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1,4-DIHYDROPYRIDINES CONTAINING SULFUR (REVIEW)

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The literature on the synthesis and reactions of monocyclic and polycyclic 1,4-dihydropyridines containing sulfur in substituents or in the ring is reviewed.

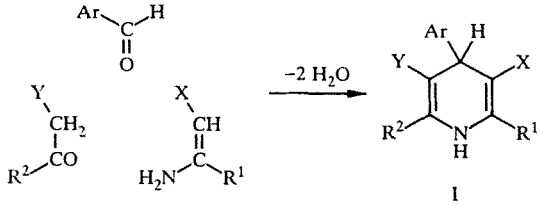
The chemistry of 1,4-dihydropyridines has been reviewed [1-6] but these reviews have only touched on the effect on the properties of 1,4-dihydropyridines of introducing sulfur in different oxidation states. It is obvious that the nature of the heteroatom in a substituent on 1,4-dihydropyridines or in the ring of polycyclic 1,4-dihydropyridines will determine the properties of the 1,4-dihydropyridine molecule as a whole.

This review does not discuss systems with exocyclic double bonds (e.g., pyridinethiones) and is not aimed at presenting the whole of the material on sulfur-containing 1,4-dihydropyridines. However an attempt is made to expose the similarities and differences in properties between sulfur-containing 1,4-dihydropyridines and their oxygen-containing analogs, with particular attention to the electronic effects of sulfur-containing ester substituents in this system.

1. MONOCYCLIC 1,4-DIHYDROPYRIDINES CONTAINING SULFUR

1.1. Sulfur-Containing Substituents in Positions 2 and 6

1,4-Dihydropyridines with alkyl (or aryl) thiomethyl substituents in positions 2 or 6 (I) are obtained from derivatives of substituted acetoacetic acid, aldehydes and derivatives of β-aminocrotonic acid [7-9]:

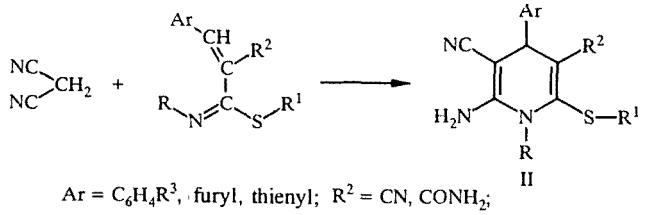


I

X, Y = COOMe, COOEt, CN

R^1 = Me, CH_2SMe; R^2 = CH_2SMe, CH_2SAr^1

1,4-Dihydropyridines of type II are obtained by cyclocondensation reactions of malodinitrile [10-13]:



II

Ar = $C_6H_4R^3$, furyl, thienyl; R^2 = CN, $CONH_2$;

R + R^1 = —N=C—NHCOPh, *o*-phenylene

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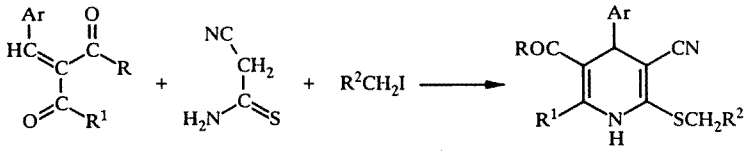
2-Alkylthio derivatives of 1,4-dihydropyridine (III) are formed by interaction of cyanothioacetamide arylidene derivatives of β-diketones with subsequent alkylation [14-18]:

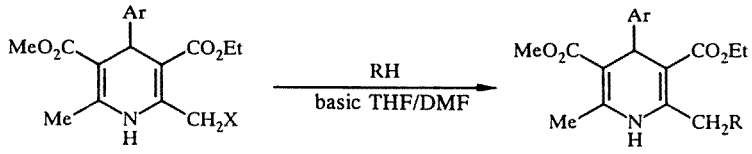


III

R = OEt, Ph; R^1 = Me, Ph; R + R^1 = $CH_2CMe_2CH_2$; *o*-phenylene

R^2 = H, $CONH_2$

Apart from these methods of cyclocondensation with the formation of 1,4-dihydropyridines with thioalkyl substituents in positions 2 or 2,6, exchange of halogens in a 2-CH_2X (X = Cl, Br) to give compounds IV is known [19-23]:

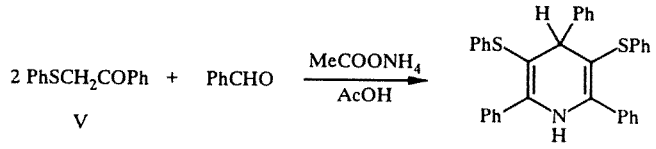


IV

R = $SCH_2CH_2NH_2$; SCH_2CH_2OH; SCH_2Ph

1.2. Sulfur-Containing Substituents in Positions 3 and 5

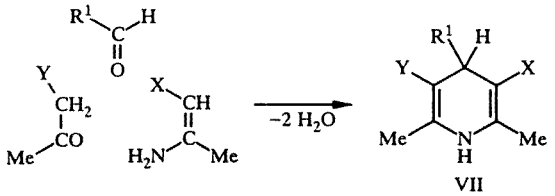
1,4-Dihydropyridine (VI) with 3,5-phenylthio substituents is formed by the reaction of phenylthioacetophenone with benzaldehyde in the presence of ammonium acetate in acetic acid [24]:



V

VI

1,4-Dihydropyridines (VII) with sulfonyl substituents Y = SO_2R, R = Alk [25], Ar [25, 26] and $SOC_6H_4R^3$ [27] in position 3 were obtained by various modifications of the Hantzsch synthesis (e.g., from enamine, aldehyde components and β-ketosulfones as the active methylene components):



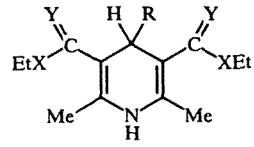
VII

R^1 = Ar, pyridyl X = COMe, COOAlk

A series of literature sources on the synthesis of 1,4-dihydropyridines with β-sulfonyl substituents is also known [9, 27-30].

Information on 1,4-dihydropyridines with sulfur-containing substituents in positions 3 and 5 with the sulfur directly bonded to a ring atom is very fragmentary. 1,4-Dihydropyridines with sulfur-containing ester substituents in the β-position have been studied more systematically as a result of which a preliminary estimate of the electronic effect of these substituents was proposed.

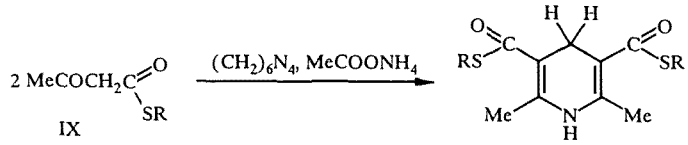
The synthesis of 1,4-dihydropyridines (VIII) with (alkylthio)carbonyl-, ethoxythiocarbonyl- and (ethylthio)thiocarbonyl substituents in the β-positions has been achieved.



VIII

R = H, Me, Ar, heteryl; X, Y = O, S

4-H-2,6-Dimethyl-3,5-di(ethylthio or benzylthio)carbonyl-1,4-dihydropyridines (X) were obtained by condensation of S-esters of acetothioacetic acid IX with hexamethylenetetramine in the presence of ammonium acetate on heating in ethanol or dioxane for a short time [31]:

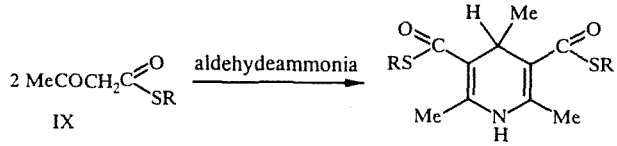


IX

R = Et, CH_2Ph

X

4-Methyl-3,5-di(ethylthio- or benzylthio)carbonyl substituted 1,4-dihydropyridines (XI) were obtained by condensation of IX with aldehyde ammonia on brief boiling in dioxane.

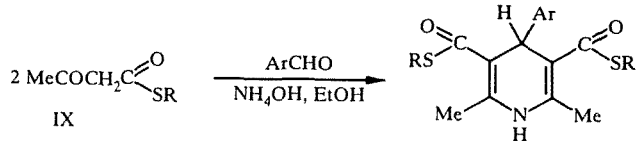


IX

R = Et, CH_2Ph

XI

IX was condensed with the corresponding aldehyde and ammonia on boiling in dioxane to obtain 1,4-dihydropyridines with aromatic or heteroaromatic substituents in position 4 (XIIa-d). 1,4-Dihydropyridines with substituents in position 4 were successfully obtained only when IX reacted with the reactive 2- and 4-nitrobenzaldehydes and 3-pyridylaldehyde. In this case the Meyer-Mohr modification of the Hantzsch synthesis was used [32]:

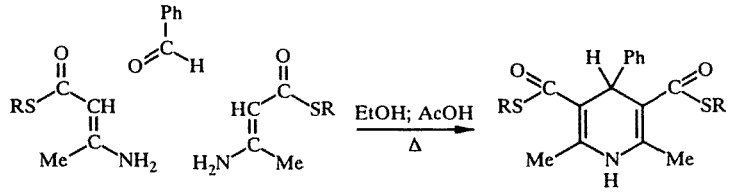


IX

XII a–d

a R = Et, Ar = 4'-$NO_2C_6H_4$; b R = Et, Ar = 2'-$NO_2C_6H_4$;
c R = Et, Ar = $C_5H_4N(3')$; d R = CH_2Ph, Ar = $C_5H_4N(3')$

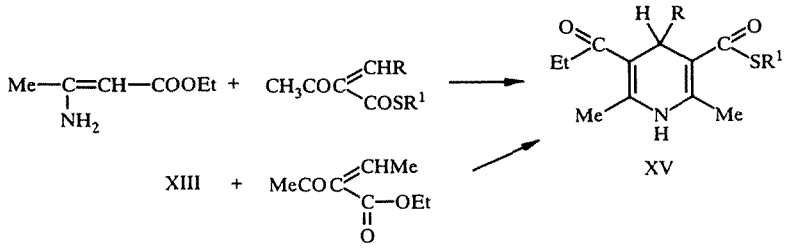
The 1,4-dihydropyridines (XIV) were obtained by the reaction of two moles of S-esters of β-aminocrotonic acid (XIII) with benzaldehyde in ethanol in the presence of acetic acid:



XIII XIV

R = Et, $PhCH_2$

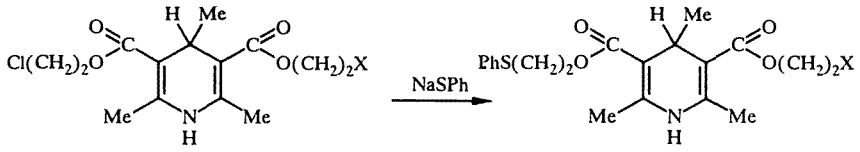
The unsymmetrical 3-ethoxycarbonyl-5-(ethylthio,benzylthio)carbonyl-1,4-dihydropyridines (XVa-e) were made by condensation of ethyl β-aminocrotonate with an S-ester of α-arylideneacetothioacetic acid or by interaction of an S-ester of β-aminothiocrotonic acid with ethyl α-ethylideneacetoacetate:



XV

R, R^1 = a Me, Et; b Me, $PhCH_2$; c Ph, Et; d Ph, $PhCH_2$;
e 4'-$NO_2C_6H_4$, Et

The reaction of β-chlorethoxycarbonyl-1,4-dihydropyridines with sodium thiophenoxide in ethanol was used to prepare the 4-methyl-1,4-dihydropyridines XVI with phenylthio substituents in the β position:

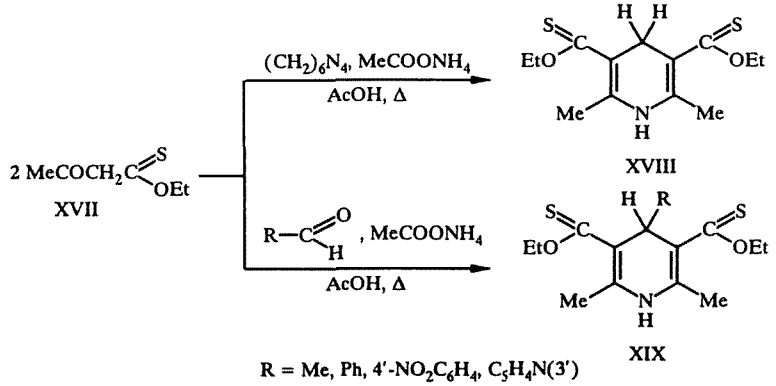


X = H, Cl XVI

X = H, SPh

This method broadens the possibilities of varying substituents in the β positions of dihydropyridine systems.

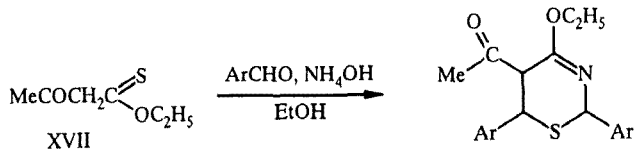
Methods for the preparation of 1,4-dihydropyridines with ethoxythiocarbonyl substituents in the β position have been developed [34]. For example, the 3,5-dithionic ester XVIII was formed when O-ethyl acetothioacetate (XVII) condensed with hexamethylenetetramine on heating in acetic acid in the presence of ammonium acetate. For the synthesis of the 4-substituted 1,4-dihydropyridines XIX the thioester XVII was condensed with aldehydes and ammonium acetate on heating in acetic acid.



XVII XVIII XIX

R = Me, Ph, 4'-$NO_2C_6H_4$, $C_5H_4N(3')$

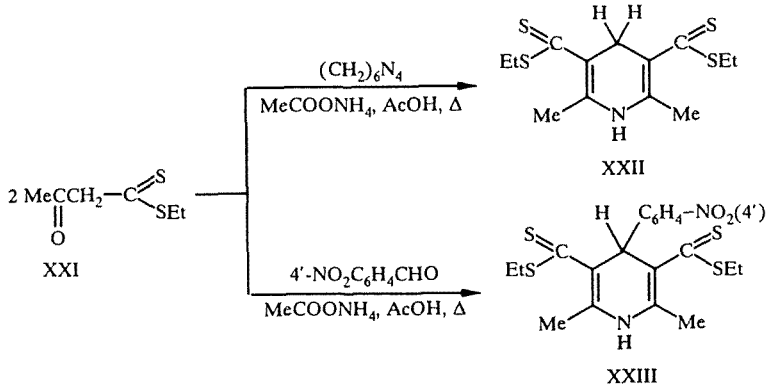
The essential condition for preparation of XIX is to carry out the reaction in acetic acid whereas 2H-5,6-dihydro-1,3-thiazine XX is formed from the thione ester XVII in ethanol solution:



XVII XX

Ar = Ph, 4'-$CH_3C_6H_4$, 4'-$CH_3OC_6H_4$, 4'-BrC_6H_4

The behavior of ethyl acetodithioacetate (XXI) under cyclocondensation reaction conditions to give 1,4-dihydropyridines has also been studied [35]. 2,6-Dimethyl-3,5-di(ethylthio)thiocarbonyl-1,4-dihydropyridine (XXII) was obtained by condensation of XXI with hexamethylenetetramine in glacial acetic acid in the presence of ammonium acetate:

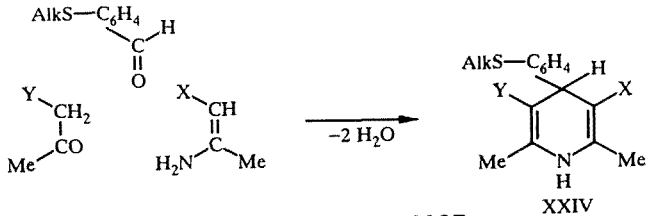


XXI XXII XXIII

Condensation of XXI with aromatic aldehydes is more difficult. The prolonged heating required for the cyclocondensation of XXI to give 1,4-dihydropyridines led to the decomposition of XXI and compound XXIII was the only substance isolated from this version of the reaction.

1.3. Sulfur-Containing Substituents in Position 4

Thioalkyl or similarly substituted phenyl groups are the most frequently encountered substituents at position 4 in 1,4-dihydropyridines (XXIV), and this results from the use of aldehydes in the Hantzsch synthesis [36-38]:



XXIV

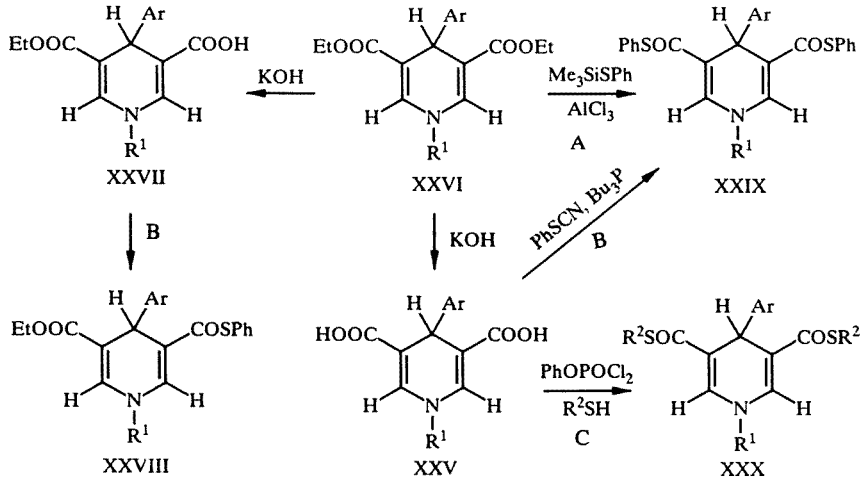
X, Y = COOMe, COOEt

Several papers which include the synthesis of 1,4-dihydropyridines with sulfur-containing heterocyclic substituents are primarily concerned with the biological properties of these compounds [5, 39-45].

1.4. Monocyclic 1,4-Dihydropyridines, Unsubstituted at Positions 2 and 6, with Sulfur-Containing β-Substituents

1,4-Dihydropyridines obtained by various modifications of the Hantzsch synthesis usually contain 2,6-dimethyl substituents. 1,4-Dihydropyridines without 2,6-substituents are usually prepared from propiolic acid esters and the sulfur atom is normally introduced into the β-position by thiolysis or thionation.

S-Esters of 2,6-unsubstituted 1,4-dihydropyridine-3,5-carbothiolic acids are not obtainable via the Hantzsch synthesis because S-alkyl (aryl) esters of thiopropiolic acid are not yet known [46, 47]. In this connection the thiolysis of 1,4-dihydropyridine-3,5-dicarboxylic acids (XXV), their diesters (XXVI) and their acid esters (XXVII) has been studied [48].

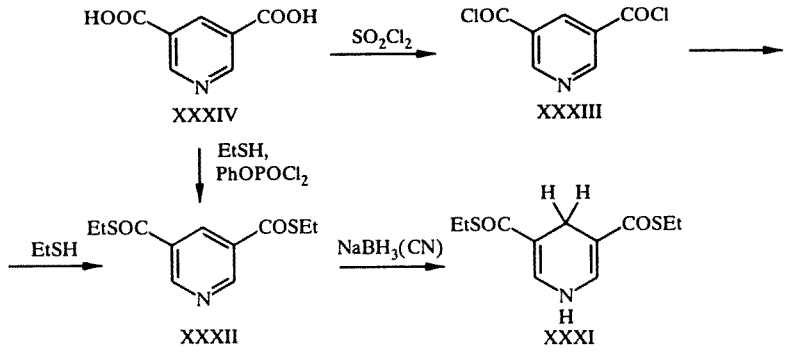


R^1 = H, Me, Ph; R^2 = Et, CH_2Ph

Trimethyl(phenylthio)silane reacts with 1,4-dihydropyridine-3,5-dicarboxylic acid esters (XXVI) in the presence of aluminum chloride (method A) to give the corresponding phenylthio esters (XXIX).

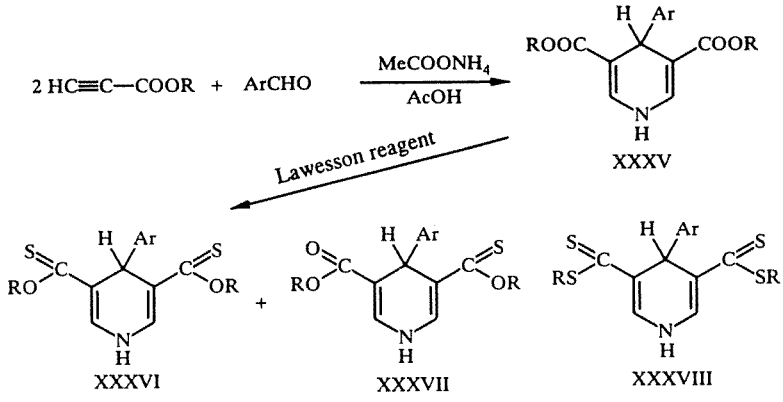
4-Aryl-1,4-dihydropyridine-3,5-dicarboxylic (XXV) and 5-alkoxycarbonyl-3-carboxylic acids (XXVII) are readily thiolated with phenylthiocyanate in the presence of an equimolar amount of tributylphosphine (method B). The most general method for the synthesis of thiol esters of 1,4-dihydropyridine-dicarboxylic acids is direct thiolysis of the corresponding acid with thiols in dimethoxyethane in the presence of phenyl dichlorophosphate as acid activator (method C).

In contrast to the 4-arylsubstituted 1,4-dihydropyridines XXVI, 1,4-dihydropyridine-3,5-dicarboxylic acids without 4-substituents are not thiolysed by thiols in the presence of phenyl dichlorophosphate. 3,5-Di(ethylthiocarboxyl-1,4-dihydropyridine (XXXI) is produced in almost quantitative yield by the reduction of pyridine XXXII with sodium cyanotrihydroborate in acetic acid:



The pyridine starting material XXXII was made by thiolysis of either the acid chloride XXXIII or of pyridine-3,5-dicarboxylic acid with ethanethiol.

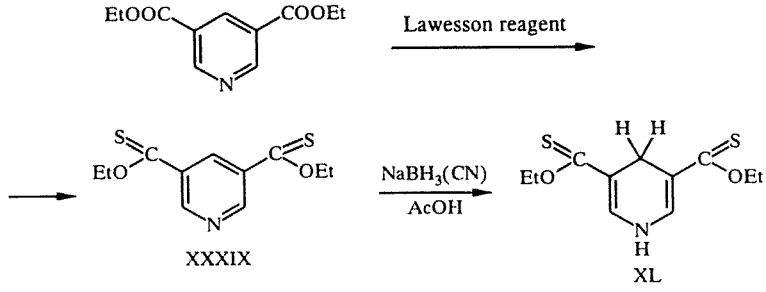
Methods have been developed for the preparation of ethyl 1,4-dihydropyridinedicarbothionates unsubstituted in positions 2 and 6. 4-Aryl-3,5-diethoxythiocarbonyl-1,4-dihydropyridines (XXVI) have not been prepared by cyclocondensation because the corresponding thionic of propiolic acid are not yet known. A method has been proposed for the thionation of carbonyl and alkoxycarbonyl groups in aliphatic and aromatic compounds and also keto groups in the indene unit of 5-oxo-4,5-dihydroindenopyridines [50, 51]. 4-Aryl-3,5-diethoxycarbonyl-1,4-dihydropyridines (XXXV) react readily with Lawesson's reagent (p-methoxyphenylthionophosphine sulfide dimer) to give the thione esters XXXVI.



The monothione esters XXXVII are also formed as byproducts. p-Electron donor substituents on the phenyl group in position 4 in compounds XXXV facilitate thionation. It is likely that both electronic and steric effects of substituents in position 4 play an important role. Neither 2,6-dimethyl- nor 2,6-diphenyl-1,4-dihydropyridine-dicarboxylate esters undergo this reaction probably because of the steric effects of the 2,6-substituents.

A substituent on nitrogen in the 2,6-unsubstituted derivatives increases the reactivity of the β-alkoxycarbonyl groups.

The thiol esters of 1,4-dihydropyridinedicarboxylic acid (XXX, R^1 = H) are more readily thionated than their oxygen analogs XXXV, which permits the ready preparation of 1,4-dihydropyridine-3,5-di(dithio)carboxylate esters (XXXVIII) which are not obtainable by any other route. In contrast to the 4-aryl-1,4-dihydropyridines (XXXV), the 3,5-dialkoxycarbonyl-1,4-dihydropyridines unsubstituted at position 4 do not undergo thionation because of their low reactivity and ease of oxidation. 3,5-Diethoxythiocarbonyl-1,4-dihydropyridine XL was made by reduction of the pyridine XXXIX with sodium borohydride in acetic anhydride:

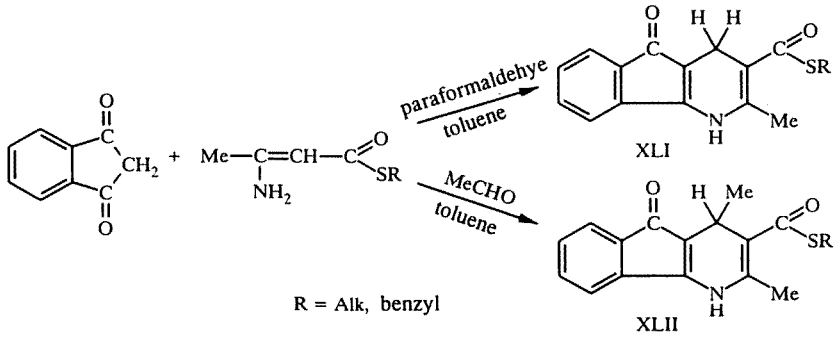


The 1,2-isomer, 3,5-diethoxythiocarbonyl-1,2-dihydropyridine, was also isolated from the reaction mixture. The 1,4-isomer exclusively in almost quantitative yield was obtained when sodium cyanotrihydroborate was used as reducing agent. Despite reports [53, 54] of the inertness of 2-, 2,6- and 3-pyridinecarboxylic acids towards the Lawesson reagent, other authors [52] obtained 3,5-diethoxythiocarbonylpyridine (XXXIX) in high yield by prolonged boiling of 3,5-diethoxycarbonyl-pyridine with Lawesson's reagent in xylene in the presence of pyridine under an inert atmosphere.

2. POLYCYCLIC 1,4-DIHYDROPYRIDINES CONTAINING SULFUR

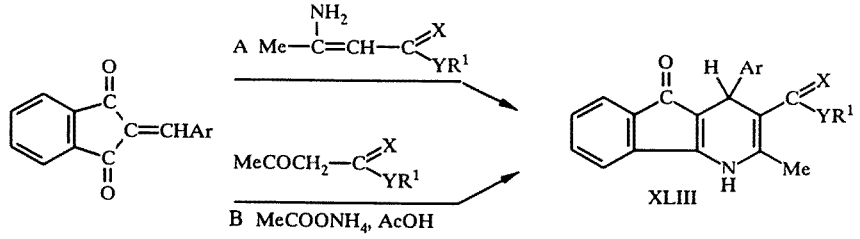
2.1. Synthesis of 5-Oxo-4,5-dihydro-1H-indeno[1,2-b]pyridines with Sulfur-Containing Substituents in Position 3

4-Unsubstituted-2-methyl-3-(alkylthio-, benzylthio)carbonyl-5-oxo-4,5-dihydro-1H-indeno[1,2-b]pyridines (XLI) and the 4-methyl derivatives (XLII) were synthesized by the reaction of 1,3-indanedione, an aldehyde and β-aminothiocrotonic acid [34, 35, 55]:



R = Alk, benzyl

4-Aryl substituted dihydroindenopyridines XLIII were prepared in two ways: 1) from 2-arylidene-1,3-indanediones and β-aminothiocrotonate esters, analogously to the known method for the synthesis of their oxygen containing analogs [56] (method A), and 2) by direct condensation of acetothioacetate and acetodithioacetate esters with 2-arylidene-1,3-indanediones in the presence of excess ammonium acetate as nitrogen source (method B). The latter is the more suitable and shorter method for preparing the desired products in one step and in considerably greater yield:

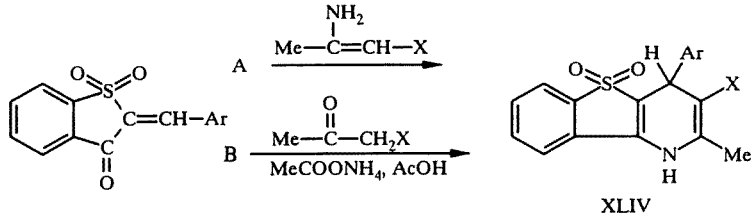


R^1 = Et, CH_2Ph, *n*-Pr; X, Y = O, S

This method can be used to prepare a variety of dihydroindenopyridines of type XLIII with other substituents in position 3 (COMe, CO_2Et, $CSNH_2$, CSNHPh).

2.2. Synthesis of 1,4-Dihydrobenzothieno[3,2-b]pyridines and Dihydrothieno[3,2-b]pyridines

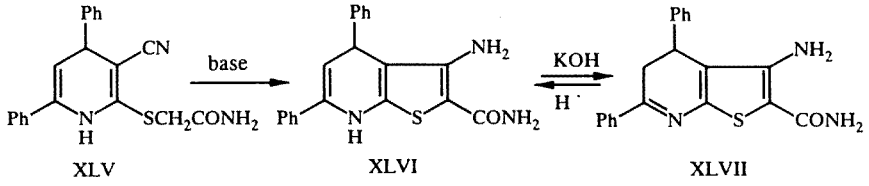
A method for preparing 1,4-dihydrobenzothieno[3,2-b]pyridine-5,5-dioxides [57] with electron accepting groups in position 3 (XLIV) consists in condensation of 2-arylidene-1-thionaphthenone-3-dioxides-1,1 with enamine derivatives of β-dicarbonyls. A series of compounds XLIV with (alkylthio)carbonyl-, ethoxythiocarbonyl-, and (ethylthio)thiocarbonyl groups in position 3. The 1-thionaphthenone-3-dioxide-1,1 and 2-arylidene derivative starting materials were made by a literature method [58-60]. Compounds of type XLIV were obtained by condensation of a 2-arylidene-1-thionaphthenone-3-dioxide-1,1 with enamine components (esters of β-aminocrotonic and β-aminothiocrotonic acids) in acetic acid with short heating (method A). An improved method (method B) is the condensation of a 2-arylidene-1-thionaphthenone-3-dioxide-1,1 with acetoacetate esters, other β-diketones or their derivatives in the presence of ammonium acetate [57]:



X = COMe, COOMe, COOEt, COSEt, CSOEt, CSSEt, CN

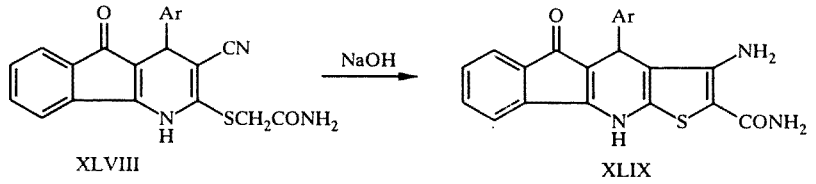
1,4-Dihydrobenzothieno[3,2-b]pyridine-5,5-dioxides unsubstituted at position 4 and their 4-methyl derivatives react with enamines and aldehyde components analogously to the dihydroindenopyridines.

It has been shown [16, 18, 61] that the 3-cyano-2-(carbamoylmethylthio) derivative XLV forms a 1:1 mixture of 3-amino-2-carbamoyl-4,6-diphenyl-4,7-dihydrothieno[2,3-b]pyridine (XLVI) and 3-amino-2-carbamoyl-4,6-diphenyl-4,5-dihydrothieno[2,3-b]pyridine (XLVII) when treated with an equimolar amount of base (KOH, MeONa) at 50-60°C. With excess base the principal product is the 4,5-dihydro compound XLVII. Acidification of a solution of XLVII causes reversible isomerization.



So facile interconversion of 1,4- and 3,4-dihydropyridines is observed during condensation of pyridine derivatives.

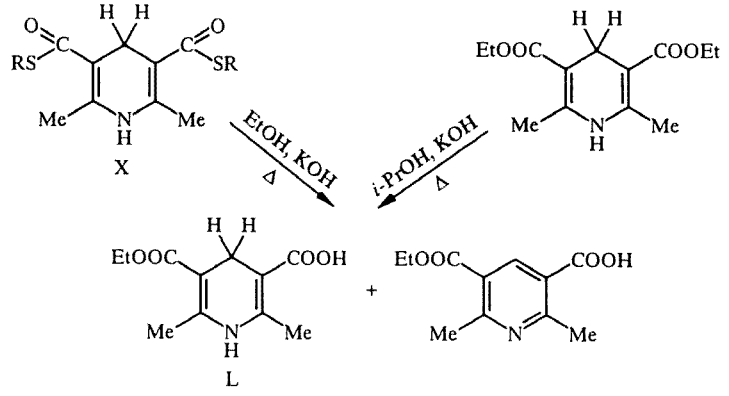
Condensation of 2-arylidene-1,3-indanediones with cyanothioacetamide in the presence of piperidine with subsequent treatment with an alkyl halide gave 5-oxo-2-alkylthio-1,4-dihydroindeno[1,2-b]pyridines (XLVIII) which readily close the thiene ring in basic media to give 3-amino-5-oxo-4-aryl-4,10-dihydro-indeno[1′,2′:6,5]pyrido[2,3-b]thiophenes (XLIX) [14]:



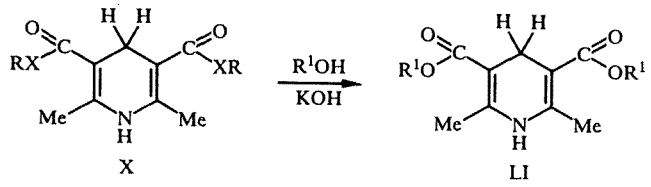
3. REACTIVITY OF 1,4-DIHYDROPYRIDINES CONTAINING SULFUR

3.1. Hydrolysis and Transesterification of Sulfur-Containing Esters of 1,4-Dihydropyridinedicarboxylic Acids

The necessary conditions for the hydrolysis of the stable esters of 1,4-dihydropyridine-3,5-dicarboxylic acids [62, 63] are the presence of a substituent on nitrogen and the absence of a substituent at position 4 [64]. S-Esters with no substituents in positions 1 and 4 undergo hydrolysis of one (ethylthio or benzylthio)carbonyl group and transesterification at the other when boiled in ethanol with three equivalents of potassium hydroxide. 2,6-Dimethyl-3-ethoxycarbonyl-1,4-dihydropyridine-5-carboxylic acid (L) was also obtained by hydrolysis of 2,6-dimethyl-3,5-diethoxycarbonyl-1,4-dihydropyridine on prolonged boiling with isopropanol and excess potassium hydroxide [65]. Yield of the acid was low because oxidation of the dihydropyridine ring accompanied hydrolysis:

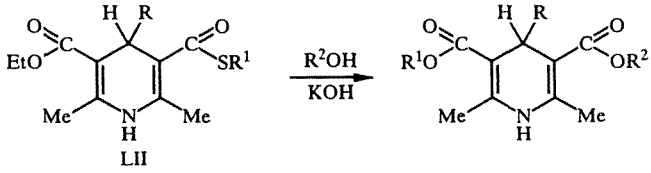


Transesterification of S-esters of 1,4-dihydropyridine-3,5-dithiocarboxylic acids with primary alcohols and potassium hydroxide to give LI occurred more readily than for the esters of 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acids [65]:



X = O, S; R = Et, CH_2Ph; R^1 = Alk

With esters of 1,4-dihydropyridinecarboxylic acids unsymmetrically substituted at positions 3 and 5 alcoholysis occurred selectively at the (ethylthio)carbonyl group which confirmed its greater reactivity with respect to transesterification [55]:

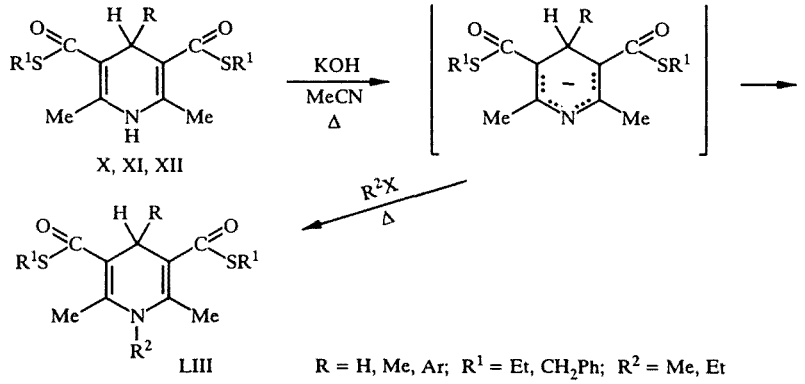


R = H, Me, Ph; R^1 = Et, Ph; R^2 = Alk

3.2. N-Alkylation of 1,4-Dihydropyridines Containing Sulfur

N-alkylation of a series of sulfur-containing monocyclic and polycyclic 1,4-dihydropyridine anions has been studied in order to elucidate the effects of sulfur-containing esters on the reactivity of 1,4-dihydropyridines. Apart from its preparative value, investigation of the alkylation of dihydropyridine anions allows the effect of electron acceptor substituents at positions 3 and 5 on the rate of formation and stability of the N-anions to be studied. In the literature [66, 67] it is reported that sodium hydride must be used to obtain the anions of 3,5-diethoxycarbonyl-1,4-dihydropyridines unsubstituted at nitrogen because they are weak N−H acids. The 3,5-dicyano-1,4-dihydropyridines are stronger N−H acids which are readily alkylated with alkyl halides in the presence of base [68].

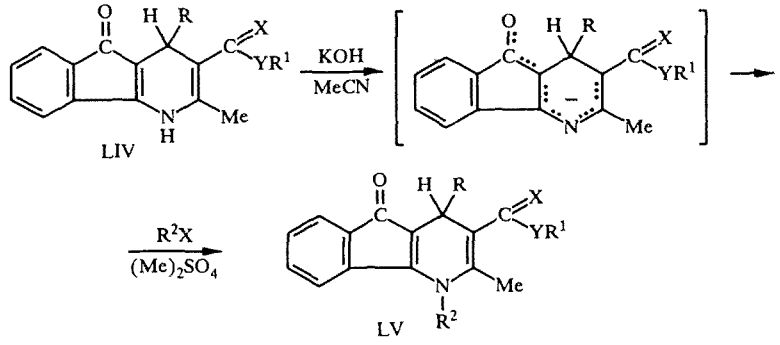
The S-esters of 1,4-dihydropyridine-3,5-dithiocarboxylic acids X, XI and XII react with alkyl halides or dimethyl sulfate on boiling in acetonitrile in the presence of potassium hydroxide [31]:



R = H, Me, Ar; R^1 = Et, CH_2Ph; R^2 = Me, Et

Substitution at position 4 makes alkylation easier in comparison with the unsubstituted 1,4-dihydropyridines: the most reactive are the 4-aryl-1,4-dihydropyridines. Consequently it is concluded that compounds X, XI and XII have greater N−H acidity than their oxygen analogs. Isolation of N-alkyl derivatives from the alkylation of the 3,5-diethoxythiocarbonyl-1,4-dihydropyridines XVIII and XIX was not successful although it has been observed spectrophotometrically that XVIII and XIX are sufficiently strong acids and form anions in the presence of potassium hydroxide in acetonitrile. It may be surmised that delocalization of the negative charge in the anion of 3,5-diethoxythiocarbonyl-1,4-dihydropyridines as a result of the polarizability of the sulfur atom in the thiocarbonyl group and that this decreases the basicity of the nitrogen atom.

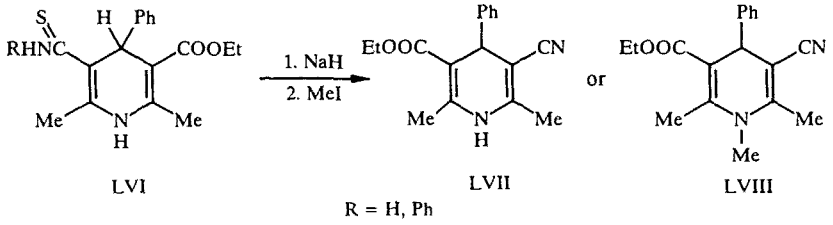
Alkylation in acetonitrile solution in the presence of potassium hydroxide of sulfur-containing 5-oxo-4,5-dihydroindeno[2,3-b]pyridines of type LIV was carried out to determine the effect of the sulfur-containing groups COSR, CSOR and CSSR on the β-aminovinyl systems in a series of compounds with greater acidity and greater stability to oxidation [55]:



X, Y = O, S; R = Me, Ar; R^1 = Et, CH_2Ph; R^2 = Me, Et

Alkylation of a series of polycyclic 1,4-dihydropyridines LIV to give the N-alkyl derivatives LV occurred considerably more rapidly than with monocyclic 1,4-dihydropyridines.

1,4-Dihydropyridines with thioamide groups in position 3 (LVI) were obtained by condensation of the amide or thioamide of β-aminocrotonic acid with benzylideneacetoacetic ester [69].

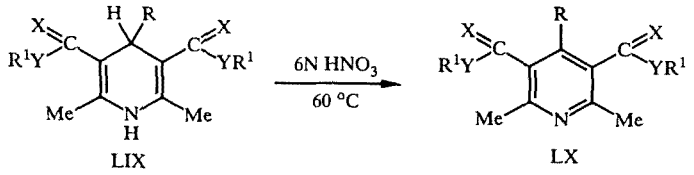


R = H, Ph

Depending on the reaction conditions, alkylation of the thioamide LVI (R = H) gave either the nitrile LVII or its N-methyl derivative LVIII. This is explained by initial methylation of the thioamide group to give an iminoether which loses methanethiol under basic conditions to form the nitrile LVII. The 1-methyl compound LVIII is formed in the presence of a large excess of lithium hydride and the alkylating agent.

3.3. Oxidation of Sulfur-Containing 1,4-Dihydropyridines

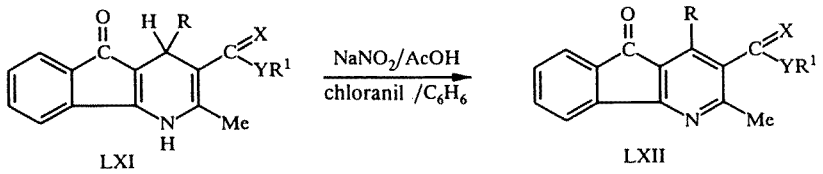
Oxidation of the dihydropyridine ring of sulfur-containing 1,4-dihydropyridines (LIX) is carried out in two ways: with tetrachloro-1,4-benzoquinone (chloranil) in benzene or by heating in 6M nitric acid [31, 34, 55]. In both cases only the dihydropyridine ring is oxidized to give the heteroaromatic system LX.



X, Y = O, S; R = H, Me, Ar; R^1 = Et, CH_2Ph

Oxidation of the oxygen-containing analogs with chloranil showed that 4-aryl-1,4-dihydropyridines were more stable with respect to the oxidant than were the 4-unsubstituted analogs.

Sodium nitrite in acetic acid and chloranil in benzene were used for the oxidation of condensed dehydrogenated sulfur-containing 1,4-dihydropyridines LXI. In both cases the corresponding heteroaromatic compounds, the pyridines LXII, were isolated.



LXI LXII

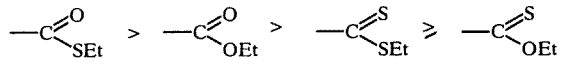
X, Y = O, S; R = H, Ar; R^1 = Et, CH_2Ph

The thioamide LVI (R = H) lost hydrogen sulfide on oxidation with sodium nitrite in acetic acid to give 5-ethoxycarbonyl-4-phenyl-2,6-dimethylpyridine-3-carbonitrile [69]. The electrochemical oxidation potentials of 1,4-dihydropyridines change in parallel with the electronegativity of the β-substituents and range between 800 and 1200 mV [71]. Introduction of the same substituent in position 4 leads to an increase in the oxidation potential by 70 to 200 mV [31, 72].

A systematic study [31] of electrochemical oxidation of sulfur-containing esters of 1,4-dihydropyridinedicarboxylic acids showed that replacement of the oxygen atom by sulfur in one ester group of LII increased the electrode potential by 30-40 mV while replacement of oxygen by sulfur in both ester groups of (X-XII) led to a doubling of the potential. This confirms that the additive electron acceptor effect of the (alkylthio)carbonyl group is greater than that of the alkoxycarbonyl group.

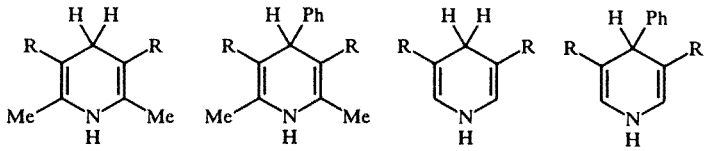
The electrochemical oxidation potentials of the thiones (XVIII, XIX) and dithioesters (XXII) are lower than those of the carbonyl analogs by 40-100 mV, presumably because these groups are weaker electron acceptors than ethoxycarbonyl substituents in the 1,4-dihydropyridine system.

From these results ester substituents fall in the following order [35] of decreasing passivating effect on electrochemical and chemical oxidation of monocyclic and polycyclic 1,4-dihydropyridines to pyridines:

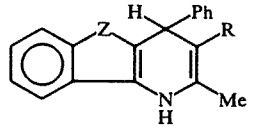


3.4. Acid-Base Properties of Monocyclic and Polycyclic 1,4-Dihydropyridines

1,4-Dihydropyridines with electron accepting substituents in the β-positions are almost devoid of basic properties [73, 74]. Before a systematic study of the acid−base properties os sulfur-containing 1,4-dihydropyridines and their oxygen analogs [34, 35] acid dissociation constants of derivatives of 1,4-dihydropyridines had only been determined for some tricyclic compounds: 5-oxo-4,5-dihydroindeno[1,2-b]pyridines [75] and 2,4,6-trioxo-5,8,8-trimethyl-1,2,3,4,5,6,7,8,9,10-decahydropyrimido[4,5-b]quinoline [76]. The NH-acidity equilibria of monocyclic 1,4-dihydropyridines (LXIII-LXVI) and indeno-1,4-dihydropyridines (LXVII) were studied more recently. The pK_a values were determined spectroscopically [34, 55] and by transmetallation [77].



LXIII LXIV LXV LXVI



LXVII

R = COOEt, COSEt, CSOEt, CSSEt, COMe, CN, NO_2; Z = CO, SO_2

pK values for the monocyclic 1,4-dihydropyridines (LXIII-LXVI) ranged from 9 to 20 pK units in DMSO and depended principally on the nature of the substituents R. The substituents fell in the following order of increasing acidifying effect: COOEt < COMe < COSEt < CSOEt < CN < CSSEt < NO_2.

The indeno-1,4-dihydropyridines (LXVII) are stronger NH acids than the monocyclic 1,4-dihydropyridines (LXIII-LXVI) [35]. Replacement of a carbonyl group by a sulfonyl group in indeno-1,4-dihydropyridines (LXVII, Z = SO_2) caused no noticeable change in the NH acidity in DMSO, whereas the pK values for derivatives of LXVII (Z = SO_2) determined spectrometrically in 50% ethanol were on average 0.5-0.7 pK units greater than those of their carbonyl analogs [60].

Analysis of the pK values for the series of compounds LXVI [78] showed an excellent linear relationship between pK and the σ_I and σ_R^- constants of the corresponding substituents R, and this made possible calculation of the previously unknown σ_R^- constants for sulfur-containing ester groups. It follows from a comparison of these σ_R^- constants that the ability of the substituents −C(X)YEt (X, Y = O, S) to conjugate with the NH acid center of 1,4-dihydropyridine increased on replacing an oxygen atom by sulfur. Replacement of the carbonyl oxygen had a particularly noticeable effect which may be due either to participation of the sulfur d-orbitals in conjugation or to the ready polarizability of the sulfur atom. Because of this resonance the contribution of the −C(S)XEt (X = O, S) substituent to stabilization of the N-anion of 1,4-dihydropyridines is considerably greater than the contribution from their inductive effects.

As a result of a systematic study of the physical and physico-chemical properties of sulfur-containing esters of 1,4-dihydropyridinedicarboxylic acids Vigante et al. [35] concluded that the (ethylthio)carbonyl group is a stronger electron acceptor than the ethoxycarbonyl group in 1,4-dihydropyridines in all reactivity series (pK, oxidation kinetics, alkylation of 1,4-dihydropyridines) and in aromatic systems (^{13}C and ^{19}F NMR spectra), largely as a result of its strong inductive effect. On the other hand the ethoxythiocarbonyl and (ethylthio)thiocarbonyl groups have stronger electron accepting properties than the ethoxycarbonyl group when the thione group participates in delocalization of the negative charge (acid ionization of 1,4-dihydropyridines), whereas in conversions of 1,4-dihydropyridines without loss of the N−H proton (electrochemical oxidation) and in aromatic compounds these groups are weaker electron acceptors than the ethoxycarbonyl group.

In summary, the results examined witness to the special place of sulfur-containing 1,4-dihydropyridines in the chemistry of hydrogenated nitrogen-containing heterocyclic compounds.

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