SYNTHESIS AND REACTIONS OF CONDENSED FURAN DERIVATIVES

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Synthesis of heterocyclic compounds containing a fused furan ring was studied. Substitution, addition and cycloaddition reactions of furo[3,2-*b*]pyrroles and their condensed derivatives involving the interesting transformations of furo[3,2-*b*]pyrrole system are presented.

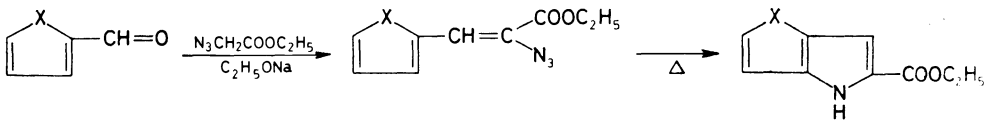
1. INTRODUCTION

During the last few years many results have been achieved in the area of the synthesis and the study of physical and chemical properties of heterocyclic compounds containing a furan ring fused with the different hetrocyclic systems.

Although these heterocycles have not previously been reviewed collectively, there are excellent reviews concerning some of the known systems[1-3]. The aim of this review is to present the chemistry of fused aromatic hetrocyclic systems containing the furan ring fused with five- or six-membered rings or their condensed derivatives and to present a wide versatility of 2-furaldehyde utilization in the synthesis of these compounds as well.

2. FURO[3,2-*b*]PYRROLES AND THEIR CONDENSED DERIVATIVES

Several furo]3,2-*b*]pyrrole derivatives were prepared by intramolecular cyclization involving nitrene intermediates. In view of the ease with which nitrenes can be generated by thermal decomposition of azido compounds or by the action of trivalent phosphorus reagents on nitroderivatives, the suitable insertion of such nitrene intermediates leads to annelated pyrrole systems. For example azidoacrylates[4-7] which were prepared by condensation of the appropriate heterocyclic aldehydes with ethyl azidoacetate, afforded upon thermolysis annelated pyrroles (Scheme 1).

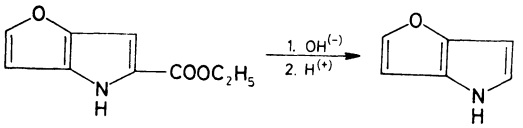


I *II* *III*

X = NH ; NCH_3 ; O ; S ; Se

SCHEME 1

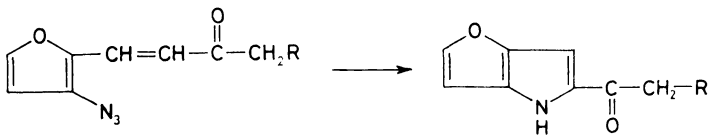
Hydrolysis of *III* (X = 0) and subsequent decarboxylation of the corresponding acid furnished the parent furo]3,2-*b*]pyrrole in low yield[8] (Scheme 2).



IV

SCHEME 2

Another way leading to furo[3,2-*b*]pyrrole derivatives, based on the thermolysis of 3-azidofuran derivatives has been reported by Gronowitz[9] (Scheme 3).

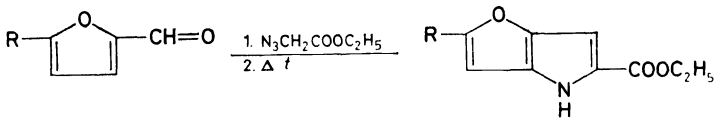


V *VI*

R = H , NO_2

SCHEME 3

By modification of the mentioned methods the series of 2-substituted furo[3,2-*b*]-pyrrole derivatives *VII* from 5-substituted-2-furaldehydes were prepared[10-14] (Scheme 4).

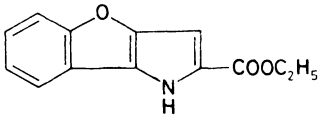


VII

R = CH_3, Br, C_6H_5, 4-$CH_3C_6H_4$, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 3,4-$Cl_2C_6H_3$, 3-CF_3-4-ClC_6H_3, 2-$NO_2C_6H_4O$, 2-CH_3-4ClC_6H_3O

SCHEME 4

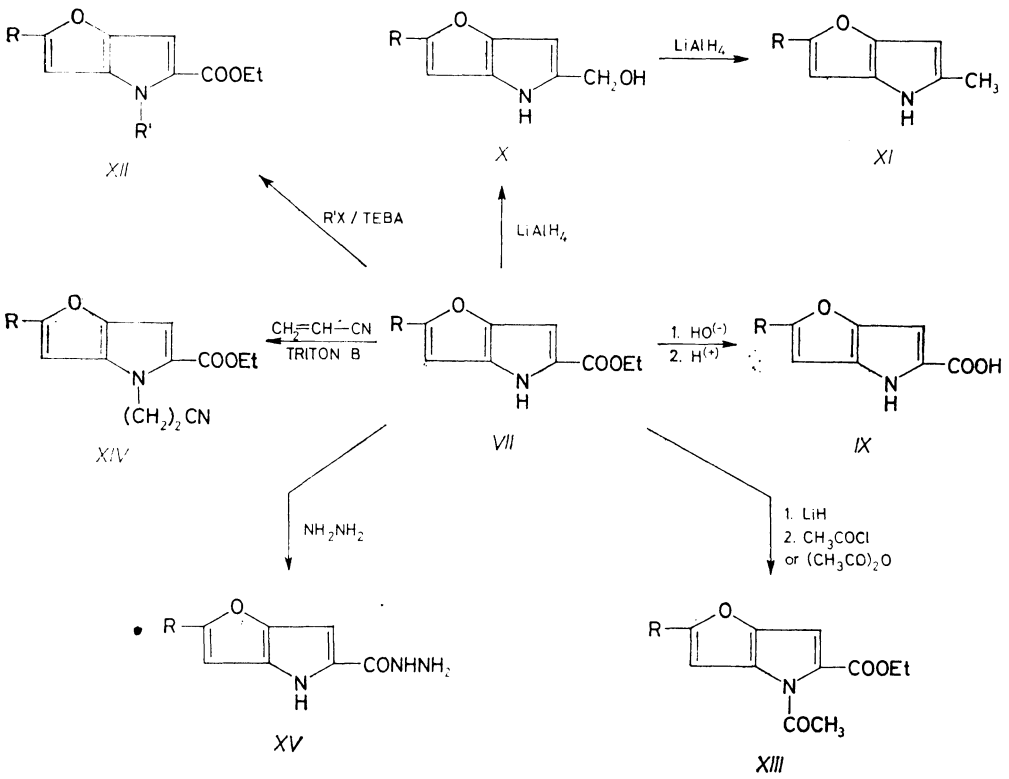
Analogously ethyl benzo[*b*]furo[3,2-*b*]pyrrole-2-carboxylate (*VIII*) from benzo-[*b*]furan-2-carbaldehyde was prepared[15].



VIII

2.1. *Reactions of Ethyl 4H-Furo[3,2-b]pyrrole-5-carboxylates (VII)*

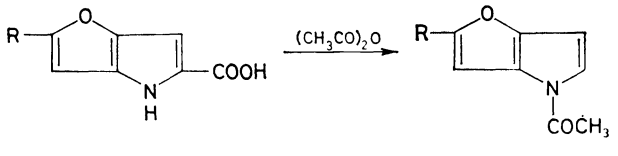
The title compounds *VII* represent the system with the several reaction centres (Scheme 5). By their hydrolysis the corresponding acids *IX* (refs[10-14]) were obtained. Reduction of *VII* with $LiAlH_4$ at room temperature afforded a mixture of 5-hydroxy-methyl (*X*) and 5-methyl- derivatives (*XI*). At temperature of boiling ether the 2-substituted-4*H*-5-methylfuro[3,2-*b*]pyrrole (*X*) was obtained[12]. The phase--transfer catalysis was found to be successful for N-alkylation of furo[3,2-*b*]pyrrole system giving the compounds *XII*. The reaction of *VII* with lithium hydride in dimethylformamide furnished N-lithium derivative, which gave with acetyl chloride the N-acetyl compound *XIII*. The same compound can be obtained by boiling of *VII* in acetic anhydride. The treatment of *VII* with acrylonitrile in pyridine afforded, in the presence of benzyltriethylammonium hydroxide, the compound *XIV*. The corresponding hydrazides *XV* were obtained by reacting *VII* with hydrazine hydrate in excess (Scheme 5).



SCHEME 5

2.2. *Substituted Furo[3,2-b]pyrrole-5-carboxylic Acids and Their Benzo[b]derivatives*

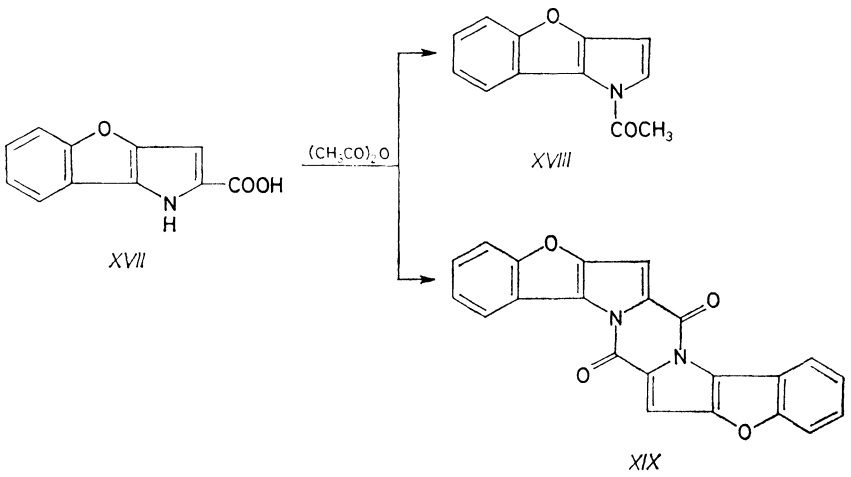
Title acids were decarboxylated[14,15] in quinoline in the presence of copper chromite catalyst promoted by barium. One of the most interesting results in this area is the acetylative decarboxylation of 4*H*-furo[3,2-*b*]pyrrole-5-carboxylic acid[16] or its



R = H, C_6H_5, 4-$CH_3C_6H_4$, 2$NO_2C_6H_4$, 4-Cl-2-$CH_3C_6H_3O$

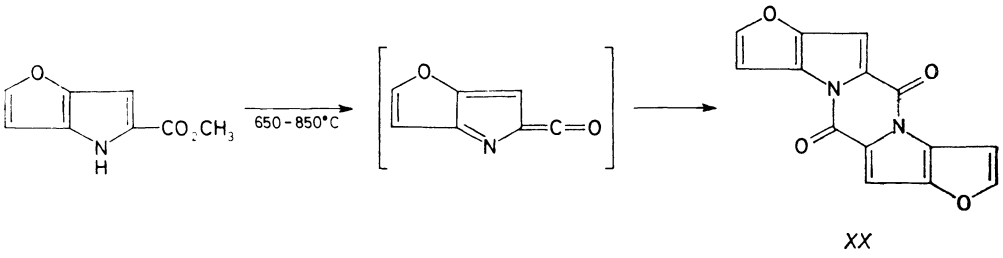
SCHEME 6

2-substituted[17] or benzo[*b*]derivative[16] prepared from corresponding ester *VIII*. During heating in the boiling acetic anhydride 4*H*-furo[3,2-*b*]pyrrole-5-carboxylic acid (*IX*, R=H) yields 4-acetylfuro[3,2-*b*]pyrrole (*XVI*) (Scheme 6); it behaves in this reaction similarly as 2-aryl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylic acids. 1*H*-Benzo-[*b*]furo[3,2-*b*]pyrrole-2-carboxylic acid (*XVII*) under the same conditions gives besides 1-acetylbenzo[*b*]furo[3,2-*b*]pyrrole (*XVIII*) also the product of an intermolecular dehydration, sparingly soluble 6,7,14,15-tetrahydrodibenzo[*b*]furo[3,2-*b*]-pyrrolo[1,2-*a* : 1′,2′-*d*]pyrazine-7,15-dione (*XIX*) (Scheme 7).



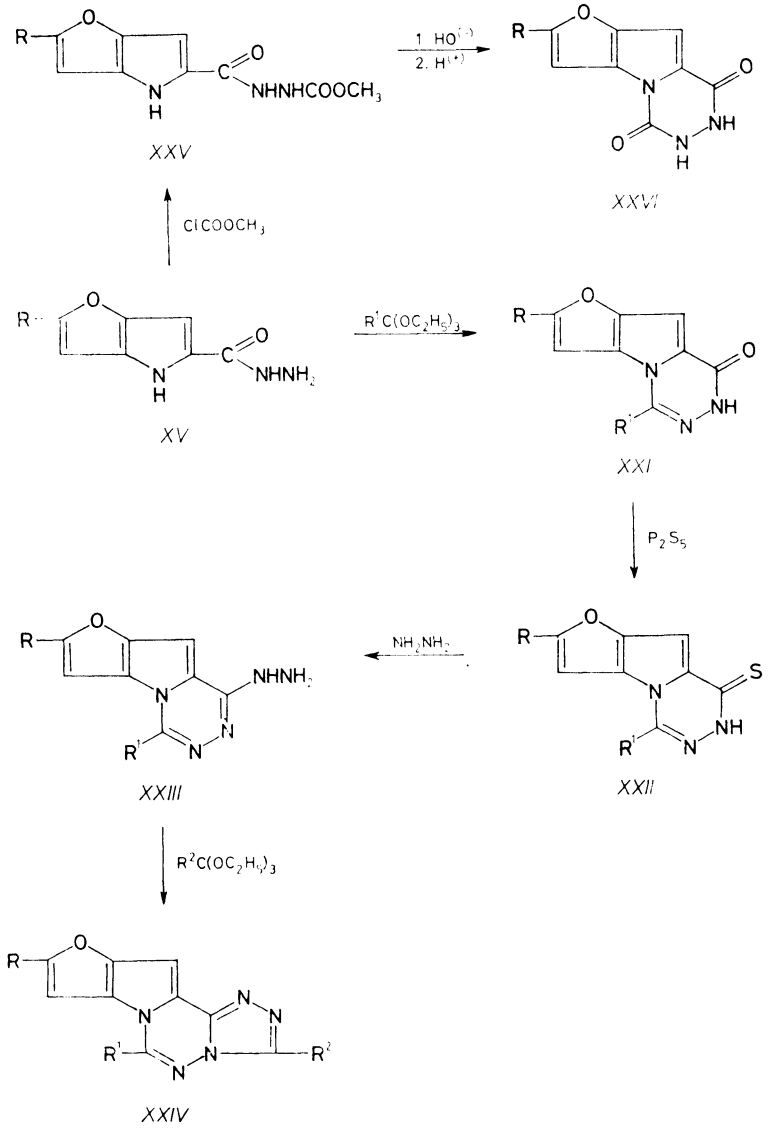
SCHEME 7

In this reaction the acid *XVII* behaves similarly as 2-pyrrolecarboxylic and 2-indolecarboxylic acids[18,19]. Since also ethyl esters of the above-mentioned acids furnished with acetic anhydride the acetylation products at nitrogen atom, one can presume a mechanism, where acetylation takes place in the first step. The presence of an acetyl group at nitrogen atom of furo[3,2-*b*]pyrrole-5-carboxylic acid or its 2-sub-



SCHEME 8

stituted derivatives increases their acidity and consequently, also the temperature of reaction medium becomes sufficient for their decarboxylation.



R = H, C_6H_5, 4-$CH_3C_6H_4$, 3,4-$Cl_2C_6H_3$; R^1 = H, CH_3; R^2 = H, CH_3

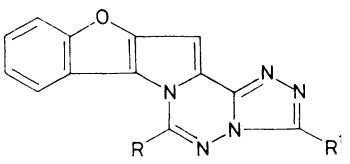
SCHEME 9

A formation of a dimer product (*XX*) in furo[3,2-*b*]pyrrole series was observed[20] under conditions of flash vacuum pyrolysis of 4*H*-furo[3,2-*b*]pyrrole-5-carboxylic acid and its ethylester respectively (Scheme 8).

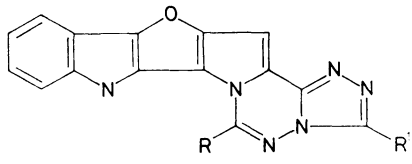
2.3. *The Utilization of* 2-R-4*H*-*Furo*[3,2-*b*]*pyrrole-5-carboxhydrazides and Their Condensed Derivatives in the Synthesis of New Heterocyclic Systems*

The synthesis of some condensation products derived from triazole[21–24] or triazine[25–29] was of special interest in the last few years owing the fact, that some of the just mentioned products are biologically effective[30,31]. Two reaction centres of 2-R-4*H*-furo[3,2-*b*]pyrrole-5-carboxhydrazides[32–35] were utilized in a cyclization reaction with triethyl orthoformate or orthoacetate leading to 7-R-furo[2′,3′ : 4,5]-pyrrolo[1,2-*d*][1,2,4]triazine-1-ones *XXI* (Scheme 9), which with phosphorus pentasulfide gave thiones *XXII*. 7-R-furo[2′,3′ : 4,5]pyrrolo[1,2-*d*][1,2,4]triazine--1-thiones yield with hydrazine hydrate 1-hydrazino-7-R-[2,′3′ : 4,5]pyrrolo-[1,2-*d*][1,2,4]triazines (*XXIII*) having two new reaction centres. Reaction with triethyl orthoformate or orthoacetate gave 9-R-furo[2′,3′ : 4,5]pyrrolo[1,2-*d*][1,2,4]-triazolo[3,4-*f*][1,2,4]triazines *XXIV* and 3- and 6-methyl, as well as 3,6-dimethyl derivatives (Scheme 9).

N-Methoxycarbonylhydrazides *XXV* were prepared[32] by treatment of 2-aryl-4*H*-furo[3,2-*b*]pyrrole-5-carboxhydrazides (*XV*) with methyl chloroformate. Non--arylated hydrazide *XV* (R = H) furnished a tarry product; this can be rationalized by a lower stability of the starting system towards hydrogen chloride liberated during reaction. An alkaline hydrolysis of *XXV* afforded 7-aryl-1,2,3,4-tetrahydro-furo[2′,3′ : 4,5]pyrrolo[1,2-*d*][1,2,4]triazines (*XXVI*) (Scheme 9).



XXVII, R, R′ = H, CH_3

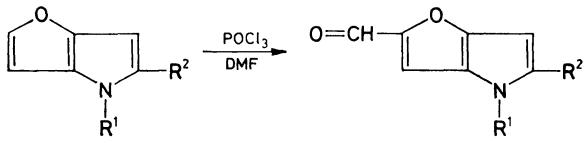


XXVIII, R, R′ = H, CH_3

Analogously were prepared benzo[*b*]furo[2″,3″ : 4′,5′]pyrrolo[1,2-*d*][1,2,4]-triazolo[3,4-*f*][1,2,4]triazines (*XXVII*) (ref.[33]) or [1,2,4]triazolo[3‴,4‴ : 6″,1″]-[1,2,4]triazino[4″,5″ : 1′,5′[pyrrolo[2′,3′ : 4,5]furo[3,2-*b*]indoles (*XXVIII*) (ref.[35]) or their 3-methyl and 6-methyl or 3,6-dimethylderivatives.

2.4. *Electrophilic Substitution Reactions of Furo[3,2-b]pyrrole Derivatives*

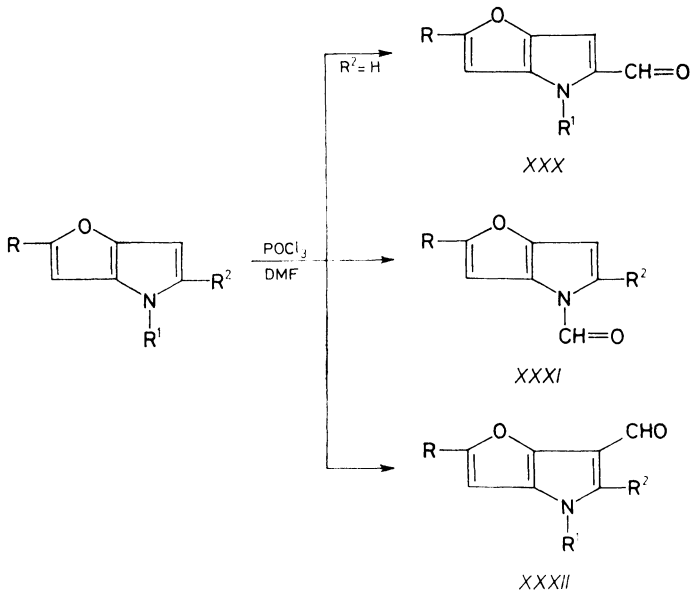
Although the electrophilic substitution reactions of substances related to furan[36,37] and pyrrole[38] are well reported, those of furo[3,2-*b*]pyrrole system have little been mentioned[11]. The papers[16,39] present the formylation, nitration, Mannich reaction and copulation of variously substituted furo[3,2-*b*]pyrroles or their benzo[*b*]derivatives. The mentioned compounds were formylated under conditions of Vilsmeier reaction. In the case that the position C-2 is not occupied formylation takes place at this position (*XXIX*) at ambient or moderately elevated temperature (Scheme 10).



XXIX

$R^1 = H, CH_3, COCH_3$; $R^2 = H, COOC_2H_5$

SCHEME 10



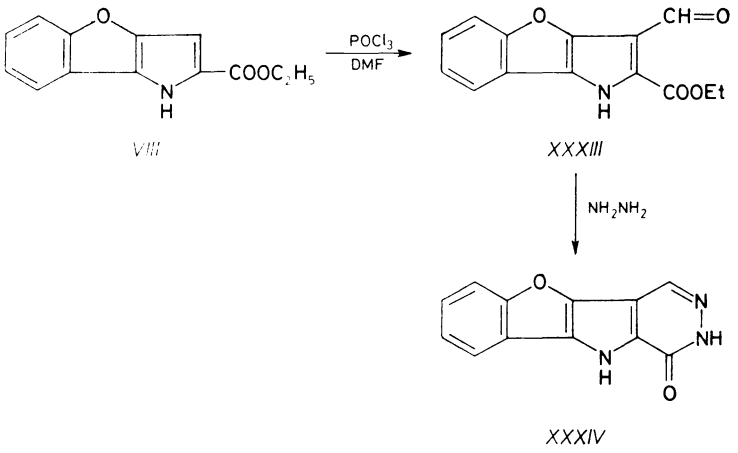
$R = C_6H_5, 4\text{-}CH_3C_6H_4, 2\text{-}NO_2C_6H_4$; $R^1 = H, CH_3, CH_3CO$

In formulae *XXXI* and *XXXII* R^2 is $COOC_2H_5$

SCHEME 11

4-Acetyl-2-arylfuro[3,2-*b*]pyrroles yield 5-formylated products undergoing a spontaneous decomposition. Heating in polar as well as nonpolar solvents resulted in cleveage of the acetyl group from nitrogen, furnishing 2-aryl-4*H*-furo[3,2-*b*]pyrrole--5-carbaldehyde (*XXX*) (Scheme 11).

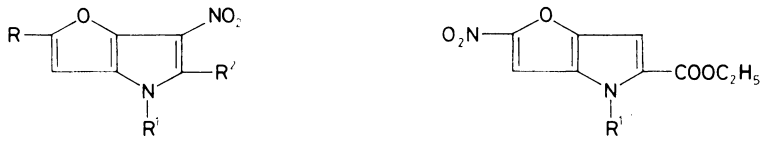
In this system, where positions 2 and 5 are occupied, the 8 h-lasting reaction afforded N-formylation products (*XXXI*). Prolonged reaction time leads to products *XXXII* formylated at C-6 i.e. in β-position of the pyrrole ring (Scheme 11).
In the case of benzo[*b*]-furo[3,2-*b*]pyrrole derivatives the 3-formylated products *XXXIII* were formed which were the suitable staring compounds for the preparation of new fused heterocycles (*XXXIV*) (Scheme 12).



VIII *XXXIII* *XXXIV*

SCHEME 12

Nitration of furo[3,2-*b*]pyrrole system was performed with the mixture of fuming nitric acid and acetic anhydride. Nitration was successful when positions 2 and 5 were occupied by at least one electron-attracting substituent. Whereas nitration of ethyl 2-aryl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate was directed to position 6 (*XXXV*)

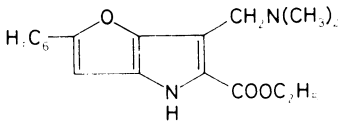


XXXV, R = C_6H_5, 4-$CH_3C_6H_4$; R^1 = H; R^2 = $COOC_2H_5$ *XXXVI*, R^1 = H, CH_3

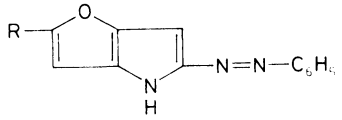
in the case of 2-formyl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate and its N-metylderivative it was accompanied by the *ipso* attack of the formyl group by the nitro group

giving 2-nitrated products (*XXXVI*) which were not possible to obtain by the direct nitration.

The Mannich reaction was investigated using ethyl 2-phenyl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate, the electrophilic displacement occured in position 6, giving *XXXVII*. 2-Aryl-4*H*-furo[3,2-*b*]pyrrole easily undergoes a reaction with benzenediazonium chloride at C-5 giving *XXXVIII*. The above-mentioned results demonstrate that the preferred positions for the electrophilic substitution reactions of furo[3,2-*b*]-pyrroles are C-2 and C-5, i.e. α-positions of the furan and pyrrole rings followed by position 4 and finally by position 6 (β-position of pyrrole).

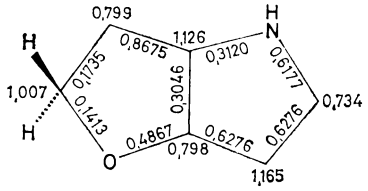


XXXVII

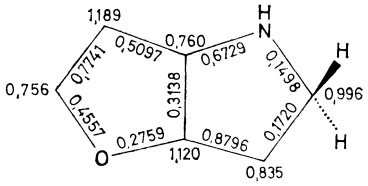


XXXVIII, R = C_6H_5, 4-$CH_3C_6H_4$

These observations were supported by MNDO calculations. To model the reaction pathway of electrophilic substitution on furo[3,2-*b*]pyrrole system the protonation reaction of it have been investigated[40] with special emphasis on the thermodynamical stability of the transient σ-complexes. The heats of formation ΔH_0^f of neutral forms as well as C-, N- and O-protonated σ-complexes of furo[3,2-*b*]pyrrole were calculated by the MNDO method[41] with full geometry optimization. It was found[40]



XXXIX



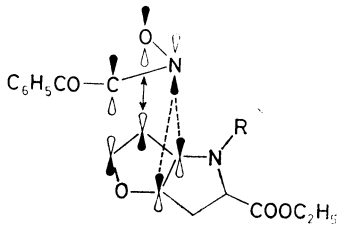
XL

SCHEME 13

that the protonation of furo[3,2-*b*]pyrrole occurs regioselectively at the C-2 and C-5 atoms to form σ-complexes which are by 11–41 kJ mol^{-1} more stable than cations resulting from protonation at C-3 and C-5 atoms what is in a good agreement with obtained results[39]. Localization of positive charge in the most stable σ-complexes (*XXXIX*, *XL*) can be inferred from both π-electron densities and π-bond orders calculated by the MNDO method (Scheme 13).

2.5. *Addition and Cycloaddition Reactions of Furo*[3,2-*b*]-*pyrroles and Their Condensed Derivatives*

The 1,3-dipolar cycloadditions of ethyl 4*H*-furo[3,2-*b*]pyrrole-5-carboxylate or its 4-methyl derivative with C-benzoyl-N-phenylnitrone and N,N-diphenylnitrone proceeded regiospecificaly in position 2 and 3 of the furan ring. During these reactions exclusively *endo*-cycloadducts originated, because their transition state *XLI* was stabilized by secondary orbital interactions[42].

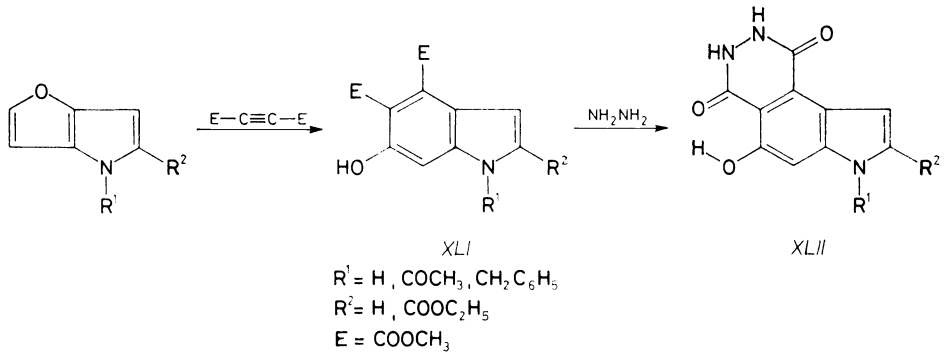


XLI

In attempt to study reactions of furo[3,2-*b*]pyrroles and their fused derivatives with dienophiles it was of interest whether this system will retain the properties of furan and pyrrole, or will behave as its isoelectronic analogue indole.

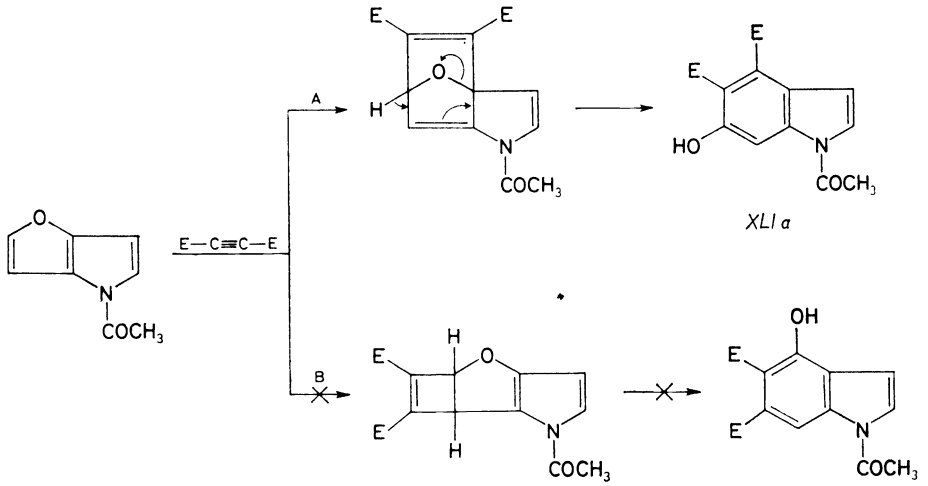
As known, pyrroles and indoles undergo Michael addition with π-deficient alkenes and alkynes in position 2 of the pyrrole ring and in position 3 of the indole ring, but also on the NH group. Under catalysis with Lewis acids, and particularly at elevated temperatures, [4 + 2] cycloaddition reactions take place[43–46]. With dienophiles, furan and its derivatives afford mainly cycloaddition products[47]; however, also products of addition in α-position of the furan ring were isolated[48].

During the study of reactions of furo[3,2-*b*]pyrroles and their condensed derivatives with dienophiles it was found out that reaction course is influenced by the substituents on the system. The reactions of the at C-2 unsubstituted furo[3,2-*b*]-pyrroles with dimethylbutynedioate proceed via [4 + 2] cycloaddition on the furan ring, giving rise to substituted indoles *XLI* (ref.[49]). The last compounds were used in the synthesis of the new compounds *XLII* containing the pyridazino [4,5-*e*]indole grouping (Scheme 14).



SCHEME 14

Since it was possible to presume that this reaction proceeds as a [4 + 2] cycloaddition or as a [2 + 2] cycloaddition (Scheme 15), the exact determination of the structure of the final product was unavoidable.

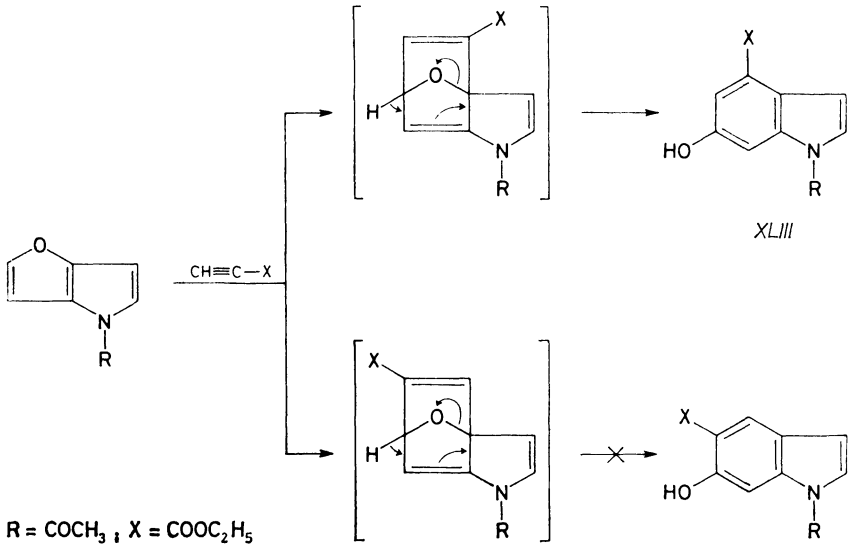


SCHEME 15

By analysis of ^{1}H and ^{13}C NMR spectra[50] as well as X-Ray analysis of the crystal structure of the final product[51] the structure *XLIa* was confirmed which enabled authors[49] conclude that studied reaction proceeds via [4 + 2] cycloaddition (Scheme 15, pathway A).

For the study of reaction with unsymmetrically substituted dienophiles ethyl propynoate and 4-acetylfuro[3,2-*b*]pyrrole were used. In principle, this reaction can

afford two regioisomeric 1 : 1 adducts which on subsequent rearrangement give isomeric 1-acetylindole derivatives (Scheme 16). As was proved by ^1H and ^{13}C NMR spectra, the reaction under given conditions proceeds regioselectively and affords ethyl 1-acetyl-6-hydroxy-4-indolecarboxylate (*XLIII*) without any side products[49] (Scheme 16).

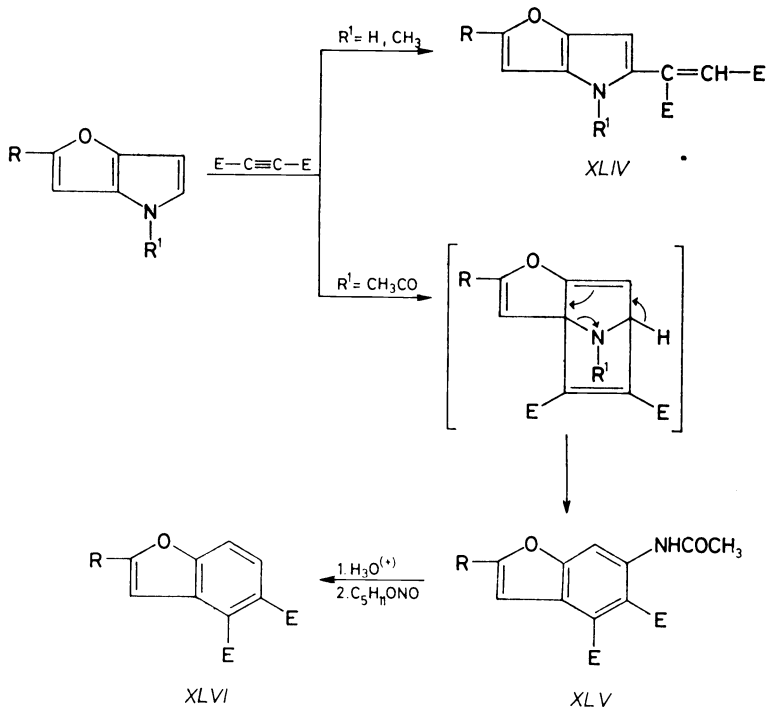


XLIII

SCHEME 16

During the study of the reactions of 2-substituted furo[3,2-*b*]pyrrole derivatives with dimethyl butynedioate it was found[17] that the substituents attached at position 4 expressively influenced their course, which was supported by the structure of isolated products (Scheme 17).

N-Benzyl, N-methyl, and N-unsubstituted derivatives afforded only the Michael reaction products i.e. the reaction takes place at C-5 of furo[3,2-*b*]pyrrole system giving rise to compounds *XLIV*. Under the same conditions the 4-acetyl-2-arylfuro-[3,2-*b*]pyrrole reacts with dimethyl butynedioate in α-positions of the pyrrole ring giving [4 + 2] cycloadduct, which due to low stability was not isolated and which by the subsequent 1,5-sigmatropic rearrangement gave substituted benzo[*b*]furan derivative *XLV* (Scheme 17). The structure of the compound *XLVI* obtained[17] from *XLV* supports the mechanism discussed above. The substituents at C-2 influenced the course of this reaction. The reaction of 4-acetyl-2-(2-nitrophenyl)furo[3,2-*b*]-pyrrole with dimethyl butynedioate afforded the product of Michael addition *XLVII* and the product of [4 + 2] cycloaddition *XLVIII* (Scheme 18).



XLIV

XLVI

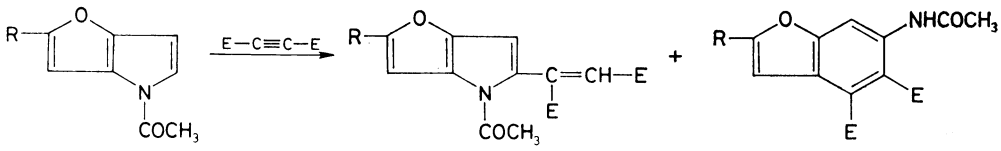
XLV

R = C_6H_5, 4-$CH_3C_6H_4$, 2-$NO_2C_6H_4$, 2-$CH_3C_6H_3O$
R^1 = $COCH_3$

SCHEME 17

Reaction of benzo[*b*]furo[3,2-*b*]pyrrole with dimethyl butynedioate afforded the Michael-type adducts at position 1 (*XLIX*) or 2 (*L*) (Scheme 19).

Concerning the reaction of 1-acetylbenzo[*b*]furo[3,2-*b*]pyrrole was assumed that mesomeric conjugation of the acetyl group with π-electron system of the skeleton leads to partial localization of the lone electron pair at the nitrogen atom enhancing

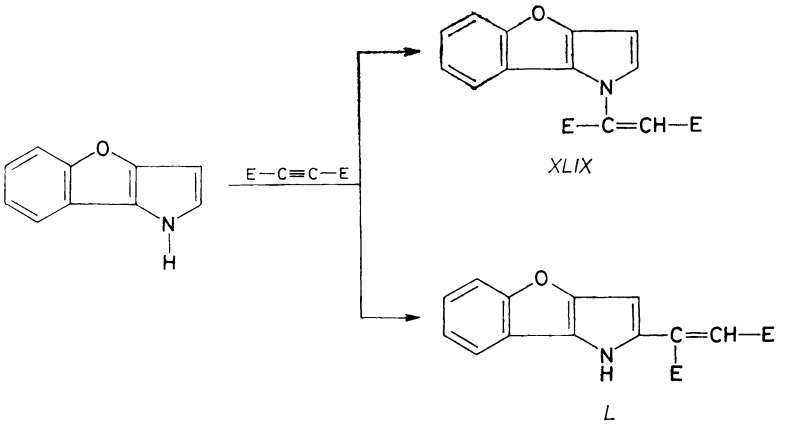


R = 2-$NO_2C_6H_4$

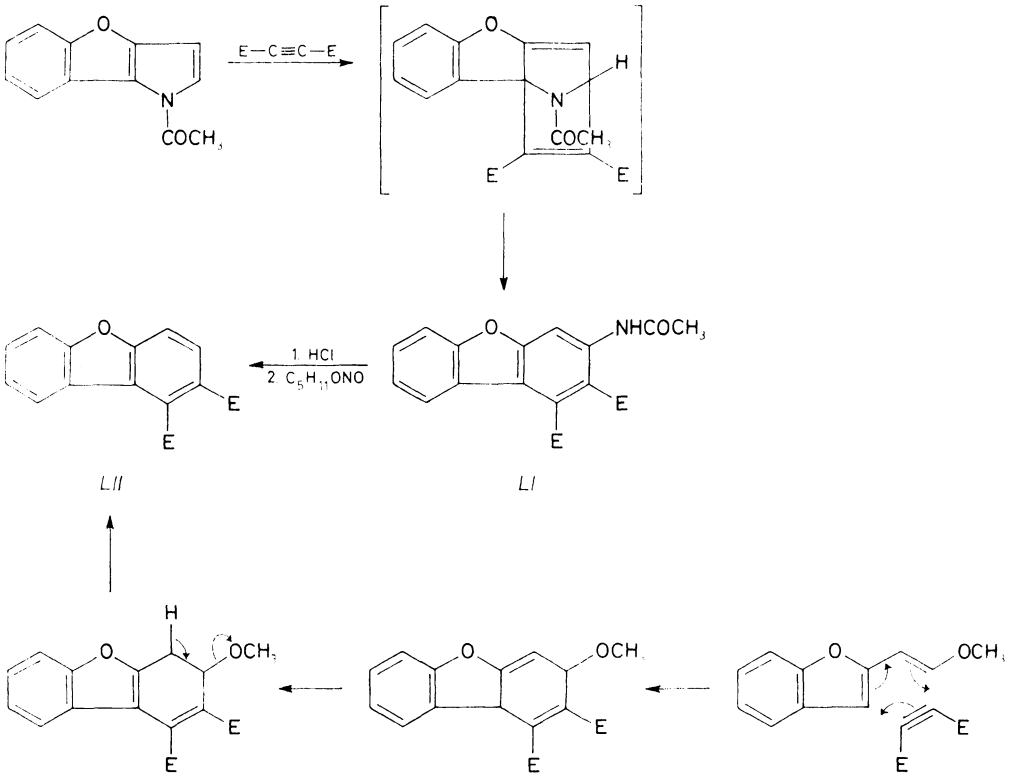
XLVII

XLVIII

SCHEME 18



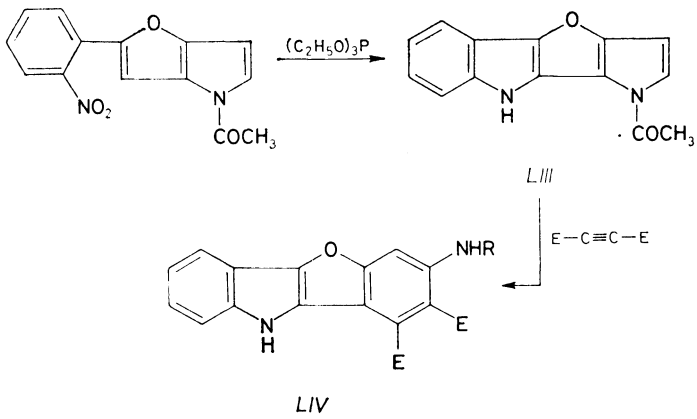
SCHEME 19



SCHEME 20

thus the diene character of its pyrrole part. This assumption has been confirmed by isolation of *LI* as a product of the [4 + 2] cycloaddition reaction and followed transformation of an arrised cycloadduct. The structure *LI* was also confirmed by independent preparation[52] of compound *LII* from dimethyl butynedioate and 2-vinylbenzo[*b*]furan (Scheme 20).

Analogously 1-acetylpyrrolo[2′,3′ : 4,5]furo[3,2-*b*]indole (*LIII*) reacts with dimethyl butynedioate in α-position of the pyrrole ring giving [4 + 2] cycloadduct which by subsequent 1,5-sigmatropic rearrangement gave[53] the isolated dimethyl-3--acetylaminobenzo[*b*]furo[3,2-*b*]indole-1,2-dicarboxylate (*LIV*) (Scheme 21).



LIV

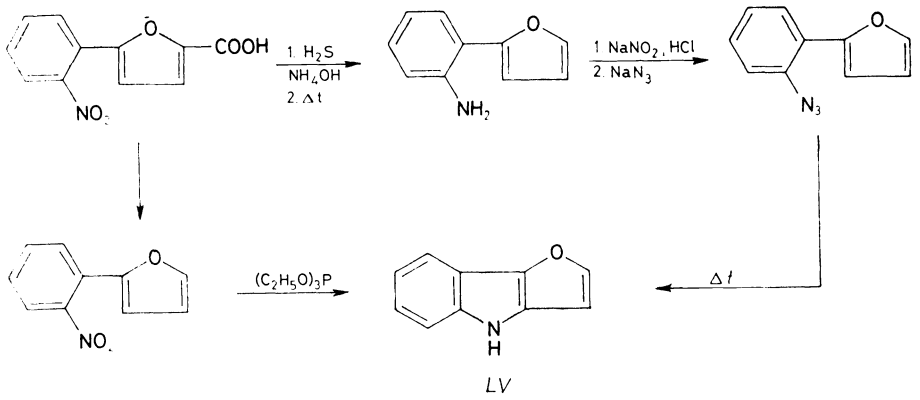
SCHEME 21

In conclusion it can be stated, that reactivity toward dienophiles in both the studied series is influenced by substituents. The furo[3,2-*b*]pyrrole series is more reactive and the cycloaddition takes place at the furan ring. If the C-2 position is occupied the reaction proceeds on the pyrrole ring and is more facile than in the benzo[*b*]-furo[3,2-*b*]pyrrole series. It is evident that in fused furo[3,2-*b*]pyrrole system each nucleus retains its original identity and the diene character increases on going from pyrrole to furan i.e. as in non-fused systems.

3. PYRROLO[2′,3′:4,5]FURO[3,2-*b*]INDOLE DERIVATIVES

A variety of pyrrole ring closure reactions are frequently formulated as proceeding via nitrene intermediates, although it is doubtful whether such a discret species is in fact involved. The deoxygenation of aromatic nitro compounds with trivalent phosphorus compounds is useful for indole and carbazole synthesis. This area is covered by works of Cadogan[54–60], Boyer[61] and others[62] who showed the conve-

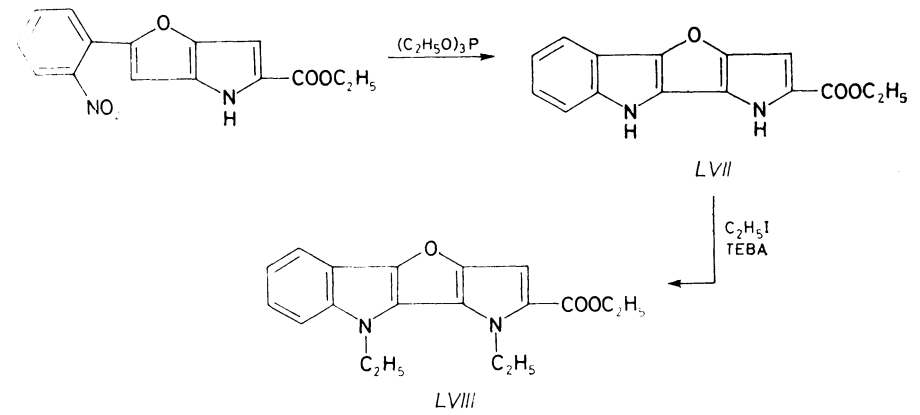
nience of this method for the synthesis of not only indole and carbazole but also benzothiazole, antranile and compounds to the similar them. Besides the trivalent phosphorus compounds can be used trivalent arsene derivatives[59,60], iron(II) oxalate[63] and disilanes[64]. The construction of furo[3,2-*b*]indole skeleton was realized by two basic methods based on analogy with Cadogan carbazole deoxygenation method and Smith carbazoles synthesis through thermolysis of 2-azidobiphenyls[65]. The synthesis of the parent furo[3,2-*b*]indole (*LV*) was published by Tanaka[66] et al. (Scheme 22).



LV

SCHEME 22

The Vilsmeier formylation of *LV* or its 4-ethyl derivative gave 2-formylated product[67]. Thus, it was estimated that the active position of *LV* relative to electrophiles would be C-2 position as in the furan ring. Attempts to realize some electrophilic substitution



LVII

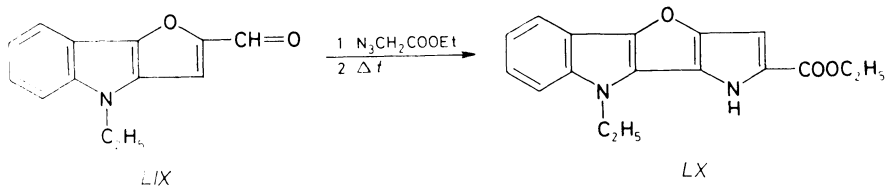
LVIII

SCHEME 23

reactions were unsuccessful. For explanation of it was suggested that compound *LV* incorporates an enamino-oxo structure element into its molecule and it is probably more unstable in acidic medium than furan and indole itself[67]. Reactions of *LV* gave the series of biologically active compounds[68-71]. N-Alkylated amides and other derivatives of furo[3,2-*b*]indole-2-carboxylic acids possess analgetic, sedative, and antipyretic activities[72,73].

In the work[11] was described ethyl 2-(2-nitrophenyl)-4*H*-furo[3,2-*b*]pyrrole-5--carboxylate (*LVI*) which was used for the synthesis ethyl 1-ethyl-9*H*-pyrrolo-[2',3' : 4,5]furo[3,2-*b*]indole-2-carboxylate (*LVII*) which afforded by further alkylation the corresponding diethyl derivative (*LVIII*) (Scheme 23).

The later could also be achieved by ethylation of *LX* obtained from 4-ethylfuro-[3,2-*b*]indole-2-carbaldehyde (*LIX*) as it is shown in Scheme 24.



LIX *LX*

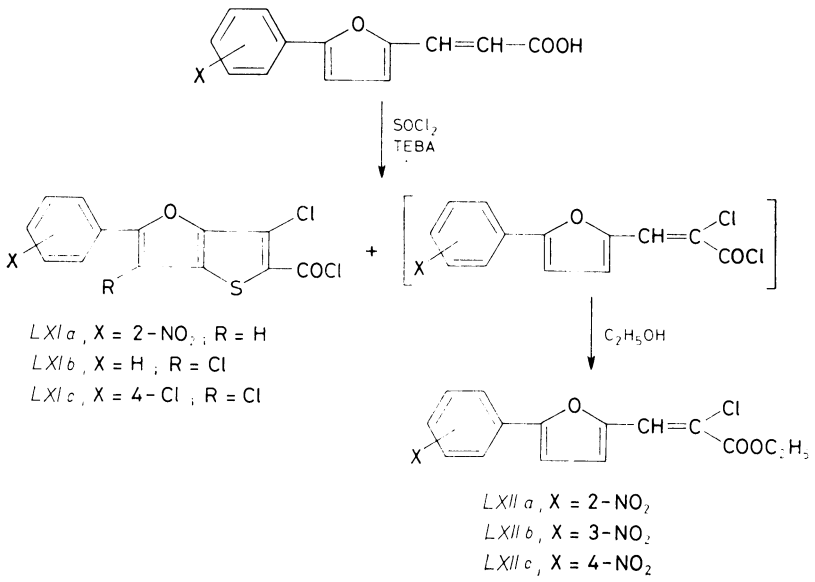
SCHEME 24

4. THIENO[3,2-*b*]FURANS AND THEIR CONDENSED DERIVATIVES

Higa and Krubsack[74] were the first who described the preparation of 3-chlorobenzo-[*b*]thiophene-2-carboxylic acid by heating 3-phenylpropanoic acid in thionyl chloride in the presence of catalytic amount of pyridine. This reaction, later studied with derivatives of 3-phenylpropanoic[75,76], and 3-phenylpropenoic[75,77,78] acids, 1,1--diphenylalkenes[79], and derivatives of propionic acid[80], proved suitable for preparation of many benzo[*b*]thiophene derivatives. This method was utilized in the series of heterocyclic compounds for preparation of theino[3,2-*b*]thiophenes[81].

For the preparation of 2-arylthieno[3,2-*b*]furan derivatives 3-(5-aryl-2-furyl)-propenoic acids in the presence of triethylbenzylammonium chloride were used[82]. During the study of this reaction was found out its dependence on the substituents attached at benzene ring. Under these conditions 3-[5-(2-nitrophenyl)-2-furyl]-propenoic acid gave a substituted thieno[3,2-*b*]furan (*LXIa*) and ethyl-2-chloro-3--[5-(2-nitrophenyl)-2-furyl]propenoate (*LXIIa*) (Scheme 25).

On the other hand, 3- and 4-nitrophenyl analogues did not yield thieno[3,2-*b*]-furan derivatives at all; but only the chlorination reaction takes place giving the reaction products *LXIIb* and *LXIIc* (Scheme 25). 3-(5-Aryl-2-furyl)propenoic acids containing phenyl and 4-chlorophenyl groups in position 5 of the furan ring afforded,



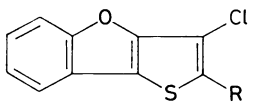
LXIa, X = 2-NO_2; R = H
LXIb, X = H; R = Cl
LXIc, X = 4-Cl; R = Cl

LXIIa, X = 2-NO_2
LXIIb, X = 3-NO_2
LXIIc, X = 4-NO_2

SCHEME 25

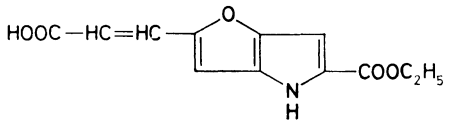
however, thieno[3,2-*b*]furan derivaties *LXIb* and *LXIc*. In comparison with *LXIa* the chlorine atom enters position 3, what was not observed in the case of derivative *LXIa* due to steric and electronic effects associated with nitro group in position 2 of the benzene ring.

3-(2-Benzo[*b*]furyl)propenoic acid yields 3-chlorothieno[3,2-*b*]benzo[*b*]furan-2--carbonyl chloride (*LXIIIa*), giving by subsequent reaction compounds *LXIIIb* to *LXIIId*.

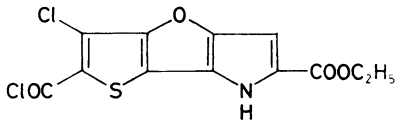


LXIIIa, R = COCl
LXIIIb, R = $COOC_2H_5$
LXIIIc, R = COOH
LXIIId, R = H

The heteronuclear skeleton *LXV* formed from mutually fused furan, pyrrole and thiophene rings was obtained from 3-(5-ethoxycarbonyl-4*H*-furo[3,2-*b*]pyrrolyl)-propenoic acid (*LXIV*) prepared by Knoevenagel condensation of the corresponding aldehyde.

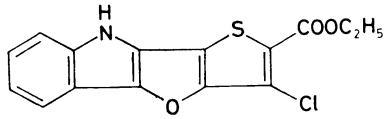


LXIV



LXV

The presence of nitro group in C-2 of the benzene ring of the compound was utilized[82] under conditions of Cadogan deoxygenation to fuse an indole skeleton to thieno[3,2-*b*]furan system *LXVI*.



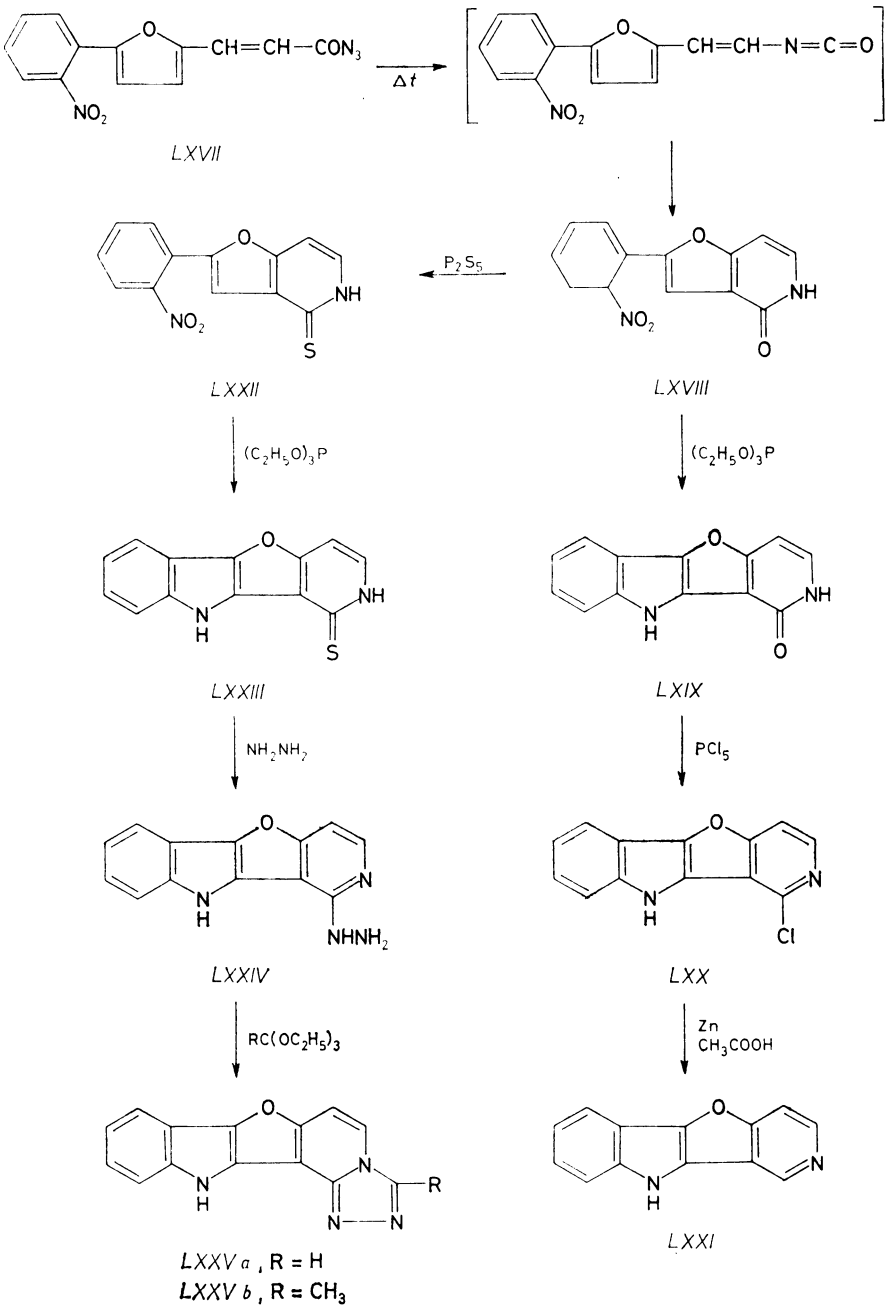
LXVI

5. FURO[3,2-*c*]PYRIDINES AND THEIR CONDENSED DERIVATIVES

Several methods have been described[83] for the synthesis of the furo[3,2-*c*]pyridine system starting either from pyridines or furans[83–86]. Electrophilic reactions[87] and the biological properties[88] of furo[3,2-*c*]pyridines were studied. A new type of the condensed heterocyclic compound, with furo[3,2-*c*]pyridine unit was prepared[89] as it is shown on Scheme 26. Thermal decomposition of 3-[5-(2-nitrophenyl)-2-furyl]-propenoyl azide (*LXVII*) prepared from the corresponding chloride, gives via 3-[5-(2-nitrophenyl)-2-furyl]propenoyl isocyanate, 2-(2-nitrophenyl)-4,5-dihydrofuro [3,2-*c*]pyridine-4-one (*LXVIII*). Under conditions of a deoxygenative cyclization of the last compound 1,2-dihydropyrido[3′,4′ : 4,5]furo[3,2-*b*]indole-1-one (*LXIX*) was formed. Upon reaction with phosphorus pentachloride compound *LXIX* was aromatized to afford 1-chloropyrido[3′,4′ : 4,5]furo[3,2-*b*]indole (*LXX*), the reduction of which led to a new type of condensed heterocycle pyrido[3′,4′ : 4,5]furo[3,2--*b*]indole (*LXXI*) (Scheme 26).

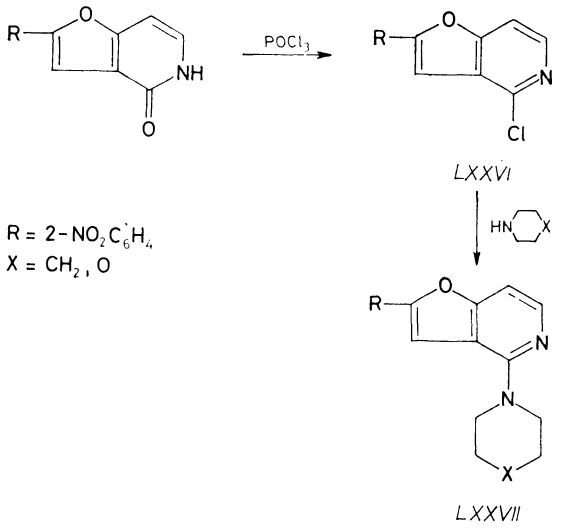
Treatment of 2-(2-nitrophenyl)-4,5-dihydrofuro[3,2-*c*]pyridine-4-one (*LXVIII*) with phosphorus pentasulfide afforded the corresponding 2-(3-nitrophenyl)-4,5-dihydrofuro[3,2-*c*]pyridine-4-thione (*LXXII*), its cyclization with triethyl phosphite gave 1,2-dihydropyrido[3′,4′ : 4,5]furo[3,2-*b*]indole-1-thione (*LXXIII*). Reaction of *LXXIII* with hydrazine hydrate yielded the corresponding hydrazinoderivate *LXXIV*, which furnished 1,2,4-triazolo[4″,3″ : 1′,2′]pyrido[3′,4′ : 4,5]furo[3,2-*b*]-indole (*LXXVa*) and its 3-methyl derivative (*LXXVb*) with triethyl orthoformiate and triethyl orthoacetate, respectively (Scheme 26).

Nucleophilic displacement reactions of halogen activated by a neighbouring nitrogen atom proceed as was expected. Treatment of *LXVIII* with phosphorus oxy-


CH=CH—CON3
Δt
CH=CH—N=C=O
NO2
LXVII
P2S5
NH
S
O
LXXII
LXVIII
(C2H5O)3P
N
H
LXXIII
LXIX
NH2NH2
PCl5
NHNH2
Cl
LXXIV
LXX
RC(OC2H5)3
Zn
CH3COOH
R
N
LXXV a, R = H
LXXV b, R = CH3
LXXI

SCHEME 26

chloride gave 2-(2-nitrophenyl)-4-chlorofuro[3,2-*c*]pyridine (*LXXVI*), which afforded with nucleophiles corresponding 4-substituted 2-(2-nitrophenyl)furo[3,2-*c*]-pyridines[89] (*LXXVII*) (Scheme 27).



SCHEME 27

6. CONCLUSION

2-R-4-Acetylfuro[3,2-*b*]pyrroles and their benzo[*b*]derivatives, which were obtained by decarboxylative acetylation of the corresponding acids, opened the way to the synthesis of furo[3,2-*b*]pyrroles and their condensed derivatives.

The rules of the attack by electrophilic species of the furo[3,2-*b*]pyrrole skeleton were found out and they are in a good agreement with theoretical calculations obtained by MNDO method. Addition and cycloaddition reactions of furo[3,2-*b*]-pyrroles and their condensed derivatives are influenced by the position and the features of the attached substituents. It was found that after the cycloaddition reactions of this type of compounds interesting transformations took place giving rise to the substituted benzo[*b*]furans, or indoles and their condensed derivatives.

This review shows the wide possibility of the 5-R-2-furaldehydes utilization in the preparation of many series of the new bi-, tri-, up to polycyclic heterocycles containing fused furan ring.

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