bicyclic intermediate and a ring opening are steps in the reaction.

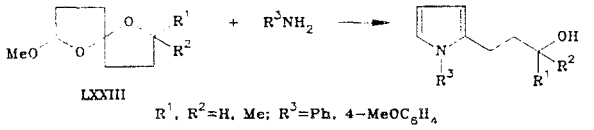
2.2. Pyrroles from 2,5-Dialkoxytetrahydrofurans

A convenient method of synthesizing pyrroles that has been developing rapidly in recent times is the acid-catalyzed reaction of amines with 2,5-dialkoxytetrahydrofurans [2] which can be thought of as substituted 1,4-diketones. The synthesis itself is a variant of the Paal—Knorr condensation.



Heterocyclization takes place when the reactants are boiled in an acidic medium.

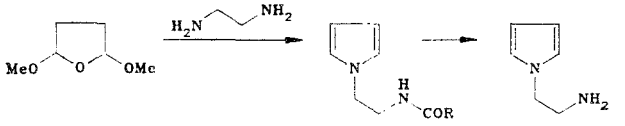
Thus, when 2-methoxy-1,6-dioxapyro[4,4]nonanes, LXXIII, are heated with amines in butyric acid, pyrrole-2-propanols are obtained in 42...98% yield [60].



LXXIII

R^1, R^2=H, Me; R^3=Ph, 4-$MeOC_6H_4$

Reaction of 2,5-dimethoxytetrahydrofuran with 1,2-diaminoethane (RCO_2H, dioxane, 100°C, 4 h) leads to 1-(2-acetylaminoethyl)pyrrole, LXXIV (75% yield), from which 1-(2-aminoethyl)-pyrrole, LXXV, is obtained by alkaline hydrolysis [61].



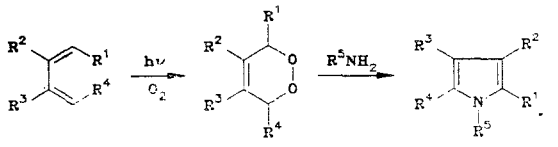
R=H, Me, i-Pr LXXIV LXXV

Aliphatic [62, 63], aromatic [63-65], and aliphatic-aromatic amines [63], phenacylamines [66], anthranilic acid derivatives [67, 68], aminosalicyclic acid [69, 70], 3-nitro-4-amino-phenylpropanoic acid [71, 72], arylsulfonamides [73, 74], benzamides [74], aminodihalodiphenyl ether [75], phenylhydrazone derivatives [76, 77], sulfamoylbenzoic acids [77-80], and amino acids [81-83] have been used as the amine component in this reaction.

2.3. Reactions with Ring Contraction

2.3.1. Pyrroles from Oxygen- and Sulfur-containing Six-membered Heterocycles.

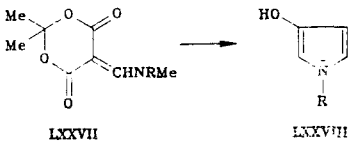
3,6-Dihydro-1,2-dioxins, LXXVI, forming by the photochemical 1,4-addition of oxygen to dienes, react with ammonia and primary amines (KOH in alcohol, 78°C, 10 h) to give pyrroles [84, 85].



LXXVI

R^1, R^2, R^4=H, t-Bu, Ph; R^3=Me; R^5=H, Et, Ph, Bz

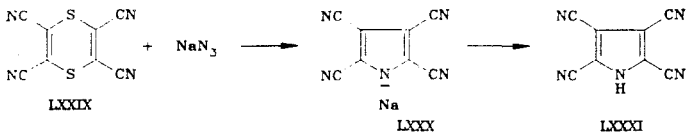
Hydroxypyrroles LXXVIII are obtained by vacuum pyrrolysis of diketones LXXVII (600°C, 10^{-2} mm Hg) [86].



LXXVII LXXVIII

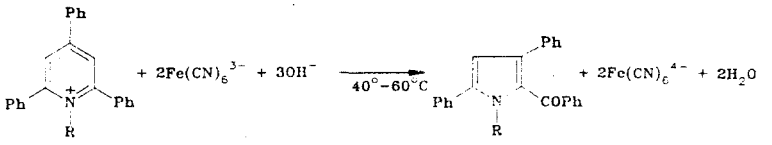
R=*t*-Bu (38%), Ph (63%)

Dithiine, LXXIX, with sodium azide in ethanol forms at 25°C the sodium salt of tetracyanopyrrole, LXXX, which is, however, more easily isolated in the form of the tetramethylammonium salt in 72% yield [87]. When an acetonitrile solution of tetramethylammonium tetracyanopyrrolate is passed through Amberlite, tetracyanopyrrole, LXXXI, is formed [87].



LXXIX LXXX LXXXI

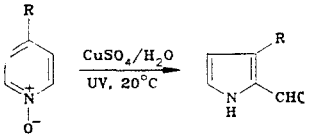
2.3.2. Pyrroles from Pyridine Derivatives. When 1,2,4,6-tetrasubstituted pyridinium salts LXXXII are oxidized with hexacyanoferrate(III) anions in alkaline medium, the pyridine ring is found to contract and 1,2,3,5-tetrasubstituted pyrroles LXXXIII form in 71...97% yield [88-90].



LXXXII R=Me, Et, Ph, 4-MeC_6H_4, 4-FC_6H_4, Bz LXXXIII

Oxidation of the same pyridinium salt with hydrogen peroxide leads to N-substituted 2,3,5-triphenylpyrrole (R = Me, Ph, 3-HOC_6H_4, 4-$MeC_6H_4CH_2$, $C_6H_5CH_2$) [91]. In both cases, the reaction goes via the intermediate dihydropyridine.

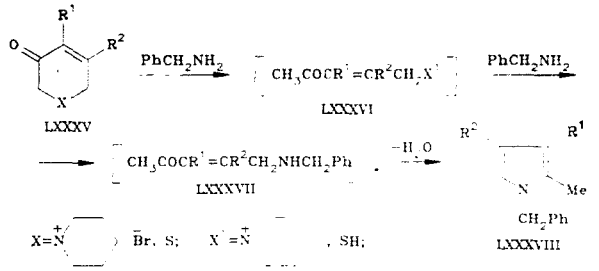
Photolysis of pyridine-N-oxides, LXXXIV, in aqueous $CuSO_4$ solution, 2-formylpyrroles are obtained in 32...42% yield. Without $CuSO_4$, the yield does not exceed 2...6% [92].



LXXXIV

R=H, Me, MeO, Cl, CN, Ph, $PhCH_2O$

When heated with benzylamine, the quarternary salt 2-methyl-3-ethyl-5-azacyclohex-2-ene-1-one (LXXXV, R^1 = Me, R^2 = Et, X = piperidine bromide) and 3-methyl-5-thiacyclohex-2-ene-1-one (LXXXV, R^1 = H, R^2 = Me, X = S) undergo ring contraction forming the corresponding 1-benzyl-2,3-dimethyl-4-ethyl- (LXXXVIII, R^1 = Me, R^2 = Et) and 1-benzyl-2,4-dimethyl- (LXXXVIII, R^1 = H, R^2 = Me) pyrroles [93].



LXXXV LXXXVI LXXXVII LXXXVIII

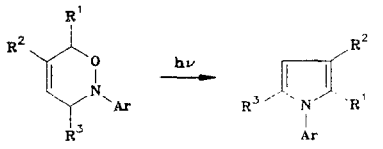
X=N⁺ Br, S; X=N SH;

R^1=H, Me; R^2=Me, Et

This reaction involves the reductive cleavage of compounds LXXXV and LXXXVI, an accompanying hydride transfer, the transamination of compound LXXXVI by the action of a second molecule of benzylamine, and the cyclization of the opened intermediate, LXXXVII, to pyrrole LXXXVIII.

2.3.3. Pyrroles from Heterocycles Containing Oxygen and Nitrogen. When morpholine is passed through a layer of alumochromia catalyst (Cr_2O_3/Al_2O_3, 1:9, 400...440°C), pyrrole is obtained [94].

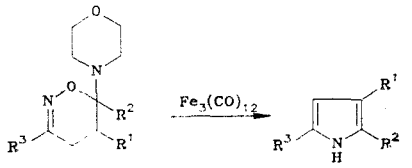
Irradiation of 3,6-dihydro-1,2-oxazines, LXXXIX (254 nm, MeOH or ether), leads to N-arylpyrroles [95].



LXXXIX

Ar=Ph, $C_6H_4CO_2Me$, 4-$MeOC_6H_4$; R^1=H, CO_2Me, CO_2H; R^2=H, Me; R^3=H, Me

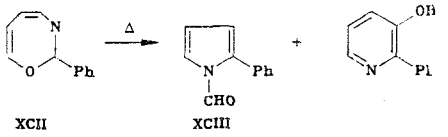
Pyrroles XCI are obtained by the reaction of oxazines XC with iron carbonyl, $Fe_3(CO)_{12}$ [96].



XC XCI

R^1=Me, Et; R^2=H, Et, Ph; $R^1-R^2=(CH_2)_n$, n=3...5; R^3=Ph, CO_2Et

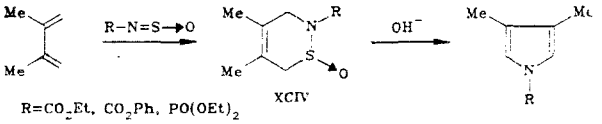
When a dry benzene solution of 1,3-oxazepine, XCII, is passed through a quartz column containing pyrex spirals, 1-formyl-2-phenylpyrrole, XCIII, and hydroxypyridine are formed as a result of the pyrolysis (450...550°C) [97].



XCII XCIII

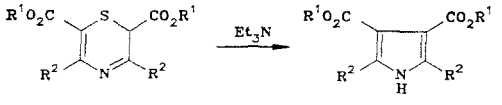
During the reaction, pyrrole XCIII is converted into a mixture of isomeric 2-phenylpyrroles having a CHO group in the 1, 3, 4, or 5 position.

2.3.4. Pyrroles from Heterocycles Containing Sulfur and Nitrogen. By treatment of 3,6-dihydro-1,2-thiazine-1-oxides, XCIV, forming the reaction of N-sulfinylic compounds with 2,3-dimethylbutadiene, with alcoholic alkalies at (78°C, 1.5 h), 3,4-dimethylpyrrole is obtained in 40...60% yield [98-100].



R=CO_2Et, CO_2Ph, $PO(OEt)_2$ XCIV

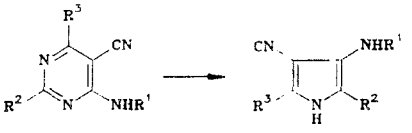
Thiazines XCV lose sulfur on treatment with triethylamine, forming pyrroles XCVI [101].



XCV XCVI

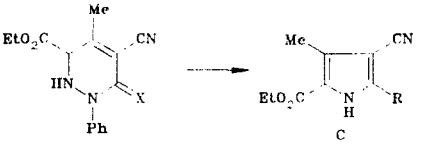
R^1=Alk; $R^2=C_nF_{2n+1}$, n=2-13

2.3.5. Pyrroles from Heterocycles with Two Nitrogen Atoms. The synthesis of 2,5-disubstituted 3-arylamino-4-cyanopyrroles, XCVIII (52...80% yield), by the ring contraction of 2,6-disubstituted 4-arylamino-4-cyanopyrimidines, XCVII, on their reaction with zinc in acetic acid (110...120°C, 3 h) [102, 103].



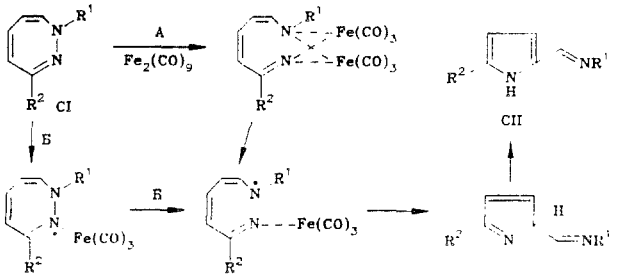
XCVII R^1, R^2, R^3=Ar XCVIII

Pyrroles C are obtained in the same way from pyridazines XCIX [104].



XCIX X=NH, O; R=NH_2, OMe, NHPh

When diazepines CI react with $Fe_2(CO)_9$, pyrroles CII are evolved along with the known π-complexes of iron in 45...72% yield [105].

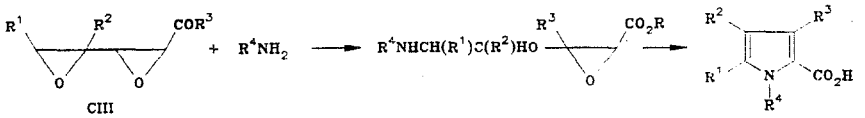


R^1=CO_2Et, COMe, COPh, Ts, SO_2Ph; R^2=H, Me

When R^2 = H, pyrroles is the major product of the reaction. It is formed as the result of the coordination of an $Fe(CO)_3$ group either at the single nitrogen ($N_{(2)}$ atom with the subsequent breaking of the N—N bond (path B) or at both nitrogen atoms, in which case two $Fe(CO)_3$ groups participate with the simultaneous breaking of the N—N bond (path A).

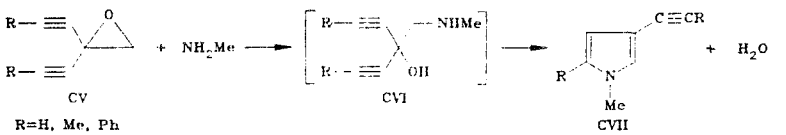
2.4. Reactions with Ring Enlargement

2.4.1. Pyrroles from Functionally Substituted Oxiranes. Diepoxides CIII are converted into pyrroles CIV when treated with primary amines in aqueous, alcoholic base [106].



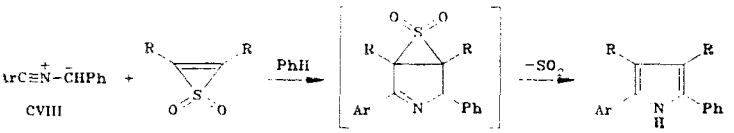
CIII R=Et, i-Pr; R^1=H, Ph; R^2=H, Me; R^3=Me, Ph; R^4=Me, Bz CIV

Diacetylenic α-oxides, CV, at room temperature or on slight heating (30...40°C) cyclize with methylamine into 4-alkynylpyrroles, CVII via the formation of diacetylenic amino alcohols CVI [107].



CV R=H, Me, Ph CVI CVII

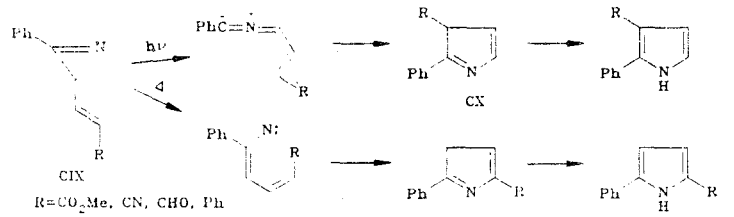
2.4.2. Pyrroles from Three-membered Sulfur Heterocycles. The reaction of nitrile ylid CVIII with thiirene dioxide in benzene (20°C, 9 h) leads to the formation of pyrroles [108]. 1,4-Thiazine-1,1-oxide is the major reaction product, which they explain by the rearrangement of the intermediate cycloadduct, the splitting off of sulfur dioxide from which gives the pyrroles.



R = Ph(34%), Me(15%); Ar = 4-$NO_2C_6H_4$

2.4.3. Pyrroles from Azirines. A large number of the papers published on the synthesis of pyrroles from azirines and aziridines were reviewed earlier [109]. Consequently, only work of the past decade not described in [109] will be briefly discussed in this review.

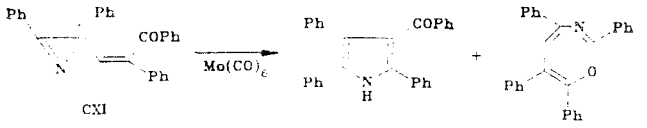
2.4.3.1. Thermal and Photochemical Cyclization of Azirines. Depending on conditions, vinylazirine, CIX, can rearrange via different mechanisms [110]. Thus, on its photolysis in benzene, an intramolecular addition of the nitrile ylid that is forming and the subsequent [1,3]-shift of hydrogen in the pyrrolene, CX, lead to the formation of 2,3-disubstituted pyrrole. On the other hand, the thermolysis of vinylazirine, CIX, leads to 2,5-disubstituted pyrroles (through an intermediate vinylnitrene).



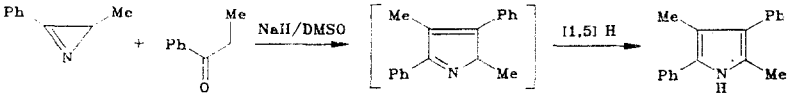
R = CO_2Me, CN, CHO, Ph

2.4.3.2. Cyclization of Azirines in the Presence of Metal Complexes. Often catalysis by metal complexes is used in the syntheses of pyrroles from azirines. Thus, for example, the reaction of with activated ketones leading to pyrroles in quantitative yield is catalyzed by bis(2,4-pentanedionato)nickel [111].

The rearrangement of ketovinylazirine CXI at room temperature [$Mo(CO)_6$, THF, 30 h] gives a mixture of pyrrole and oxazepine [112].



2.4.3.3. Cyclization of Azirines with Unsaturated Compounds. The nucleophilic attack on methylphenylazirine by the carbanion of ethyl phenyl ketone, generated in the superbasic system of NaH/DMSO, with a subsequent rearrangement of the intermediate leads to 2,4-diphenyl-3,5-dimethylpyrrole in 90% yield [113, 114].

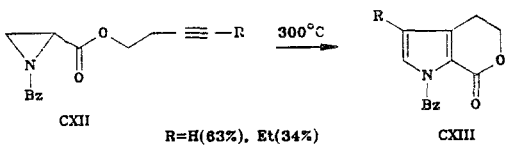


N,N-Trimethylhydrazonium salts under these conditions also give pyrroles, probably via a 2-phenylazirine intermediate [113].

2.4.4. Pyrroles from Functionally Substituted Azirines. N-Alkyl- and N-arylazirines form, on ring opening, azomethinylides, which react with acetylenes or olefins to form substituted pyrroles or pyrrolidines. This reaction of 1,3-dipolar addition has a high regio- and stereospecificity with the majority of dipolarophiles. The yield of the cycloadducts depends on the electronic characteristics of the substituents on the dipolarophile. As dipolarophiles in this reaction, methyl-4-(tert-butyldimethylsilyloxy)-1-butynyl ketone [115], tolan, diphenylacetylene, 1,4-diphenylvinylacetylene [116, 117], other acetylenes $R^1C{\equiv}CR^2$ (R^1 = CO_2Me, H, Ph; R^2 = CO_2Me, Ph, CN) [118-121], chlorotrifluoroethylene, [122], and perfluoropropene and perfluorobutene [123].

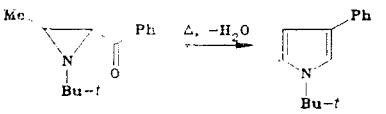
The reaction with alkynes takes place on boiling the reactants in aromatic hydrocarbons [115-121]; with alkenes, on heating the reactants for 12 h at 180°C in an autoclave followed by boiling the pyrrolidine formed with sodium methoxide [122, 123].

Pyrroles CXIII and CXIV are obtained by the intramolecular cyclization of some functional derivatives of aziridines [115, 124]. Thus, on vacuum pyrolysis (300°C) of aziridine CXII, the intramolecular cycloaddition of it to the pyrrole CXIII formed is observed [115].



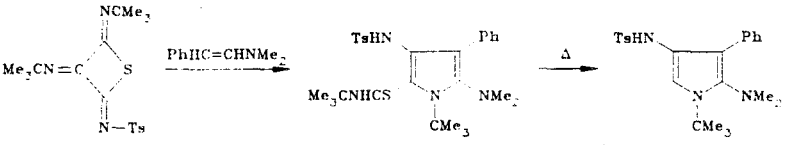
CXII CXIII

On the thermolysis of cis- and trans-aziridinyl ketones in methanol at 120°C for 3 h, N-tert-butyl-3-phenylpyrrole (CXIV) is formed in 80% yield [124].



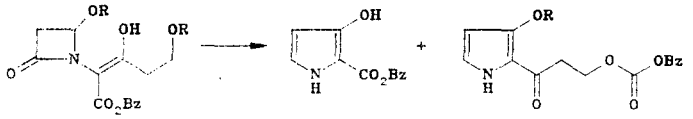
CXIV

2.4.5. Pyrroles from Other Small Heterocycles. Tris(imino)thietanes, CXV, react with trans-β-dimethylaminostyrene to form pyrroles CXVI and CXVII in 71...84% yield [125] via the scheme:



CXV CXVI CXVII

4-Substituted azetidinones, CXVIII in the presence of acetic acid (Me_3N, 20°C, 7 days) are changed to a mixture of pyrroles CXIX and CXX [126].



CXVIII CXIX CXX

R=COMe, Me, CO

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