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HYDROFURANS IN THE SYNTHESIS OF HETEROCYCLES — A REVIEW

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The use of hydrofurans in the synthesis of heterocyclic compounds is reviewed.

Hydrofuran derivatives have been widely used as reagents. This results from their great reactivity in combination with the possibility of obtaining them from cheap sources — furfural, furan, and tetrahydrofurfuryl alcohol [1]. Recently satisfactory methods have been developed based on hydrofurans for the synthesis of many 5- and 6-membered nitrogen-containing heterocycles, furans, thiophenes, tropinones, monosaccharides, and a number of condensed systems.

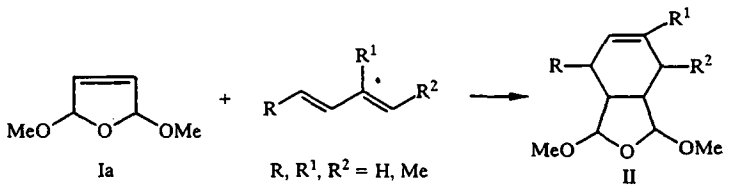
The extensive material on the use of hydrofurans in heterocyclic synthesis has not yet been reviewed. We have decided to give a survey of methods and not a complete bibliography on the use of these compounds, which could not be contained within a single paper. For example the Clauson-Kass method for the synthesis of pyrroles alone has been cited as a routine procedure in tens of publications and patents. The literature on 2,5-dialkoxyhydrofurans is cited in a volume in which N. Él'ming has presented an additional review of these compounds [2].

1. DIHYDROFURANS

Most reactions of dihydrofurans which lead to the formation of other heterocycles can be divided into two large groups:

a) various types of cycloaddition to the double bond with the formation of stable adducts which then undergo further conversions;

b) nucleophilic scission of the C–O bond with recyclization (intramolecular recyclization is possible if a substituent on the furan ring contains a nucleophilic group in the chain).



Tetrahydrophthalanes (II) can be obtained by the addition of 1,3-butadiene and other dienes to 2,5-dimethoxy-2,5-dihydrofuran (Ia) [3, 4].

The unsubstituted adduct IIa (R = R^1 = R^2 = H) is used in the synthesis of isoindole [5] and porphyrins [6]. The authors of the latter paper boiled compound IIa and its oxide (III) with benzyl carbamate in glacial acetic acid for many hours to give pyrroles which were converted further into the corresponding porphyrins (IV and V).

*Deceased.

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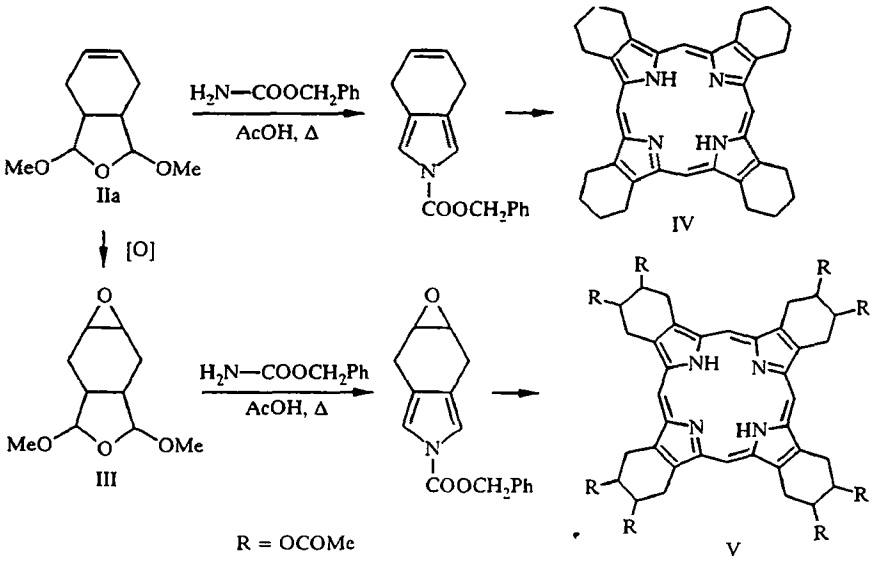
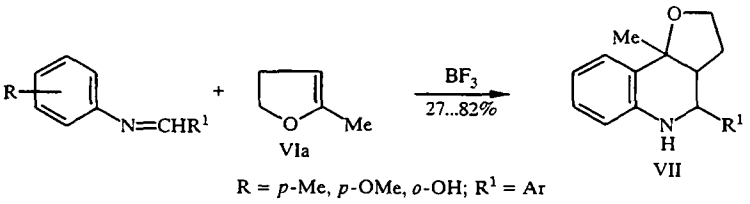
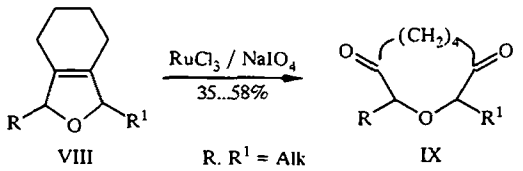


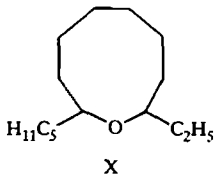
Derivatives of tetrahydroquinoline (VII) were synthesized by the cycloaddition of 4,5-dihydrosylvane (VIa) to aromatic imines [7]:



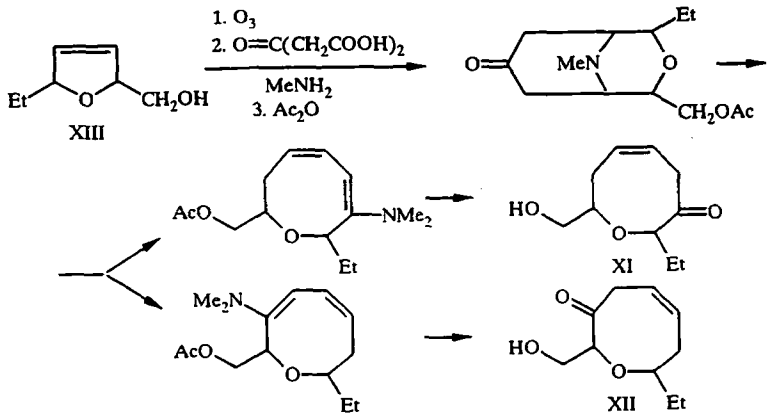
9-Membered oxacycles (IX) were obtained by oxidative scission of the tetrahydrophthalanes (VIII) in the presence of $RuCl_3/NaIO_4$ [8]:



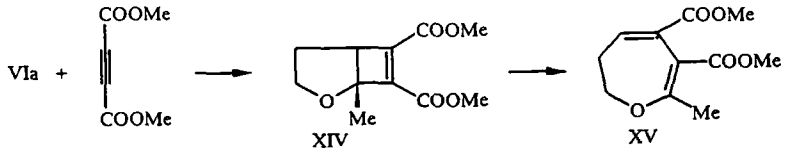
This method was used for the synthesis of obtusane X which contains the basic skeleton of obtusenine, a metabolite of the red alga *Laurensia*.



8-Membered oxacycles (XI, XII), which are the predecessors of laurensine, were obtained in a few steps from 5-ethyldihydrofurfuryl alcohol (XIII) [9]:

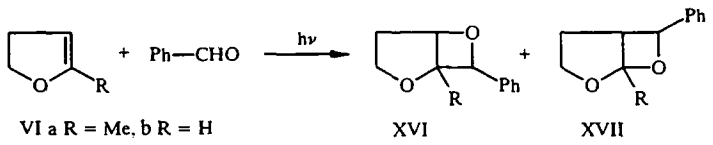


Nicolau et al. [10] studied the addition of methyl acetylenedicarboxylate to 2,3-dihydrofuran (VIb), 2,3-dihydropyran and 4,5-dihydrosylvane (VIa). The bicycle (XIV) obtained in the last case was then recyclized into the 7-membered oxacycle (XV) by heating for 12 h at 200°C:

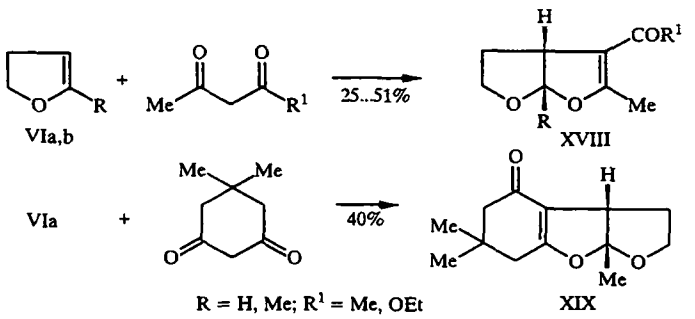


It was noted in the same paper that the corresponding adduct from 2,3-dihydrofuran appeared to be extremely thermally stable. It did not undergo recyclization even at 700°C right up to the start of pyrolysis.

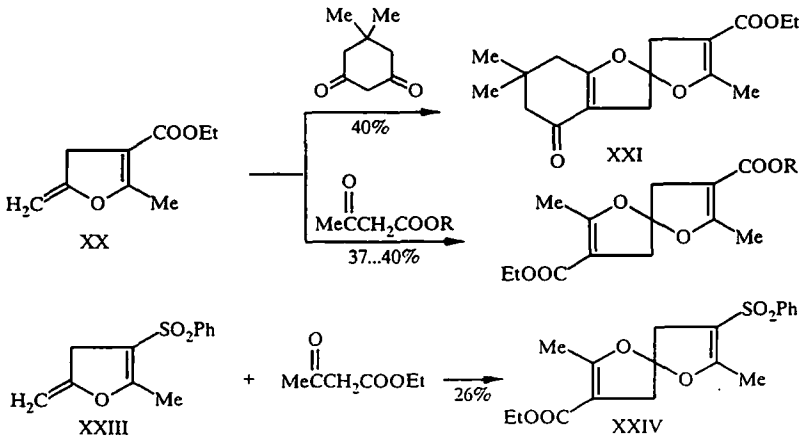
Photochemical cycloaddition of benzaldehyde to 4,5-dihydrosylvane VIa and 2,3-dihydrofuran VIb gave 1,4-dioxabicyclo[3.2.0]heptanes (XVI) with yields of 68-98% [11]. The reaction occurred very selectively. The amount of the isomeric bicycles (XVII) did not exceed 2% of the reaction mass:



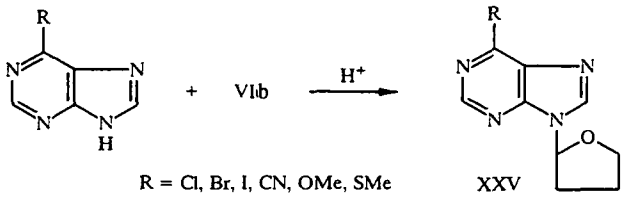
Derivatives of 2,8-dioxabicyclo[3.3.0]octene (XVIII, XIX) were formed in moderate yield in the manganese acetate promoted addition of 1,3-dicarbonyl compounds to the dihydrofurans VIa and b [12]:



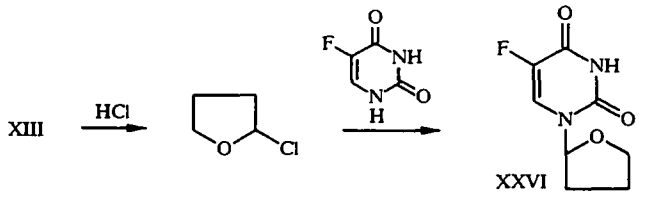
Under the same conditions the spirocyclic products XXI and XXII were obtained from 3-carbethoxy-2-methyl-5-methylene-4,5-dihydrofuran (XX). The sulfur analog of ester XX (XXIII) added acetoacetic ester to give the spirane (XXIV):



A very important aspect of the use of 2,3-dihydrofuran VIb is in the synthesis of tetrahydrofuranyl derivatives of purine and pyrimidine bases [13]. For example, addition of this compound to 6-substituted purines gave tetrahydrofuryl derivatives of the purine bases (XXV) [14-16]:

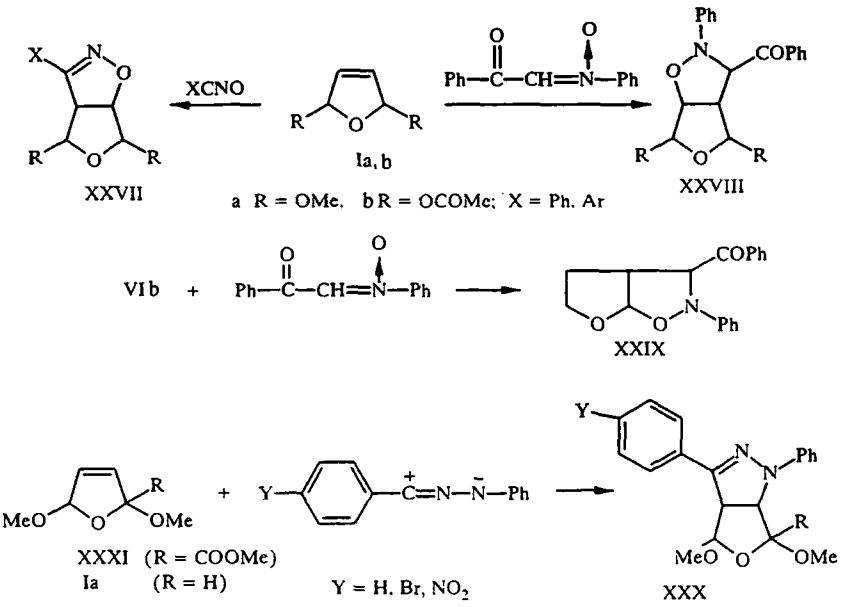


1-(2-Tetrahydrofuryl)uracil was obtained by the reaction of activated derivatives of uracil with 2,3-dihydrosylvane VIb [17, 18]. Addition of HCl to VIb gave 2-chlorotetrahydrofuran which gave the anti-tumor agent fluorafur (XXVI) on reaction with fluorouracil:

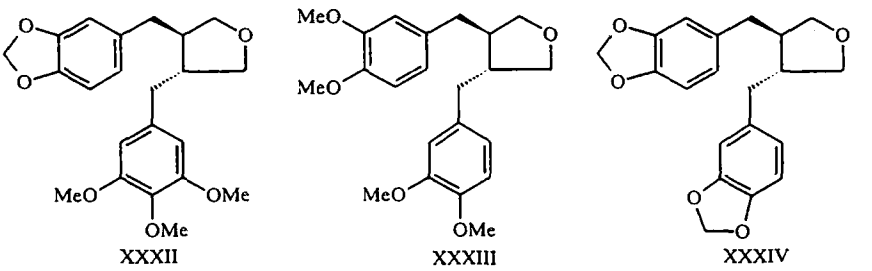


The dihydrofuran VIb reacted with thymidine in the presence of *p*-toluenesulfonic acid to give 3- and 3′-O-(2-tetrahydrofuryl)thymidine or 3′,5′-di-O-(2-tetrahydrofuryl)thymidines depending on the conditions [19].

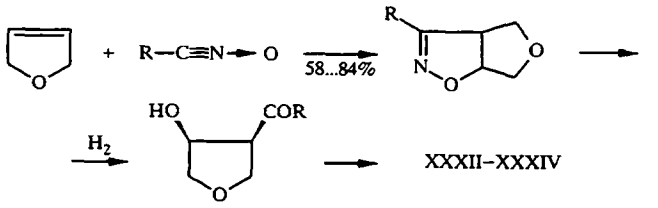
The condensed isoxazoles (XXVII-XXIX) and pyrazoles (XXX) were synthesized by 1,3-dipolar cycloaddition to the dihydrofurans Ia, Ib, VIb and XXXI of nitrile oxides, diarylnitrilimines and C-benzoyl-N-phenylnitrone respectively [20-27]:



The dipolar cycloaddition of nitrile oxides to 2,5-dihydrofuran is the key step in the syntheses of the tetrahydrofuryl lignanes (−)burserane (XXXII), (−)-brassilignane (XXXIII) and (−)-dehydroxycubebine (XXXIV) [28]:

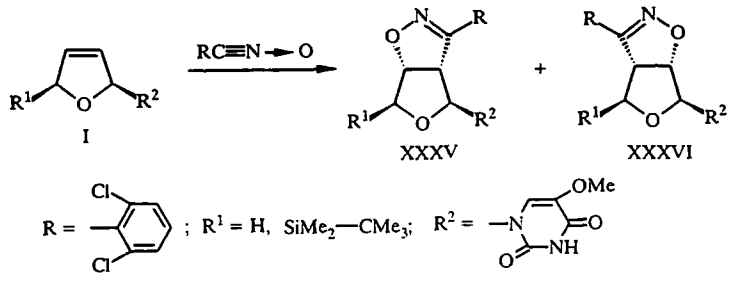


The isoxazoles synthesized in the first step underwent reductive scission to give 3-hydroxy-4-acyltetrahydrofurans which were the precursors of the desired lignanes XXXII-XXXIV:

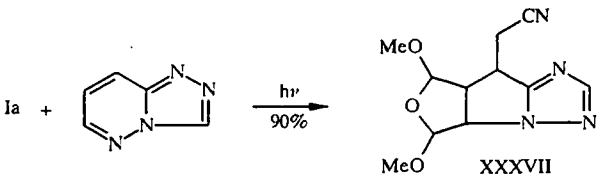


2,3-Dihydrofuran was also used for the synthesis of *dl*-isoretronecanol [29].

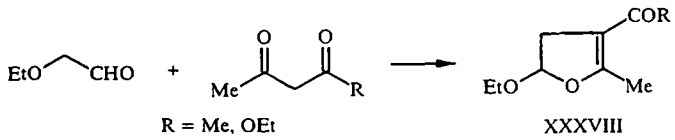
The tetrahydrofuroisoxazoles XXXV and XXXVI prepared from the dihydrofurans I were studied for antimicrobial activity [30]. The yields of these compounds varied from 67 to 96% and the ratio XXXV:XXXVI varied from 3:2 to 3:1 for different substituents.



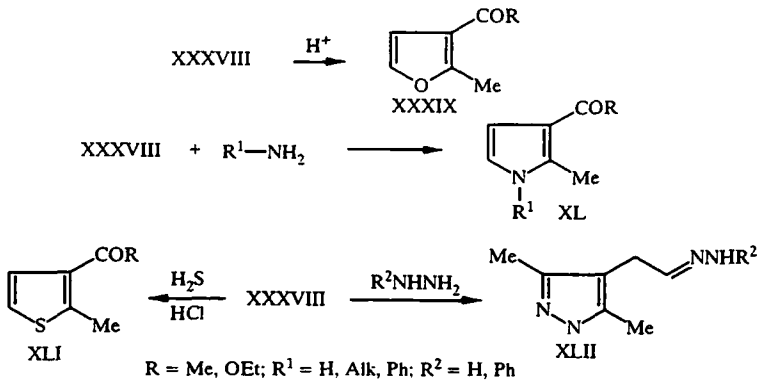
New heterocyclic systems, XXXVII in particular, were obtained by photochemical addition of *s*-triazolo[4,3-*b*]pyridazine to 2,5-dimethoxy-2,5-dihydrofuran Ia and other cycloolefins [31]:



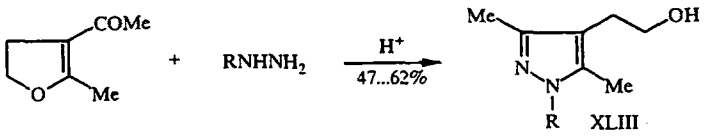
The promising reagents 3-acetyl- and 3-carbethoxy-4,5-dihydrofuran (XXXVIII) were prepared from ethoxyacetaldehyde and 1,3-dicarbonyl compounds [32, 33]:



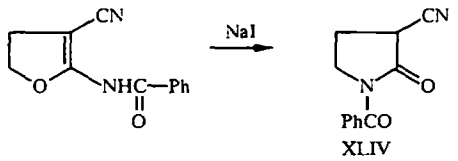
One step syntheses based on compound XXXVIII have been developed for the synthesis of 3-functionally substituted furans, pyrroles, thiophenes, and pyrazoles (XXXIX-XLII) [34-37]:



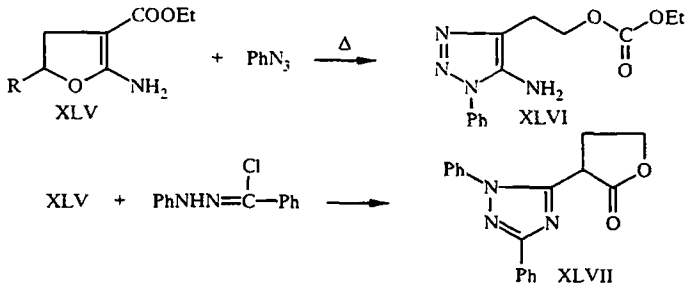
3-Acetyl-4,5-dihydrosylvane reacted with hydrazine and its derivatives to give hydroxyethylpyrazoles (XLIII) in average yield [38]:



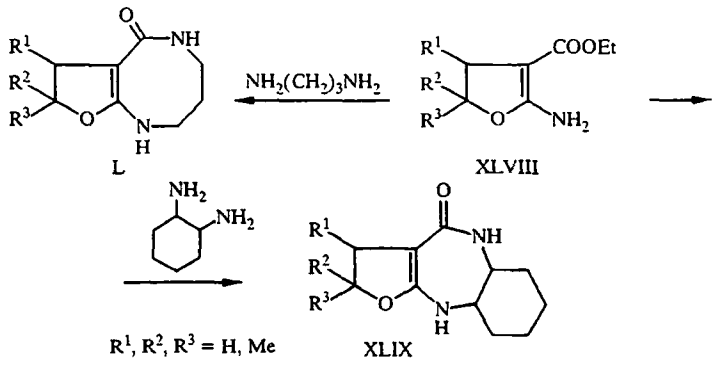
Recyclization of 2-benzoylamino-3-cyano-4,5-dihydrofuran in the presence of sodium iodide gave the pyrrolidone (XLIV) [39]:



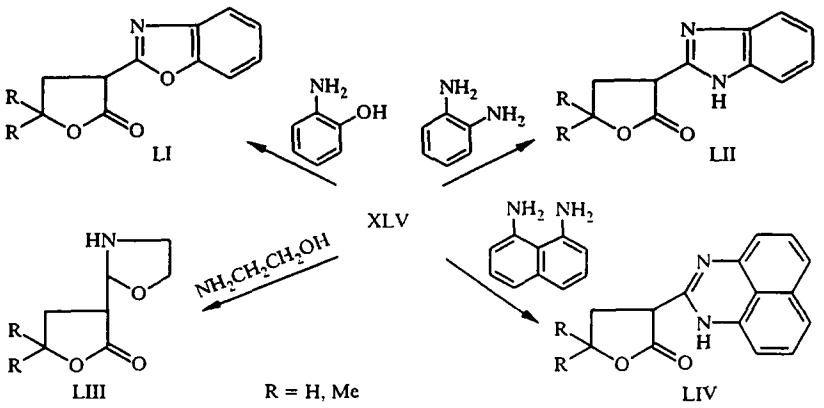
Wamhoff et al [40-44] have studied a variety of reactions of 2-amino-4,5-dihydrofurans. Condensation of 2-amino-3-carbethoxy-4,5-dihydrofurans (XLV) with phenyl azide and benzphenylhydrazonochloride gave functionally substituted triazoles (XLVI, XLVII) [40]:



Benzo[*b*]furo[2',3'-*e*][1,4]diazepins (XLIX) and furo[2,3-*b*]diazocins (L) were synthesized by the reaction of the aminoesters XLVIII with 1,2-diaminocyclohexane and 1,3-diaminopropane respectively [41]:

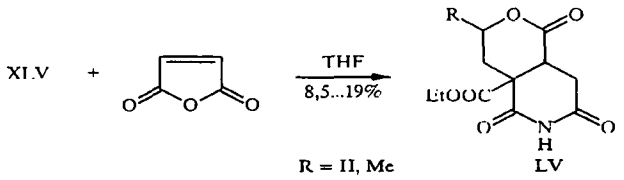


The reactions of compound XLV with aromatic amines and aminoethanol occurred quite differently to give butyrolactones (LI-LIV) with 3-heteraryl substituents:



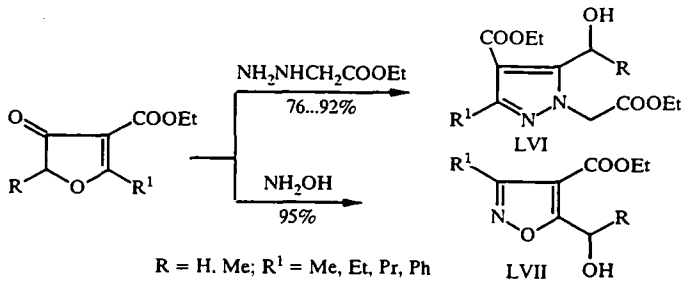
A mechanism for the reactions is proposed in the same paper.

The dihydrofurans XLV react with maleic anhydride even at room temperature to give small yields of pyranopiperidones (LV) [42]:

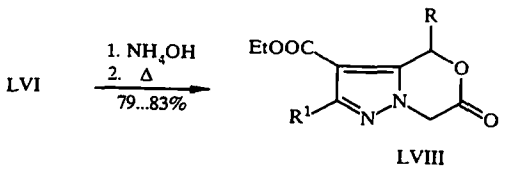


A wide range of new functionally substituted azolopyrimidines was obtained by condensation of the esters XLV and 2-amino-3-cyano-4,5-dihydrofurans with 3-aminopyrazoles, 3-amino-1,2,4-triazoles and 2-aminobenzimidazoles [43, 44].

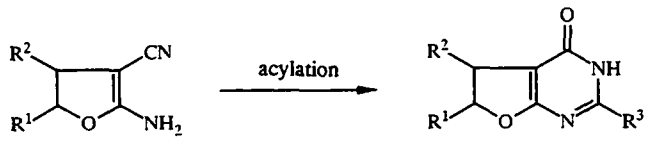
Gelin et al. [45, 46] synthesized functionally substituted pyrazoles (LVI) and isoxazoles (LVII) in high yields by the condensation of 3-carbethoxy-4-oxo-4,5-dihydrofurans with ethyl hydrazinoacetate and hydroxylamine respectively:



The pyrazoles LVI can be further converted into 4H-pyrazolo[5,1-*c*][1,4]oxazines (LVIII):

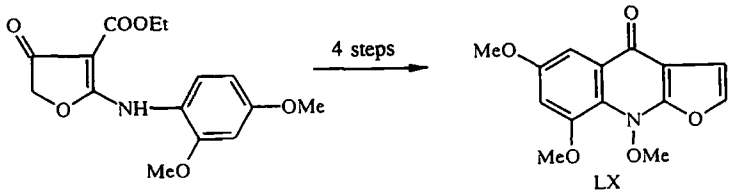


A method for preparing fluoropyrimidines (LIX) by the acylation of 2-amino-3-cyano-4,5-dihydrofurans is described in a Japanese patent [47]:

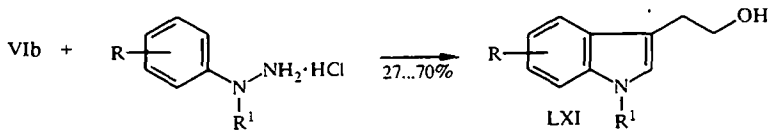


R^1, R^2 = Alk, Ph, Het; R^3 = Alk, Ar, Het

Synthesis of the alkaloid isomasculosidine (LX) was based on 4-carbethoxy-5-(2,4-dimethoxyphenylamino)-3(2H)-furanone [48]:

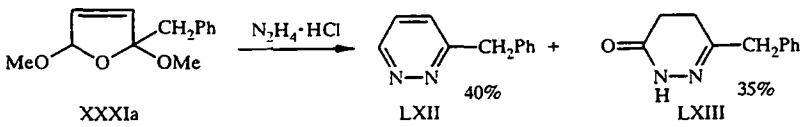


The interaction of 2,3-dihydrofuran VIb with arylhydrazine salts under Fisher condition gave tryptophols (LXI) [49]:

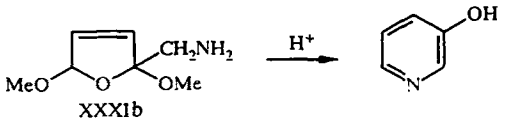


A known method for the synthesis pyridazines includes the reaction of 2,5-dialkoxy-2,5-dihydrofurans with hydrazine.

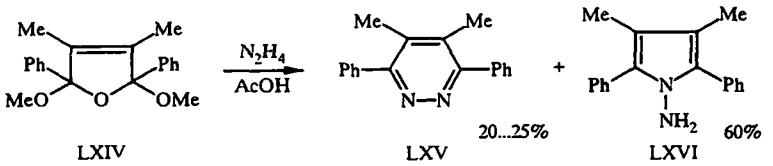
As a result of the reaction of 2-benzyl-2,5-dimethoxy-2,5-dihydrofuran with hydrazine hydrochloride in sodium pyrophosphate buffer Heinisch and Huber [50] obtained not only the desired product (LXII) but also a reasonable yield of the pyridazin-3-one (LXIII):



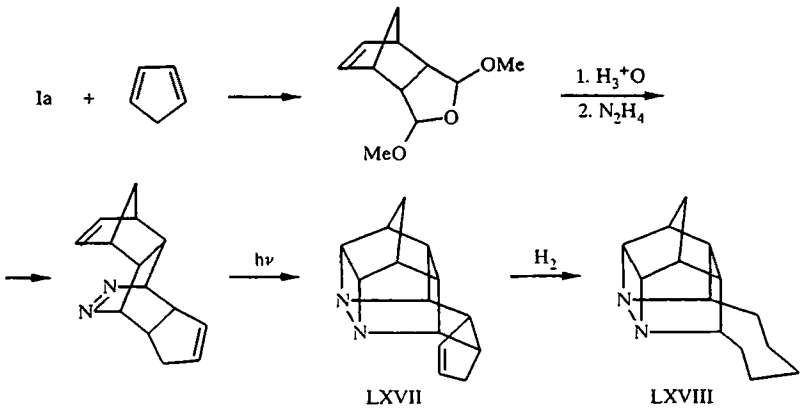
3-Hydroxypyridine was obtained by recyclization of 2-aminomethyl-2,5-dimethoxy-2,5-dihydrofuran XXXIb [51]:



Recyclization of 2,5-dialkoxy-2,5-dihydrofuran (LXIV) with hydrazine gave derivatives of pyridazine LXV and N-aminopyrrole (LXVI) [52]:

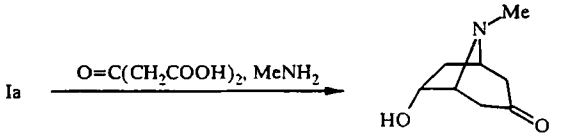


N-Heterocycles with new skeletons (LXVII, LXVIII) were synthesized from 2,5-dimethoxy-2,5-dihydrofuran Ia.



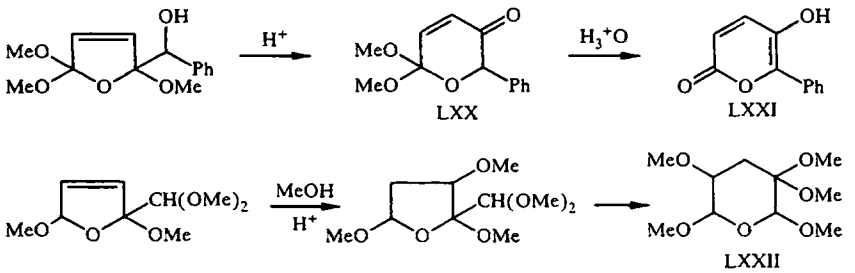
LXVII LXVIII

6-Oxytropinone (LXIX) was obtained for the first time from 2,5-dialkoxy-2,5-dihydrofuran Ia in the presence of methylamine and acetonedicarboxylic acid [54]. This reaction was used in the total synthesis of the alkaloid anisodamine [55]:



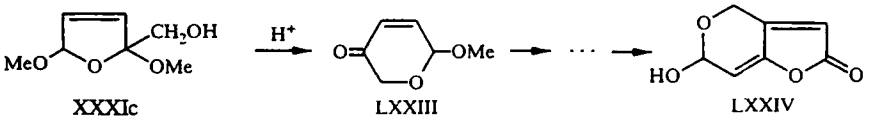
LXIX

Recyclization of 2,5-di- and 2-substituted 2,5-dialkoxy-2,5-dihydrofurans led to the pyran derivatives LXX-LXXII [56, 57]:



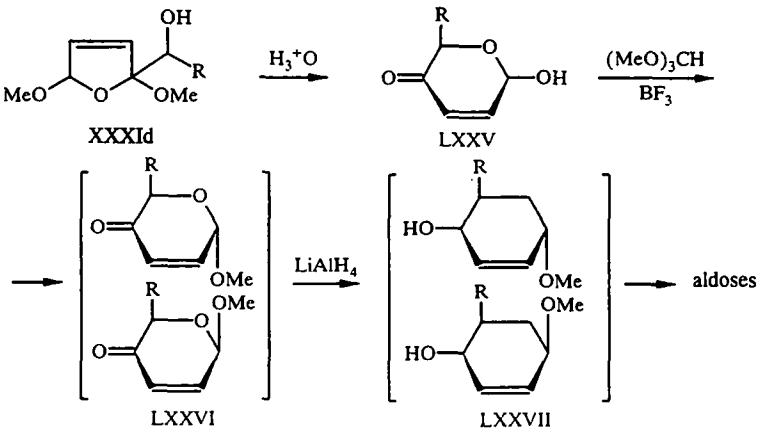
LXX LXXI LXXII

The pyranone (LXXIII), made from 2-hydroxymethyl-2,5-dimethoxy-2,5-dihydrofuran XXXIc, was converted into neopatulin (LXXIV) in several steps [58]:

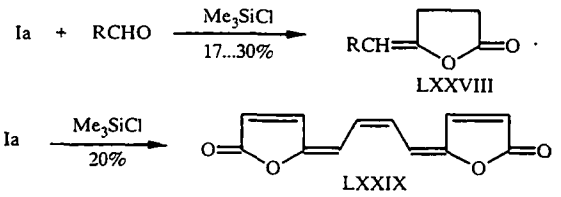


XXXIc LXXIII LXXIV

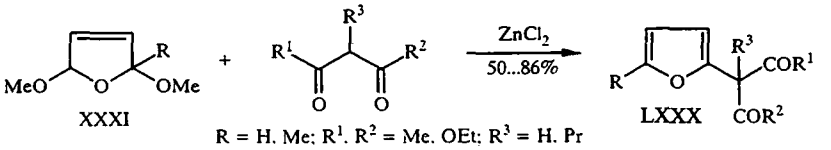
O. Akhmatovich [59, 60] proposed a new route for the synthesis of higher saccharides which included the recyclization of the 2,5-dialkoxy-2,5-dihydrofurans XXXId into the pyranosiduloses (LXXV) which were then converted into monosaccharides via the intermediate compounds LXXVI and LXXVII:



Reactions of 2,5-dialkoxy-2,5-dihydrofuran Ia with aldehydes in the presence of chlorotrimethylsilane [61-63] gave the furanones LXXVIII and LXXIX, but only in poor yields (17-30%):

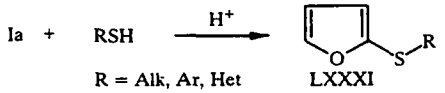


Italian chemists [64, 65] produced a new method for the synthesis of functionally substituted furanes (LXXX) from 2,5-dialkoxy-2,5-dihydrofurans of type XXXI and 1,3-dicarbonyl compounds:



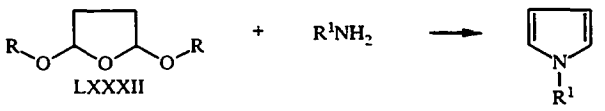
R = H, Me; R^1, R^2 = Me, OEt; R^3 = H, Pr

Silverman and Burness [66] proposed the synthesis of 2-furylthioethers by the ready reaction of 2,5-dialkoxy-2,5-dihydrofurans I with aliphatic and aromatic thiols in the presence of *p*-toluenesulfonic acid, e.g.,



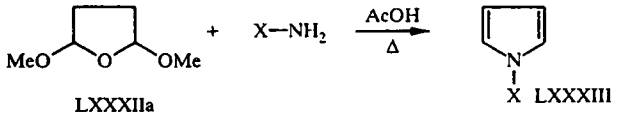
2. TETRAHYDROFURANS

In a discussion of the use of tetrahydrofurans in the synthesis of heterocycles, first place must be given to the Clauson-Kaas synthesis of pyrroles from 2,5-dialkoxytetrahydrofurans LXXXII and primary amines [67-69]:



The reaction is catalyzed by acids — phosphoric and hydrochloric acids have been used — and also aluminum oxide and zeolites. The most widespread technique is to boil the starting materials in glacial acetic acid. Sodium acetate is often added to the reaction mixture. The industrial synthesis of polyalkyl- and arylpyrroles in the gas phase over borosilicate zeolites and metal oxides is described in a patent [70]. Unsubstituted pyrrole has been obtained by passing a 1:3 mixture of 2,5-dimethoxytetrahydrofuran (LXXXIIa) and ammonia over a zeolite (94.2% SiO_2, 2.3% B_2O_3) at 400°C at a space velocity of 3 h^{-1}, with a yield of 85.7% with a 100% conversion of the tetrahydrofuran.

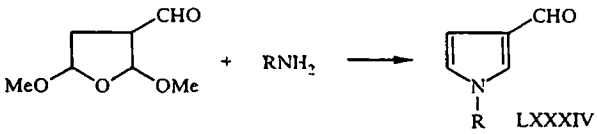
Amides and sulfonamides also react with 2,5-dialkoxytetrahydrofurans [71] to give average to excellent yields of N-arylsulfonylpyrroles (LXXXIII):



LXXXIIa LXXXIII

X = SO_2Ph, $SO_2C_6H_4Cl$-*p*, $SO_2C_6H_4OMe$-*p*, COPh etc.

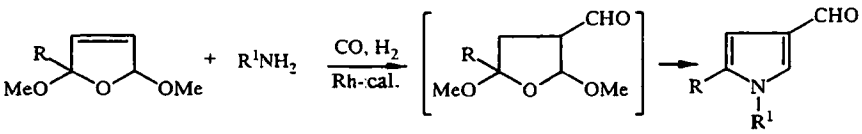
3-Formylpyrroles (LXXXIV) are frequently difficult to obtain because direct formylation of unsubstituted pyrrole occurs primarily at position 2. However these compounds can be easily obtained from 3-formyl-2,5-dialkoxytetrahydrofurans and primary amines [72, 73]:



LXXXIV

Hirsch et al [72] used urethane as the amine component and then decarboxylated the first formed N-carbethoxy-3-formylpyrrole to give unsubstituted 3-formylpyrrole in high yield.

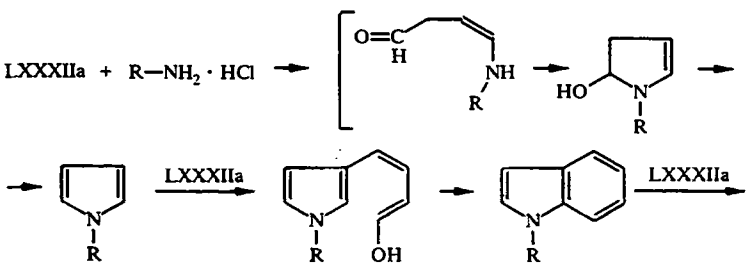
A. Lapidus and co-workers [74, 75] prepared 1,2,4-substituted pyrrole (LXXXV) indirectly from 2-R-2,5-dialkoxytetrahydrofurans via synthesis of the corresponding aldehydes followed by their amination:

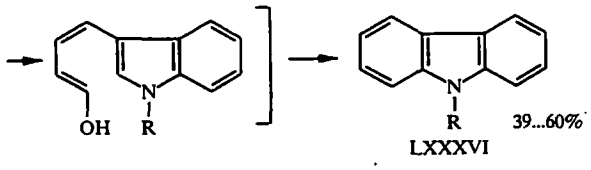


R = H, Me; R^1 = Me, Bu, Ph LXXXV

The process is carried out in an autoclave at 130°C, with a synthesis gas pressure of 10 MPa in the presence of a homogeneous rhodium catalyst. The relative disposition of the substituents in a series of products (LXXXV, R = Me) confirmed that the hydroformylation of unsymmetric 2,5-dialkoxytetrahydrofurans is regioselective.

Japanese chemists have reported an original method for the synthesis of carbazoles (LXXXVI) from 2,5-dimethoxytetrahydrofuran (LXXXIIa) and salts of primary amines [76]. A mixture of benzene and water used as the best solvent for both solutes and boiling was prolonged. Maximal yields were obtained with equimolar amounts of the reactants and a 25:1 benzene:water ratio. The following scheme is proposed for the reaction:





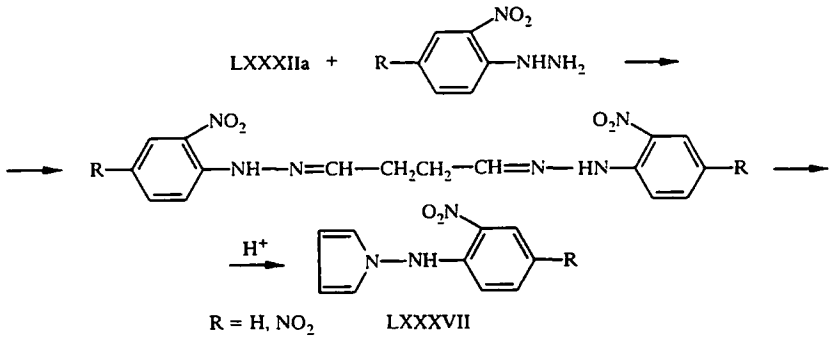
LXXXVI

R = Alk, CH_2CH_2OH, Ph, C_6H_4Me-*p*, C_6H_4OMe-*p*

It is interesting that pyrroles could not be converted into carbazoles in the presence of 2,5-dialkoxytetrahydrofurans under these conditions.

The influence of steric and electronic factors on the reaction of 2,5-dialkoxytetrahydrofurans with C-substituted anilines has been studied [77]. The yield of pyrroles is not reduced by the presence of electron donor substituents (Alk, OMe) at any position on the phenylamine. The reactivity of mono- and dinitroanilines depends on the relative positions of the nitro groups. The pyrrole from 3,5-dinitroaniline was obtained in 79% yield while that from 2-nitroaniline was obtained in only 34% yield. No pyrroles were obtained from reactions of 2,5-dialkoxytetrahydrofurans with either 2,4- or 2,6-dinitroanilines.

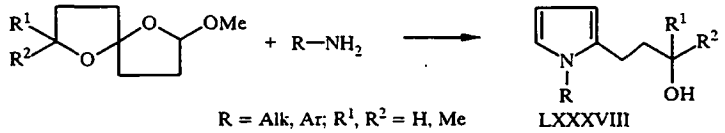
N-Arylaminopyrroles (LXXXVII) were obtained from 2,5-dialkoxytetrahydrofurans and phenylhydrazines in two steps [78]:



R = H, NO_2 LXXXVII

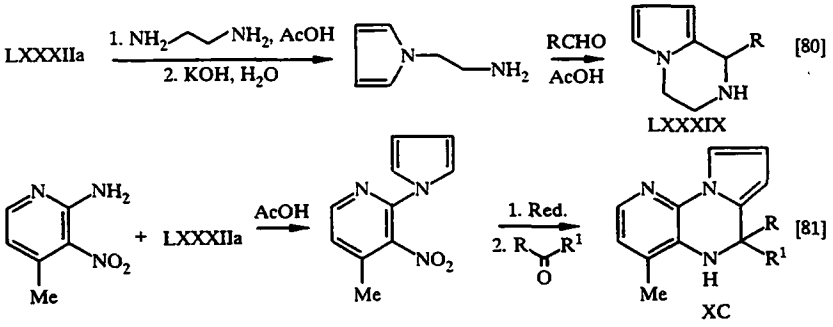
An excess of 2,5-dialkoxytetrahydrofurans led to the formation of indoles and carbazoles.

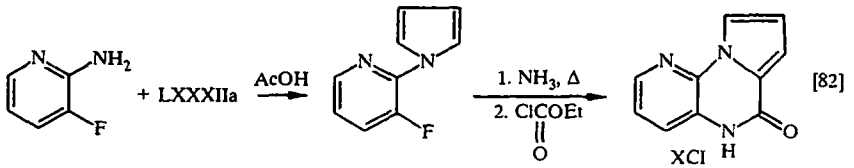
I. S. Monakhova and A. V. Malev synthesized a series of 2-(3-hydroxypropyl)pyrroles (LXXXVIII) in 42-98% yields by boiling primary amines with 1,6-dioxaspiro[4,4]nonanes [79]:

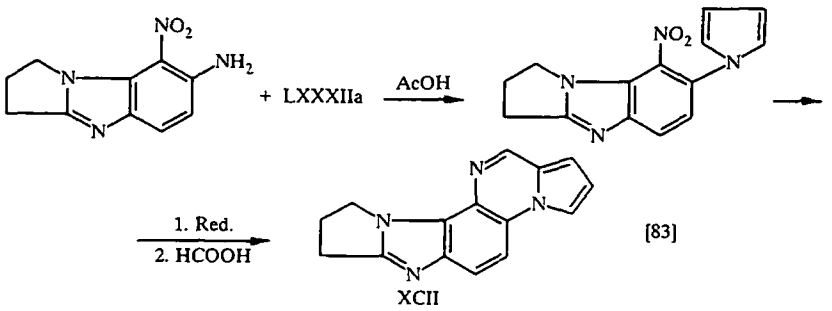


R = Alk, Ar; R^1, R^2 = H, Me LXXXVIII

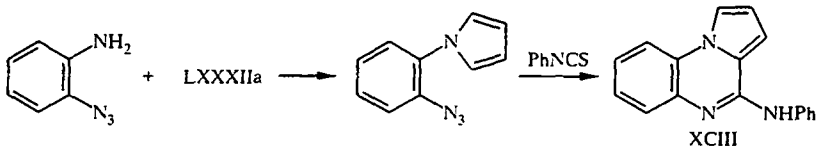
The 2,5-dialkoxytetrahydrofurans were treated with functionally substituted amines to obtain the condensed pyrroles LXXXIX-XCII. One stage of the synthesis involves cyclization at the α-position of the pyrrole ring.



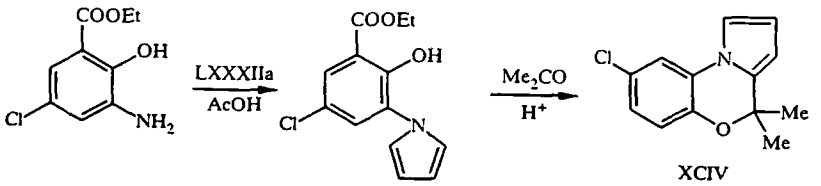




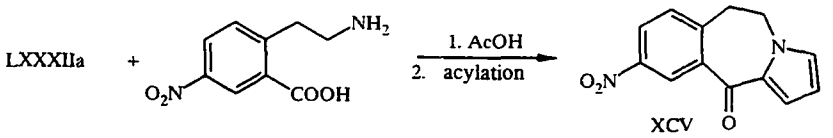
P. Molina et al. synthesized pyrrolo[1,2-*a*]pyrazine XCIII from 2,5-dimethoxy-2,5-dihydrofuran and 2-azidoaniline [84, 85]:



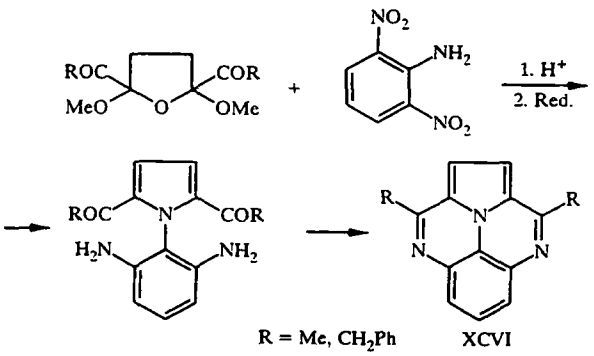
The 2,5-dialkoxytetrahydrofuran LXXXIIa was also used in syntheses of pyrrolobenzoxazines (XCIV) [86]:



and pyrrolobenzazepinones (XCV) [87]:

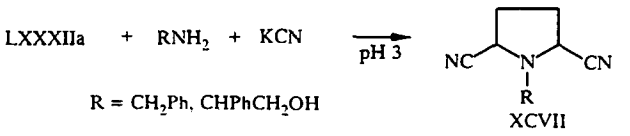


The synthesis and spectroscopic properties of 4,8,9b-triazacyclopenta[*c*,*d*]phenalenes (XCVI) have been reported [88]:



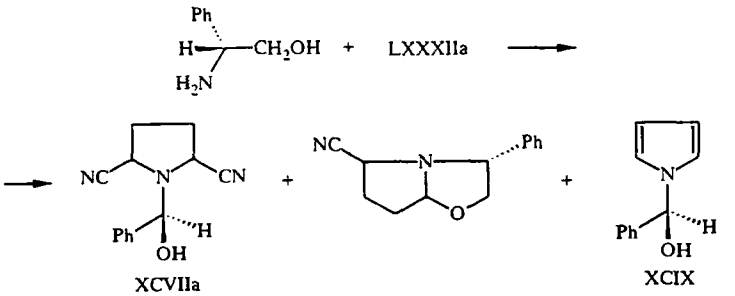
The Clauson-Kass has interesting uses in the chemistry of peptides. 2,5-Dialkoxytetrahydrofurans have been proposed as protecting groups for amino groups [89]. The amino group is regenerated in two steps: ozonolysis of the pyrrole and reduction with sodium tetrahydridoborate. A possible method for the photometric determination of primary amines is also based on reaction with a 2,5-dialkoxytetrahydrofuran [90].

2,5-Dicyanopyrrolidines XCVII were obtained from 2,5-dialkoxytetrahydrofurans LXXXIIa, primary amine, and KCN under conditions of the Robinson-Schopf condensation [91, 92]. The reaction was carried out in aqueous citric acid solution at room temperature:

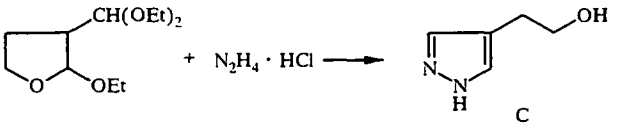


In the former paper [91] the isomeric compounds XCVII were separated by flash chromatography. However, small amounts of the corresponding pyrrole were also isolated and this became the only product when the reaction was carried out at pH 6.

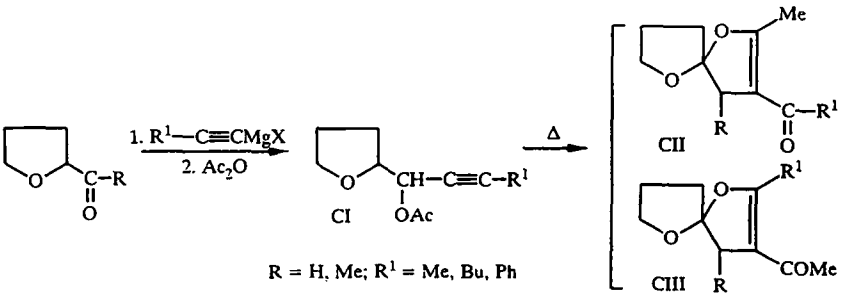
In the second study [92] the initial product of the reaction of the 2,5-dialkoxytetrahydrofuran with R-(−)phenylglycine was boiled in ethanol for 96 h to give the pyrrole (XCIX) and the pyrrolidine (XCVIIa):



The acetal of 2-ethoxy-3-formyltetrahydrofuran reacted with hydrazine hydrochloride to give the substituted pyrazole (C) as part of the synthesis of 4-(2-aminoethyl)pyrazole, an analog of histamine [93]:

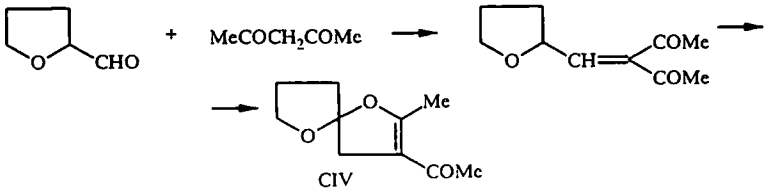


R. A. Karakhanov and co-workers have discovered an effective catalytic system for the oxidation of tetrahydrofurfuryl alcohol to tetrahydrofurfural [94] and they have also investigated the synthetic utility of this aldehyde. The propargyl esters (CI), which were obtained from tetrahydrofurfural and 2-acetyltetrahydrofuran, recyclized thermally into 2,3,4-substituted 1,6-dioxaspiro[4,4]non-2-enes (CII, CIII) [95, 96]:

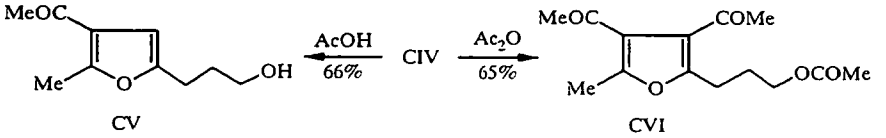


The isomeric spirocyclanes CII and CIII were separated by flash chromatography. Partial inversion of the substituents on long storage was noted.

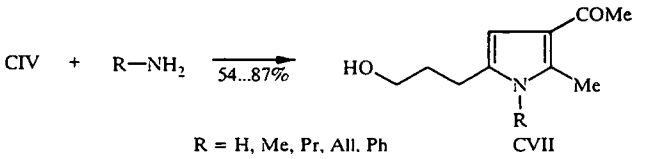
3-Acetyl-2-methyl-1,6-dioxaspiro[4,4]non-2-ene (CIV) was also obtained by condensation of tetrahydrofurfural with acetylacetone under Knoevenagel conditions with subsequent thermal isomerization [97]:



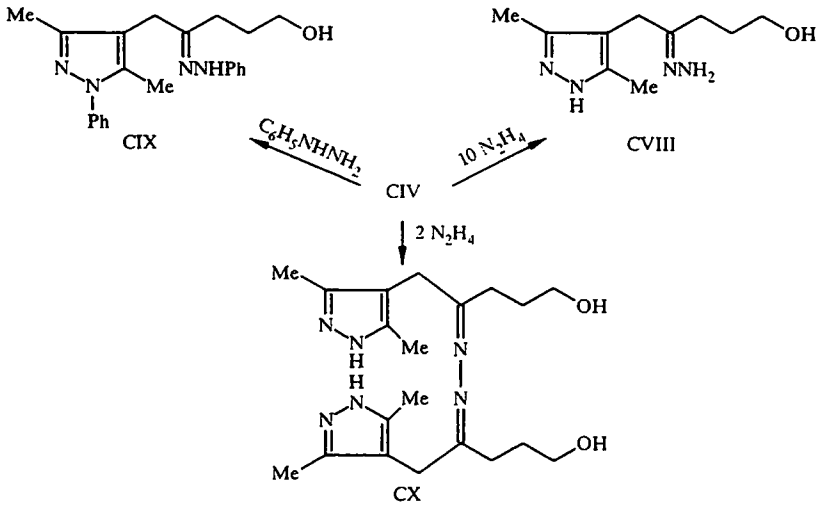
The spirocyclane CIV has considerable synthetic possibilities [97, 98]. On heating it with DMSO and acetic acid or acetic anhydride the substituted furanes CV and CVI were obtained:



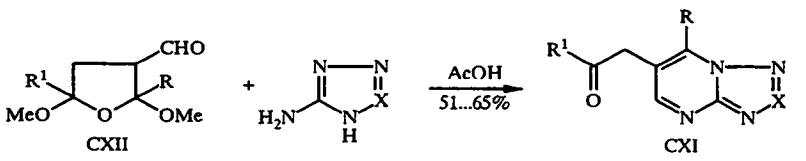
Compound CIV reacts particularly readily with primary amines to give 2-(3-hydroxypropyl)-3-acetylpyrroles (CVII):



Reaction of the spirocyclane CIV with hydrazine hydrate and phenylhydrazine under different conditions gave the pyrazole derivatives CVIII-CX:

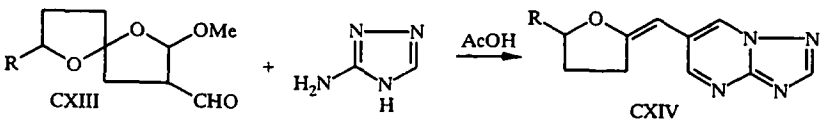


Condensation of 3-formyl-2,5-dimethoxytetrahydrofurans (CXII) with aminoazoles is a method for preparing 6-functionally substituted azolo[1,5-*a*]pyrimidines (CXI) [99, 100]:



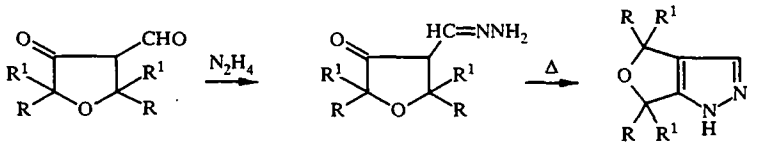
R = H, Me; R^1 = Me, CH_2OH, CH_2OMe, CH_2OCOMe; X = CH, N

The spiroanalogs of the aldehydes CXI-CXIII reacted with 3-amino-1,2,4-triazole to give triazolopyrimidine (CXIV) [101]:



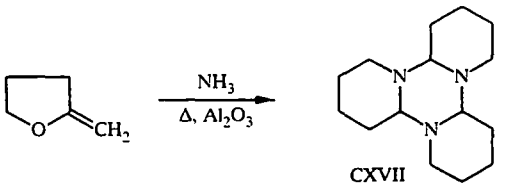
CXIII CXIV

3-Oxo-4-formyltetrahydrofurans (CXV) react with hydrazine in the normal way to give the hydrazone of the formyl group. When these compounds are sublimed in vacuum or heated above the melting point they are converted into condensed pyrazoles (CXVI) [102]:



CXV R, R^1 = H, Alk CXVI

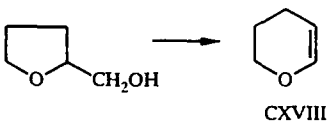
2-Methylenetetrahydrofuran reacts with ammonia over aluminum oxide to give α-tripiperidein (CXVII) [103]:



CXVII

One method for the preparation of furans is the demethoxylation of 2,5-dimethoxytetrahydrofurans. The pyrolysis of 3-formyl-2,5-dimethoxytetrahydrofuran has been patented as a preparative method for 3-formylfuran but the yield did not exceed 20% [104].

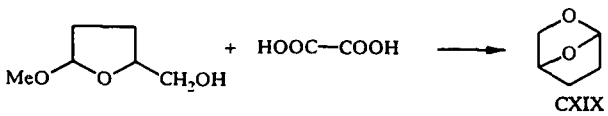
Rearrangements of tetrahydrofuryl alcohols have been used in the syntheses of oxygen containing heterocycles. R. Paul has proposed a method for the preparation of 3,4-dihydro-2H-pyran (CXVIII) [105]:



CXVIII

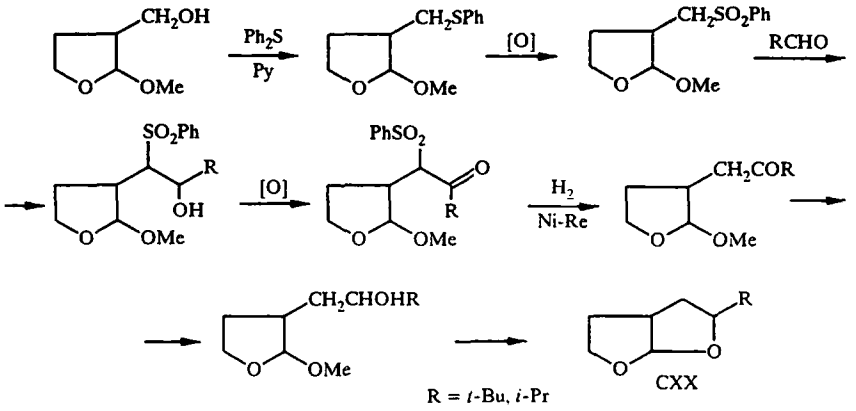
The carbonium ion mechanism of this reaction was demonstrated 30 years later using ^{14}C labelling [106].

2,7-Dioxabicyclo[1.2.2]heptane (CXIX) was obtained from 5-methoxy-2-hydroxymethyltetrahydrofuran and oxalic acid [107]:

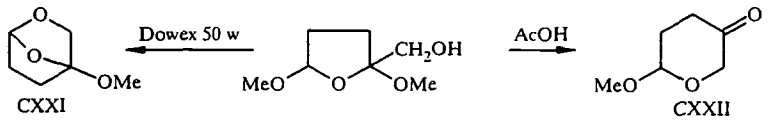


CXIX

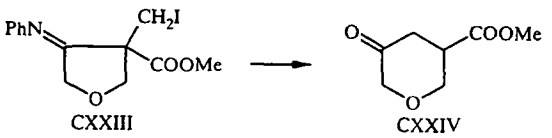
Alkyl substituted 2,8-dioxabicyclo[3.3.0]octanes (CXX) were synthesized from derivatives of tetrahydrofuran in several steps [108]:



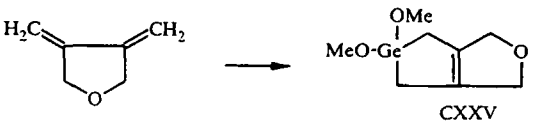
2,5-Dimethoxytetrahydrofurfuryl alcohol has been converted to compounds CXXI and CXXII depending on the conditions [109, 110]:



Methyl 3-oxotetrahydropyran-5-carboxylate (CXXIV) was prepared by free radical scission of the tetrahydrofuran ring of compound CXXIII [111]:

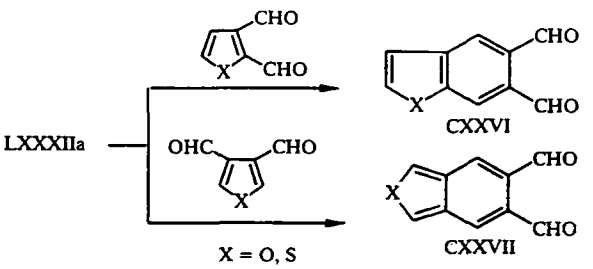


The germanium containing bicycle CXXV was synthesized from 3,4-bismethylenetetrahydrofuran [112]:



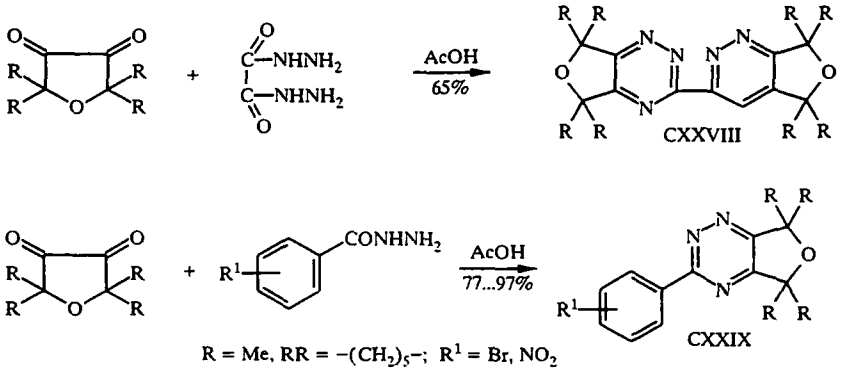
A patented method for the preparation of 3-formylthiophene from 2,5-dimethoxy-3-formyltetrahydrofuran includes the interaction of the latter with H_2S, alkali metal sulfide or hydrosulfide in the presence of a strong acid [113, 114].

Benzofurans and benzothiophenes (CXXVI, CXXVII) were obtained by condensation of 2,5-dialkoxytetrahydrofurans with diformylfurans and diformylthiophenes [115]:



Thiophene containing polymers were obtained based on 2,5-dialkoxytetrahydrofurans [116].

Kazakh chemists [117, 118] have synthesized derivatives of furo[3,4-*e*]1,2,4-triazines (CXXVIII, CXXIX) from 3,4-dioxatetrahydrofurans and hydrazides of oxalic and benzoic acids:



R = Me, RR = $-(CH_2)_5-$; R^1 = Br, NO_2

Thus hydrofurans have been successfully used in the synthesis of a variety of heterocyclic systems. Further studies in this field face real and important problems.

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