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CHEMISTRY OF PYRIDO[c]COUMARINS (REVIEW)

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Information on methods of synthesis and the chemical conversions of pyrido[c]coumarins has been correlated and arranged systematically.

The chemistry of coumarins condensed with aromatic, heteroaromatic (chiefly furo- and pyranocoumarins), and alicyclic systems has received much attention. This is due to the fact that some occur in natural products, they possess important biological and physical properties, and display chemical properties interesting for synthetic practice. Information on the useful properties of coumarins condensed with a pyridine ring is limited by the small number of publications on the synthesis and study of certain derivatives of pyridocoumarins as laser dyestuffs [1-3], luminescence intensifiers [4], and as spasmolytics [5]. In addition, pyridocoumarins linking in their structure combined nuclei of benzene, α-pyrone, and pyridine enable the mutual influences of these aromatic fragments on their chemical properties to be considered.

Studies of the chemistry of the pyridocoumarins reduce mainly to the development of methods of synthesizing them. In the overwhelming majority of cases coumarins were obtained condensed with a pyridine ring at the C_3-C_4 bond, i.e. pyrido[c]coumarins, information on which is the subject of this review. Scientific papers on pyridocoumarins published up to 1980 were correlated in a single review, which however was not complete since the authors had set themselves the broader problem of describing methods of obtaining coumarins annelated at the C_3-C_4 bond with five- and six-membered N-, O-, and S-heterocycles [6]. The chemical conversions of pyridocoumarins have as yet not been analyzed in reviews.

1. METHODS OF SYNTHESIZING PYRIDO[c]COUMARINS

It is possible to obtain four isomeric pyridocoumarins when joining a pyridine nucleus with a coumarin fragment at the C_3-C_4 bond. These are also known in the literature as coumarinopyridines of benzopyridopyranes.

The known methods of synthesizing pyridocoumarins may be subdivided into the following groups.

1. Cyclization of pyridines substituted with aryl groups.
2. Cyclization of substituted coumarin and chromones:
   - 2.1. Synthesis from hydroxy(amino)coumarins.
   - 2.2. Pyridocoumarins from acyl(alkoxycarbonyl)coumarins.
   - 2.3. Synthesis from chromenes.
3. Condensation of phenols with alkoxycarbonyl-substituted piperidones – the method of Pechman.
4. Condensation of salicylic aldehydes with derivatives of acetoacetic ester or malonic acid in the presence of ammonia.

1.1. Cyclization of Aryl-Substituted Pyridines

The first syntheses of pyridocoumarins were effected in the early fifties [7-9]. A fairly obvious route was used, i.e. the condensation of pyridinecarboxylic acid derivatives (esters, nitriles, etc.) having a 2-hydroxy-(alkoxy)phenyl substituent in the position ortho to the functional group. This approach has also been used successfully to synthesize almost all the possible isomeric pyridocoumarins [10, 11].

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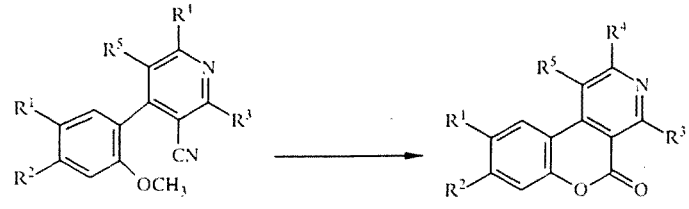
The 3-cyano derivatives of 4-(2-methoxyphenyl)-pyridines (I) are cyclized in the presence of HBr (48%), HCl, or in an Fe/HCl system to pyrido[3,4-c]coumarins (II) in yields of 22-82% [8, 9].

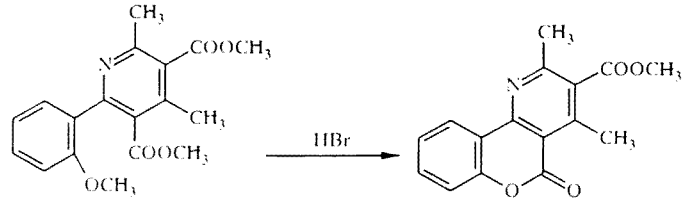


I II

R^1 = H, NO_2, NH_2; R^2 = H, OCH_3, OH; R^3 = R^4 = CH_3, C_6H_5; R^5 = H, CN, COOH

On using 4-aryl-substituted pyridinecarboxylic acids or their acid chlorides as starting materials, the analogous derivatives are formed in high yield (55-91%) [7, 11].

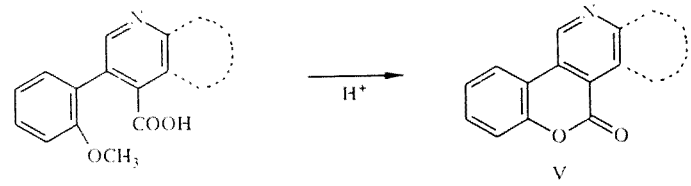
Heating esters of pyridine-3,5-dicarboxylic acid (III) with HBr leads to the formation of the pyrido[3,2-c]coumarin (IV) in 55% yield [11].



III IV

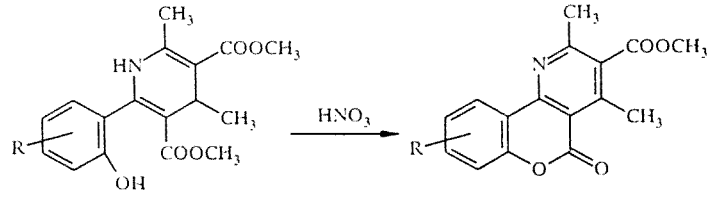
Treatment of 1,4-dihydro derivatives of 3,5-di-carbethoxy-4-(2-methoxyaryl)pyridine with boron tribromide in methylene chloride leads to dihydropyrido[3,4-c]coumarins in 90% yield [12].

The unsubstituted pyrido[4,3-c]coumarin (V) was obtained in quantitative yield by heating 3-(2-methoxyphenyl)pyridine-4-carboxylic acid in HBr (or CH_3COOH) [13]. The analogous lactonization also proceeds readily when using arylquinolines [14-16].



V

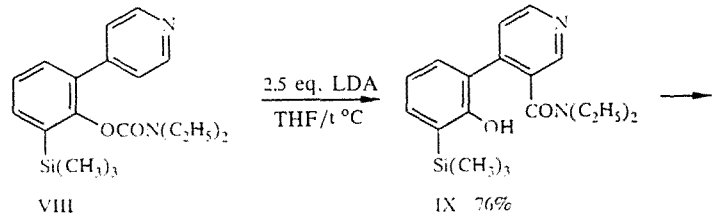
The substituted pyrido[3,2-c]coumarins (VII) were obtained in moderate yields (up to 35%) by the oxidation of the 2-(2-hydroxyphenyl)-1,2-dihydropyridines (VI) with 2 N HNO_3 [11].



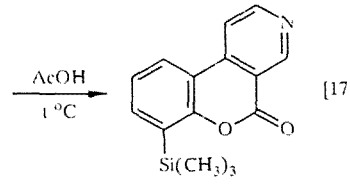
VI

VII
R = H (24%), 8-OCH_3 (22%), 9-OCH_3 (30%), 9-Cl (35%)

The pyridinecarboxylic acid derivatives required were generated during the synthesis in a series of studies.

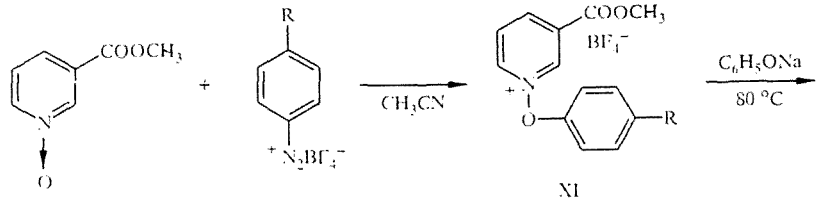


VIII IX 76%



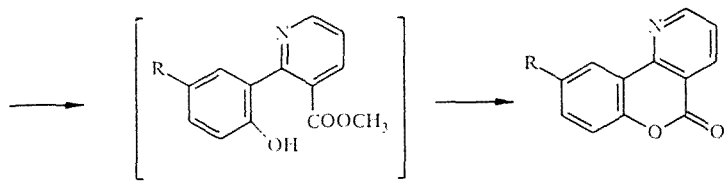
[17]

X 90%



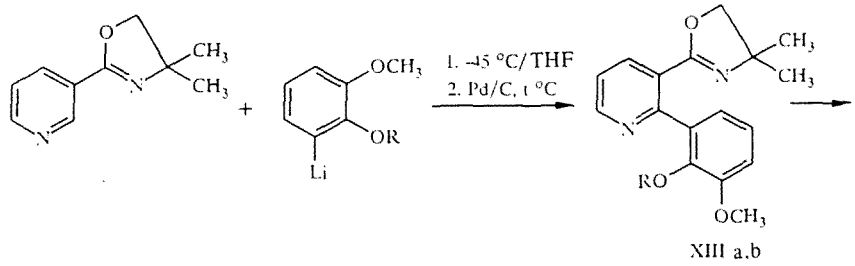
XI

[18]

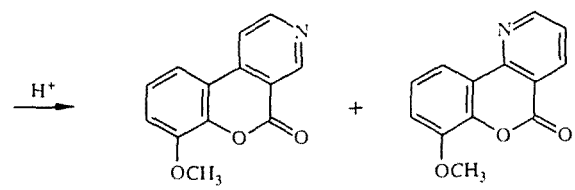


XII

R = NO_2 (50%),
R = CN (49%)



XIII a,b



[19]

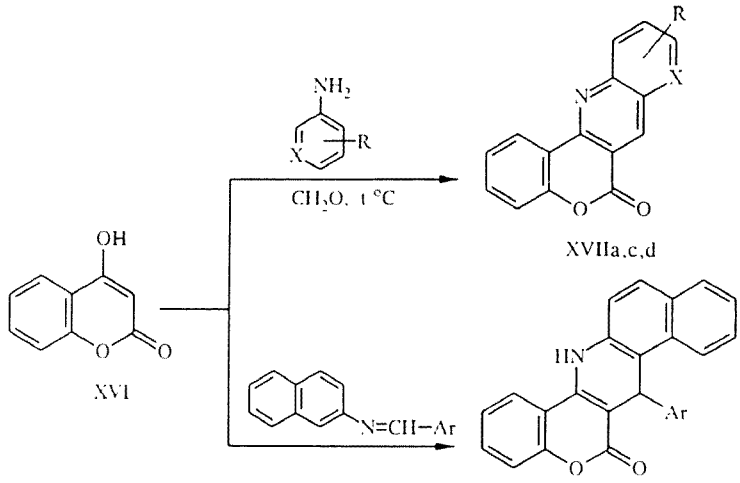
XIV 70% XV 4%

R = CH_3, CH_2OCH_3

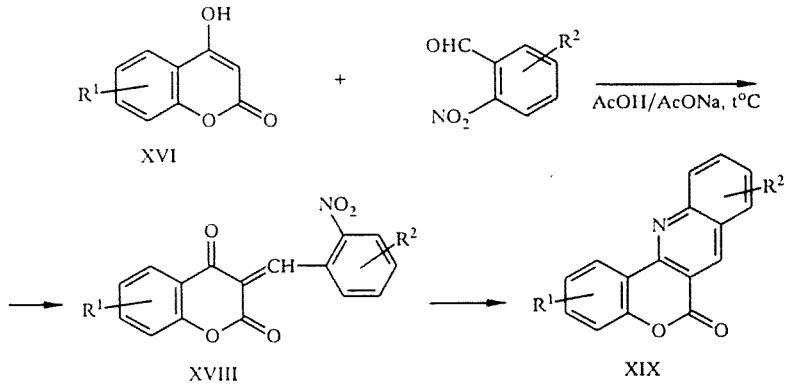
In spite of the obvious general nature of this method no pyrido[4,3-c]- and [2,3-c]coumarins have been obtained up the present, which is probably connected with the poor availability of β-aryl substituted pyridinecarboxylic acids and their derivatives.

1.2. Cyclization of Substituted Coumarins and Chromones

1.2.2. Syntheses from Hydroxy(amino)coumarins. An original and productive approach to the synthesis of various pyrido[3,2-c]coumarins (XVIII) annelated at the C_2-C_3 position of the pyridine fragment with benzene, naphthalene, thienobenzene, fluorene, pyridine, and quinoline fragments was proposed in 1966 [20]. It consisted of the condensation of the hydroxycoumarin (XVI) with aniline (or naphthylamines or other aromatic amines including heterocyclic amines) and paraformaldehyde by heating to 220-240°C in vacuum [21-24]. The arylamine component may be used in the form of a Schiff's base [25]. Yields of the desired polycyclic compounds were 20-45%.

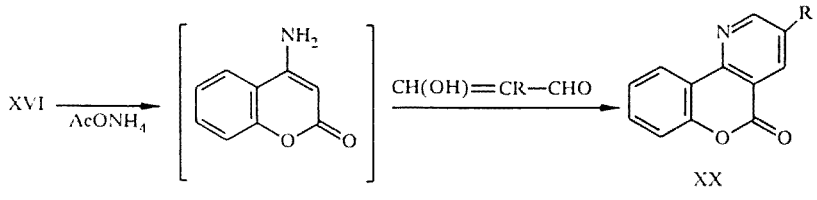


The quinolino[3,2-c]coumarin XIX was also obtained by boiling (XVI) for 10 h with 2-aminobenzaldehyde in the presence of piperidine [24] or by the reduction of 3-(2-nitrobenzylidene)chroman-2,4-diones (XVIII) (40-70% yield) [5].

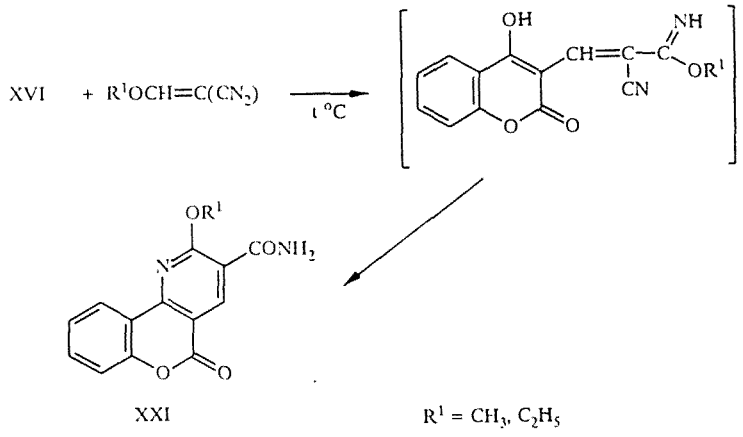


These compounds possess marked spasmolytic activity. A pentacyclic chromonocoumarinopyridine has been synthesized by an analogous condensation of the derivative (XVI) with 2-amino-4-oxochromene-3-carbaldehyde [26].

On heating compound (XVI) with ammonium acetate in glacial acetic acid it is converted into a 4-aminocoumarin which reacts without isolation with substituted malondialdehydes to form the pyrido[3,2-c]coumarins (XX) in 59-65% yield [27].

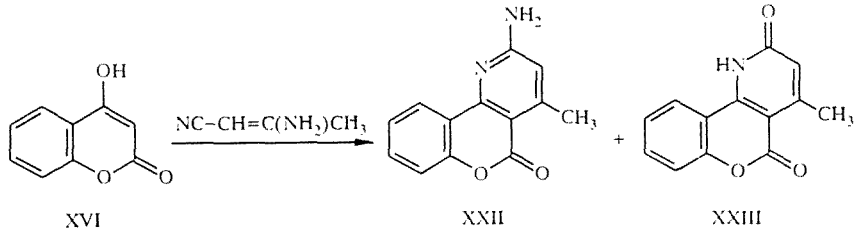


Condensation of the hydroxycoumarin (XVI) or its sodium salt with ethoxy(methoxy)methylenemalononitrile also leads to the formation in moderate yield of the pyrido[3,2-c]coumarin derivatives (XXI) [28].



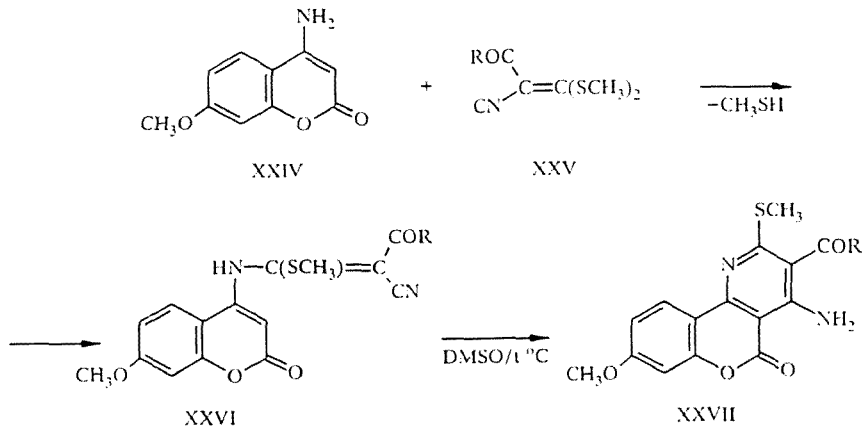
XXI $R^1 = CH_3, C_2H_5$

The reaction of the 4-hydroxycoumarin (XVI) with aminocrotonitrile leads in one step to a mixture of 4-methyl substituted 2-amino- (XXII) and 2-oxopyrido[3,2-c]coumarins (XXIII) [29].



XVI XXII XXIII

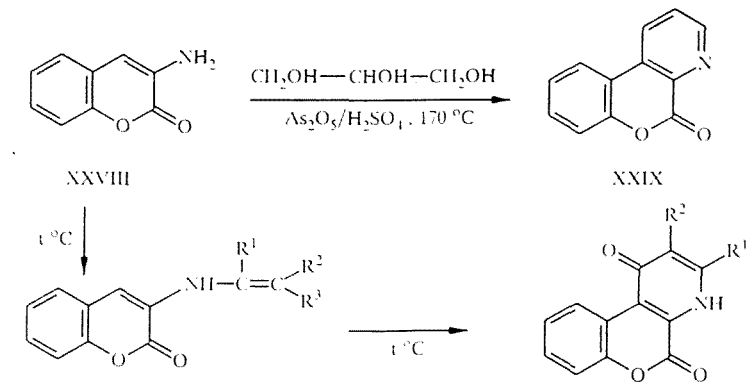
The intermediate amine (XXVI) was successfully isolated when obtaining the 2-methylthio substituted pyrido[3,2-c]coumarins (XXVII) from the 4-aminocoumarin (XXIV) with the di(methylthio)methylene derivative of malonitrile ester (XXV) [30].



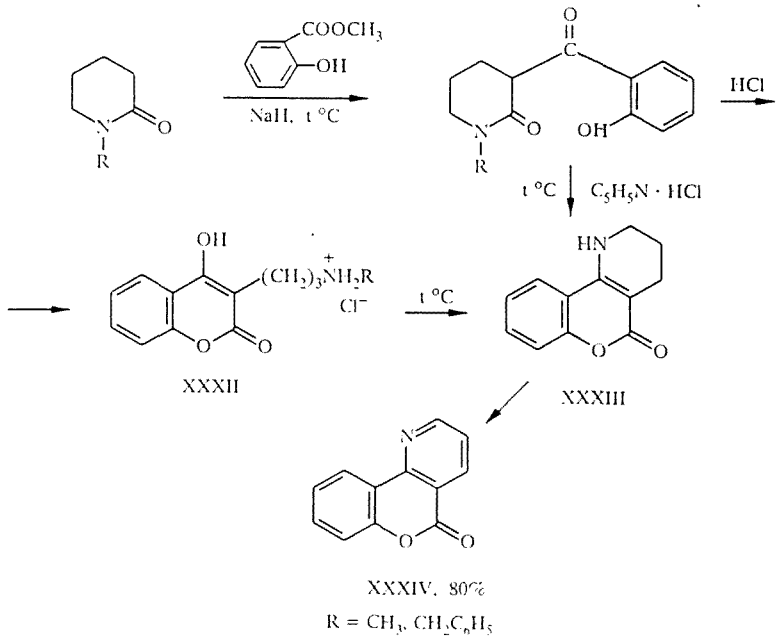
XXVI XXVII

R = OCH_3, OC_2H_5, $NHC_6H_4CH_3$-*p*

The difficulty available pyrido[2,3-c]coumarin system (XIX) was constructed on the same principle. The synthesis was effected for the first time in 1977 [31] using the Skraup reaction from 3-aminocoumarin (XXVIII) in 55-60% yield.

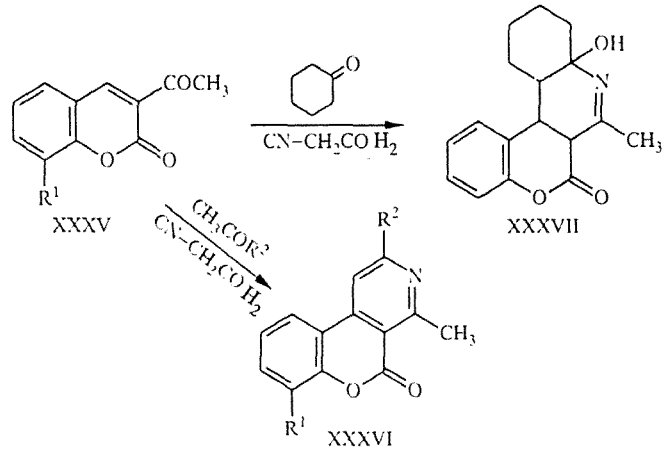


The synthesis in good yield of the pyrido[3,2-c]coumarin (XXXIV) by the thermal cyclization of the 3-(3-alkylamino-1-propyl)-4-hydroxycoumarin salt (XXXII) has been reported according to the following scheme [32].



The tetrahydro derivative (XXXIII) may also be obtained in one step without isolating the 4-hydroxycoumarin (XXXII) by heating 3-(2-hydroxybenzoyl)-2-piperidone with piperidine hydrochloride (30-42% yield).

1.2.2. Pyridocoumarins from Acetyl(alkoxycarbonyl)-coumarins. In the first study of this route a series of pyrido[3,4-c]coumarins (XXXVI) was obtained in 21-64% yield by the reaction of the 3-acetylcoumarins (XXXV) with ketones (acetone, methyl ethyl ketone, acetophenone) [33]. The amide group of cyanoacetamide was used as nitrogen source (the use of ammonia or ammonium acetate did not lead to cyclization). The reaction with cyclohexanone stops at the stage of the intermediate alcohol (XXXVII) (48% yield) which indicates the sequence of the similar multistage conversion of acetylcoumarin to pyridocoumarin.



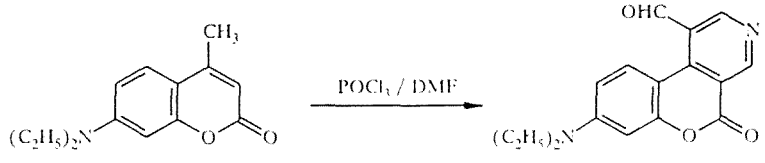
XXXV XXXVII XXXVI

R^1 = H, OCH_3; R^2 = CH_3, C_2H_5, C_6H_5, 3-coumarinyl

It is interesting that acetylcoumarin itself may partake in this reaction as a methyl ketone forming a 3-coumarinylpyrido-coumarin. In this latter case the supplier of nitrogen is cyanoacetamide, malonamide (49% yield), formamide (11%), a mixture of formamide and ammonium formate (4:1, 47% yield), and also urea (47%). The use of ammonium acetate or ammonia again did not lead to the desired result [33].

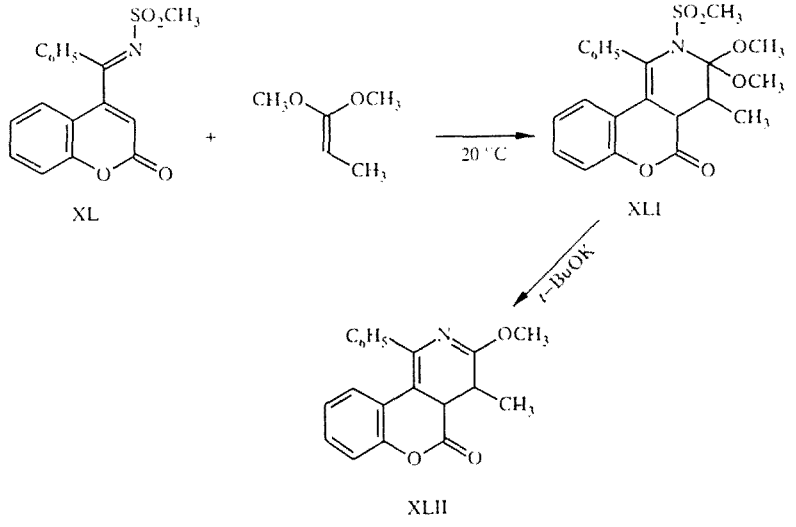
Acylcoumarins or their derivatives may react with other functionalized compounds.

The 4-methylcoumarin (XXXVIII) is formulated at the methyl group under the conditions of the Vilsmeier reaction and condenses with the dimethylamine fragment with the formation of the pyrido[3,4-c]coumarin (XXXIX) in good yield [34]



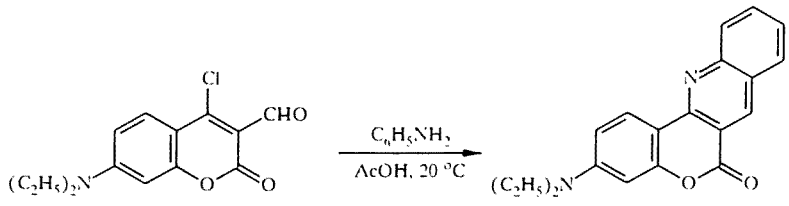
XXXVIII XXXIX

The use of the azadiene (XL) has been proposed as starting material for the synthesis of the substituted pyrido[4,3-c]coumarins (XLII) [35].



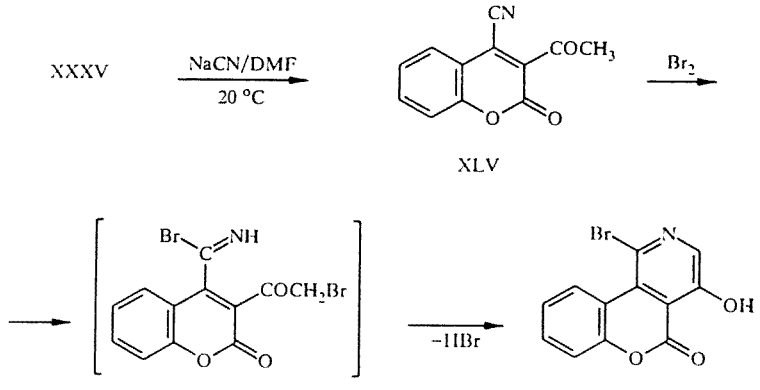
XL XLI XLII

The presence of one more functional group in the coumarin nucleus may change the position of the nitrogen atom in the ring [34].



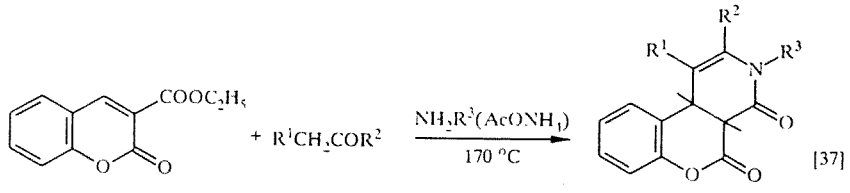
XLIII XLIV

Compound (XXXV) is first cyanated oxidatively to the 4-cyano derivative (XLV), then brominated, and leads by an intramolecular cyclization to the 1-bromo substituted 4-hydroxypyrido[4,3-c]coumarin (XLVI) in yields up to 65% [36].



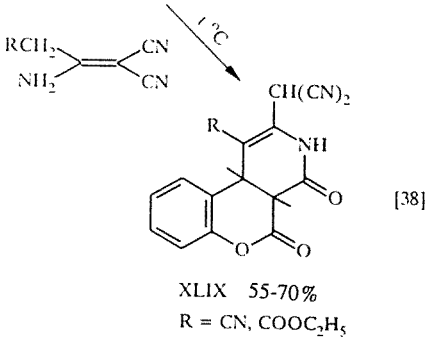
XLV XLVa XLVI

The use of coumarincarboxylic acid derivatives leads to the formation of 4-oxo compounds.

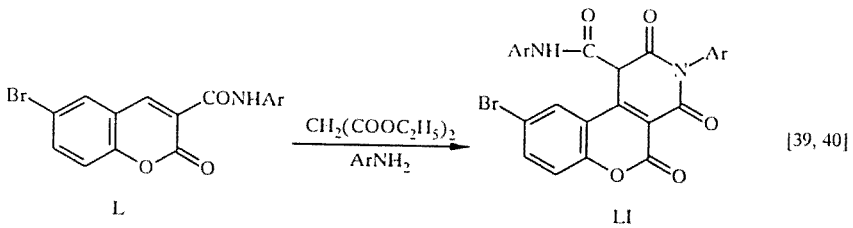


XLVII XLVIII [37]

R^1 = H, CH_3, C_nH_5; R^2 = CH_3;
$R^1 + R^2$ = $-(CH_2)_4-$, $-(CH_2)_5-$;
R^3 = H, α-naphthyl



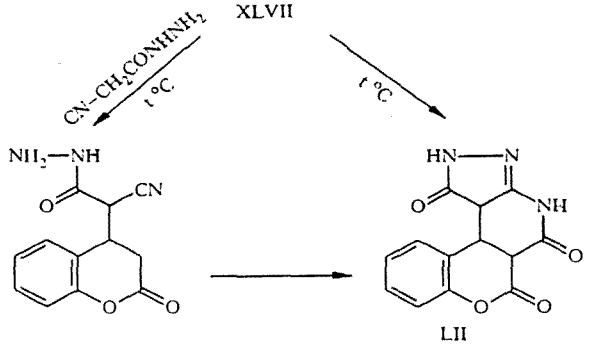
XLIX 55-70% [38]
R = CN, $COOC_2H_5$



L LI [39, 40]

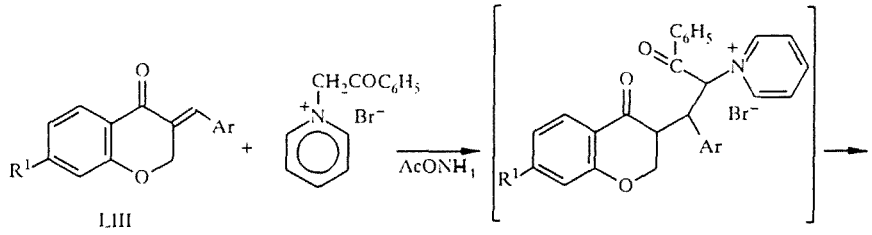
The coumarin (XLVII) also readily condenses with 3-amino-2-pyrazolin-5-one or with its synthon (cyanoacetic acid hydrazide) with the formation of the pyrido[3,4-c]coumarin system (LII) [38]. An analogous polycycle (5-methyl substitute) is formed under the same conditions from the acetylcoumarin (XXXV) (60-70% yield).

It is reported that these tetracyclic compounds display marked antibacterial activity.

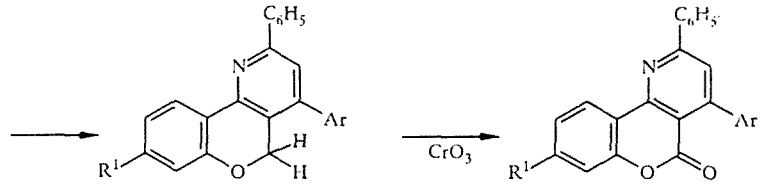


LII

1.2.3. Syntheses from Chromenes. Only in one case has the synthesis of pyridocoumarins from chromenes used oxidation of an intermediate pyridopyran (LIV) [41].

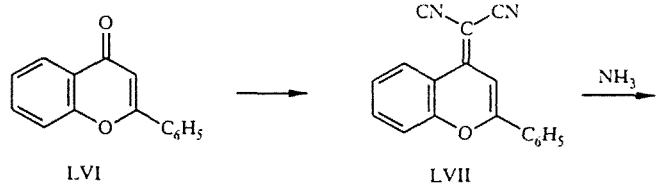


LIII

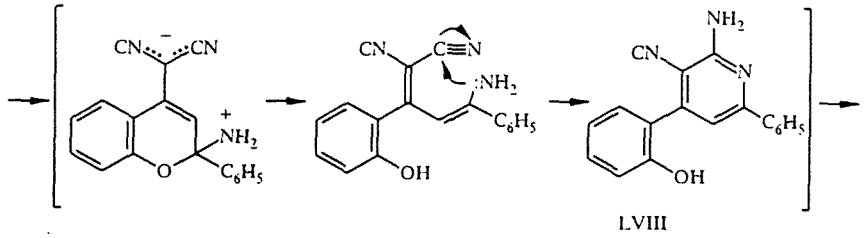


LIV LV

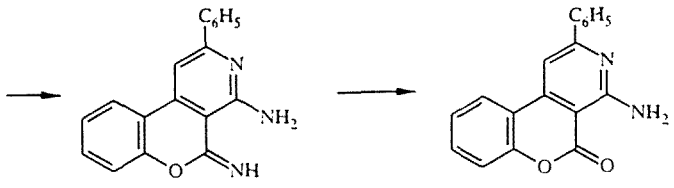
All the remaining methods of preparation from chromenes are based on the ability of the pyrane ring to be decomposed by the action of nucleophilic reagents. Thus 4-amino(imino) substituted pyrido[3,4-c]coumarins may be obtained in high yield from the flavone (LVI) and malondinitrile with subsequent heating of the 4-dicyanomethylene-2-phenyl-4H-benzopyran (LVII) formed in the first stage with ammonia [42].



LVI LVII

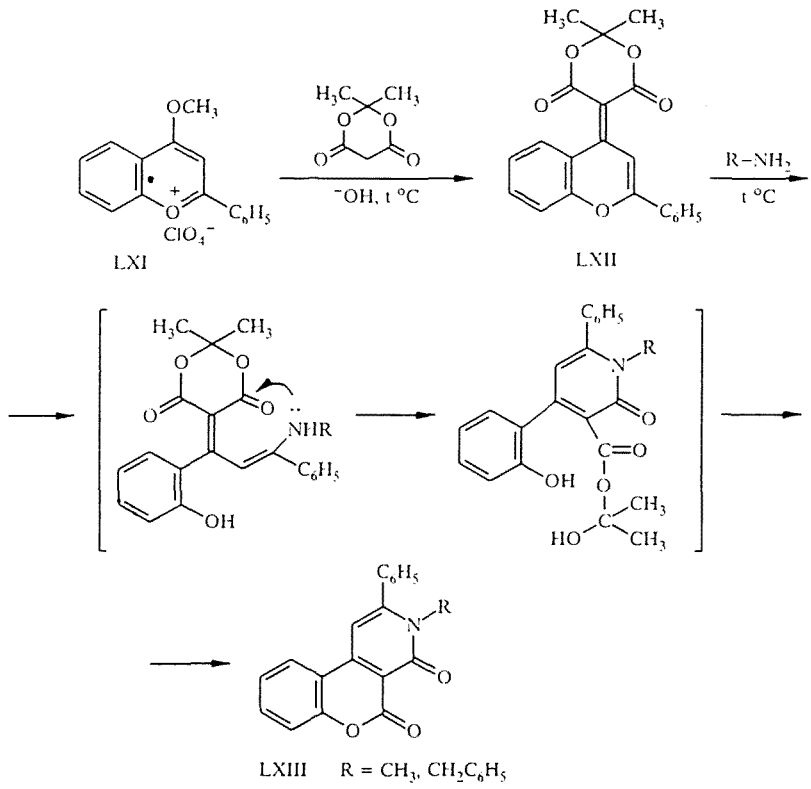


LVIII



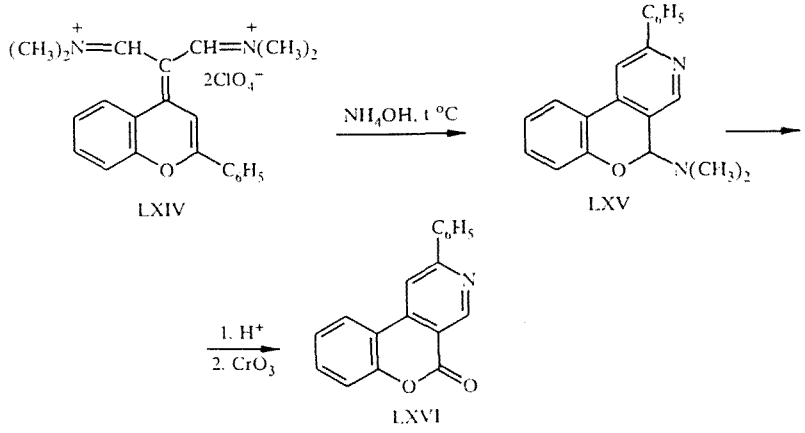
LIX LX

4-Alkylaminopyridocoumarins (50-80°C) or 3-alkyl-4-imino-3,4-dihydropyridocoumarins (depending on the temperature) are formed when using primary amines. A series of benzo annelated pyridocoumarins and pyridothiocoumarins was obtained by an analogous route. The 1,2,3,4-tetrahydro-pyrido[3,4-c]coumarin-4-ones (LXIII) were obtained from the 4-methoxyflavilium perchlorate (LXI) [43].



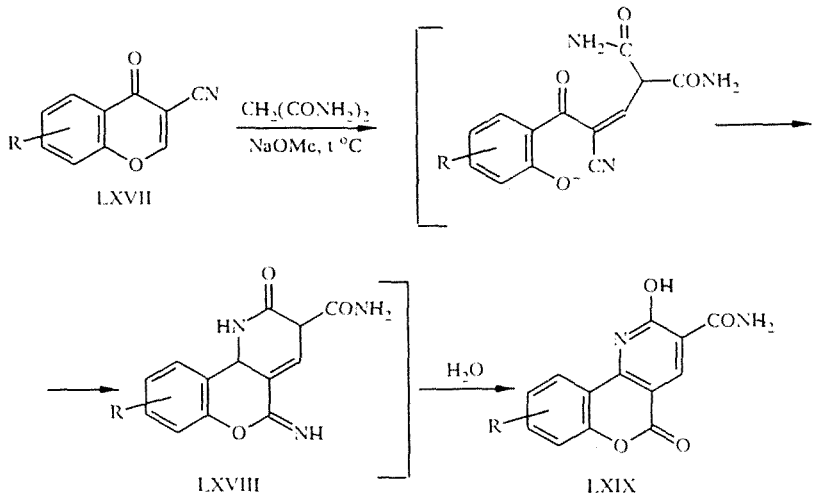
LXI LXII LXIII R = CH_3, $CH_2C_6H_5$

The bisiminium salts of the 4-propanediylidenebenzopyrane (LXIV) react with ammonia forming 5-dimethylamino-2-phenylpyrido[3,4-c]benzopyran (LXV), which is readily transformed (70%) by the action of acid into the corresponding 5-hydroxy derivative and then oxidized to the lactone (LXVI) (75%) [44].



LXIV LXV LXVI

The malondiamide anion is the nucleophilic reagent in the synthesis of a group of pyridocoumarins with [3,2-c]linkage from derivatives of 4-oxo-4H-1-benzopyran-3-carbonitrile (LXVII) [45, 46].



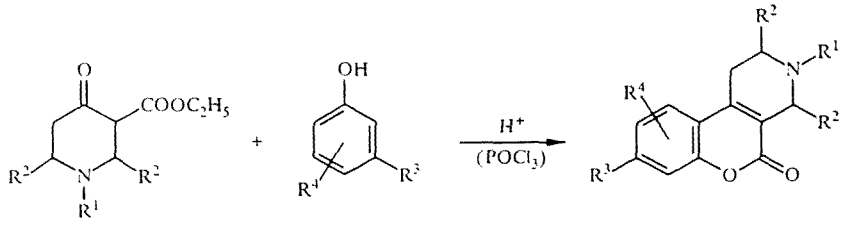
LXVII LXVIII LXIX

R = H, 9-C_2H_5, 9-azophenyl 7,9-$(CH_3)_2$

The effectiveness of using these compounds as antiallergic preparations has been reported in a patent [45].

1.3. Condensation of Phenols with Alkoxycarbonyl Substituted Piperidones

The possibility of obtaining the tetrahydropyrido[3,4-c]coumarins (LXXI) by the reaction of resorcinol with 3-carbethoxy-4-oxopiperidines (LXX) in the presence of sulfuric acid (by the Pechman reaction) was shown for the first time in 1955 [47]. This method was developed and used to obtain a whole series of similar derivatives in high yield [48, 49].

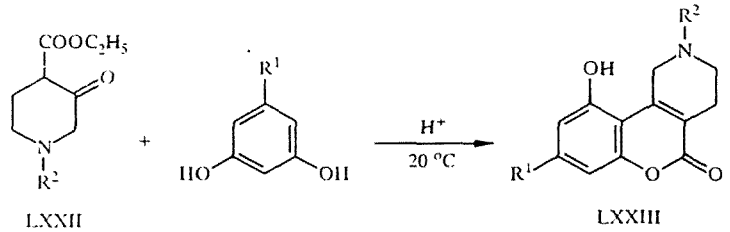


LXX LXXI

R^1, R^4 = H, Alk; R^2 = H, Ph; R^3 = H, OH, CH_3

Piperidones may be used in this condensation in the form of hydrochlorides. Certain derivatives possess a moderate fungicidal action [49].

The use of 4-carbethoxy substituted 3-piperidones (LXXII) in this reaction leads to the formation of analogous derivatives with a [4,3-c]linkage. The yields of the target products (LXXIII) were small (23-62%) [50-55].



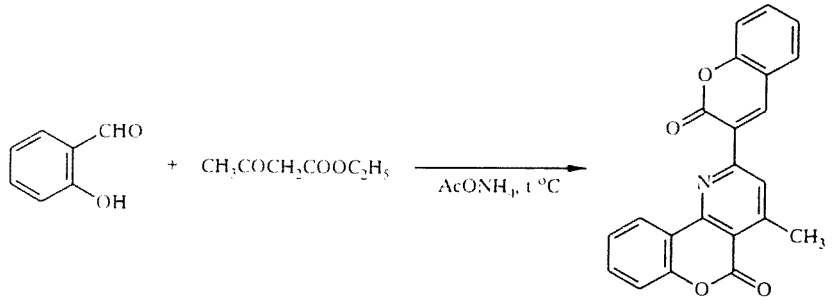
LXXII LXXIII

R^1 = CH_3, C_5H_{11}, C_7H_{15}, $C_{14}H_{29}$; R^2 = CH_3, $CH_2C_6H_5$

1.4. Condensation of Salicylic Aldehydes with Derivatives of Acetoacetic Ester or Malonic Acid in the Presence of Ammonia

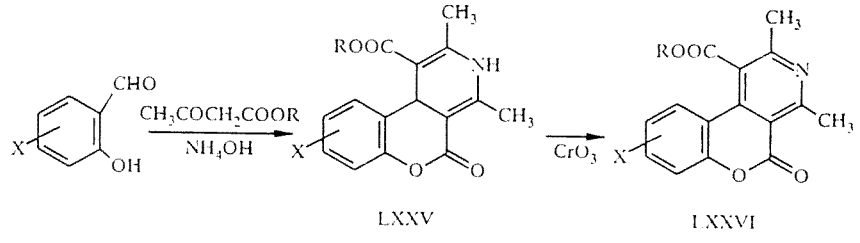
Readily available derivatives of salicylic aldehyde are frequently used to construct pyridocoumarin polycycles with [3,2-c] and [3,4-c]linkages. This route was first developed by Sakurai and collaborators [10, 56].

Salicylic aldehyde and acetoacetic ester are condensed in the presence of ammonium acetate with the formation of 2-(3-coumarinyl)-4-methylpyrido[3,2-c]coumarin (LXXIV) which is particularly interesting for a comparative study of the reactivity of the two coumarin fragments [56]. The yield of this polycycle was 31%.



LXXIV

The route of the condensation depends to a significant extent on the reaction conditions, viz. nitrogen source, solvent, reaction temperature, etc. Thus the analogous condensation of salicylic aldehyde with acetoacetic ester conducted in a mixture of acetic acid with 33% aqueous ammonia and ethanol leads to the preparation in low yield (7-12%) of 3,10b-dihydro derivatives of pyrido[3,4-c]coumarin (LXXV) [11], which were previously incorrectly designated as pyrido[3,2-c]coumarins [57].

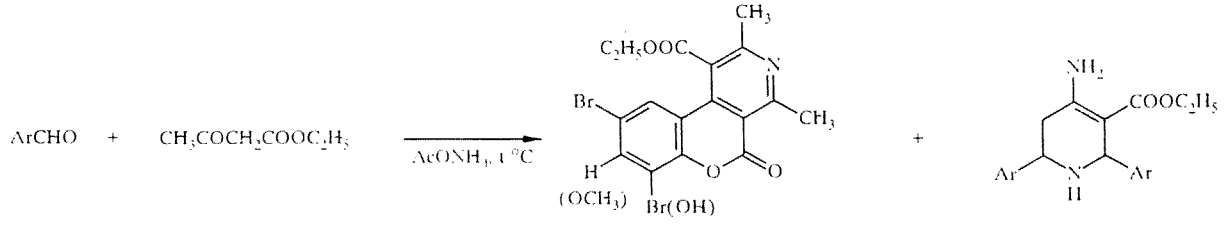


LXXV LXXVI

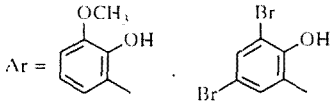
X = H, OCH_3, Alk; R = CH_3, C_2H_5

The dihydropyridocoumarins (LXXV) are then readily oxidized to the pyridocoumarins (LXXVI).

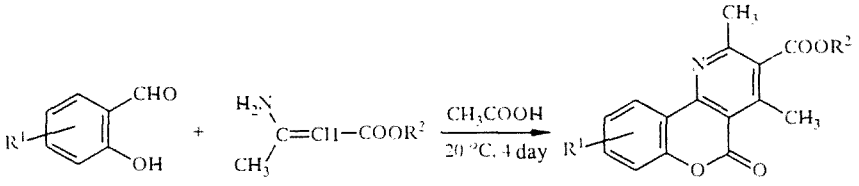
It is interesting that the condensation of 3-methoxy or 3,5-dibromo substituted salicylic aldehydes with acetoacetic ester in the presence of ammonium acetate (boiling in ethanol, 0.5 h) leads directly to the completely aromatized pyrido[3,2-c]coumarin (LXXVII), which in this case is a byproduct and was obtained in 7-10% yield [10]. The main product here is the tetrahydropyridine (LXXVIII) (50-53% yield).



LXXVII LXXVIII

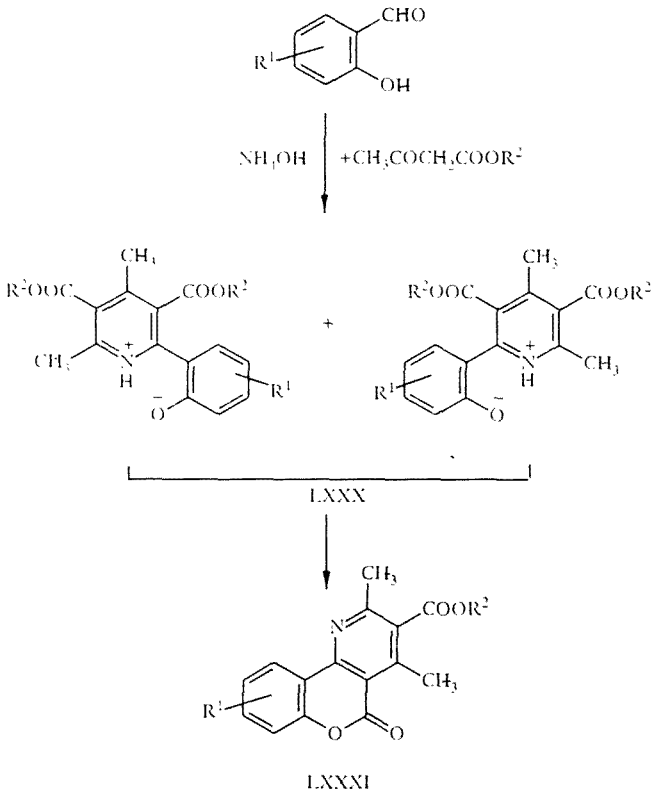


A single stage synthesis of the pyrido[3,2-c]coumarin (XXIX) has ben described by the condensation of substituted salicylic aldehydes with aminocrotonic ester in acetic acid. The yields of pyridocoumarins were small (15-36%) [11].



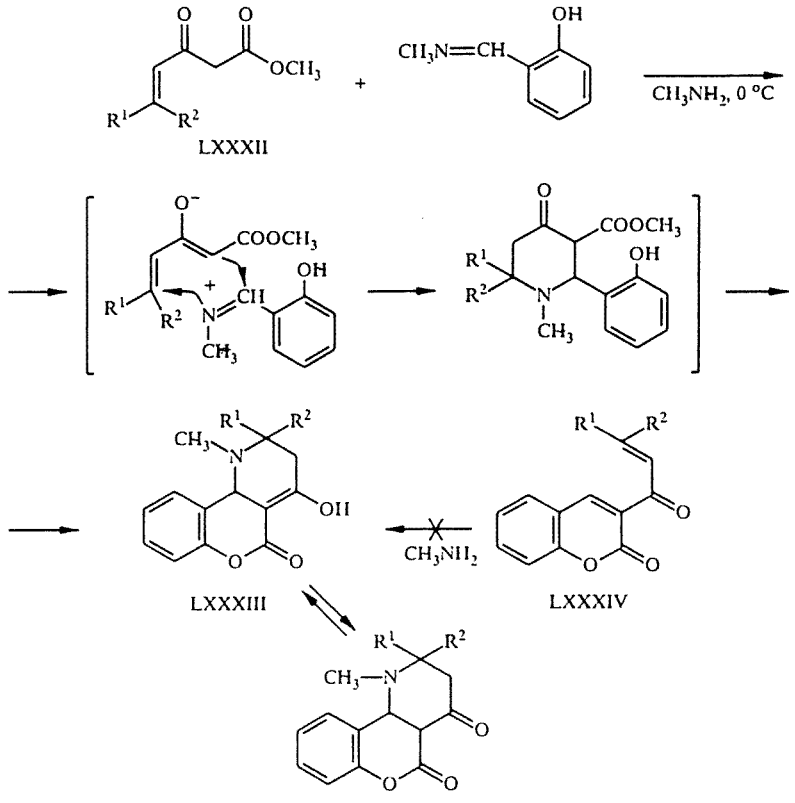
LXXIX

It must be noted that the condensation of salicylic aldehyde with acetoacetic ester and ammonia, effected without heating, may stop at the stage of forming the anomalous Hantzsch esters (LXXX). Further treatment with an oxidizing agent (nitric acid) is required for cyclization to the pyridocoumarins (LXXXI) [11].



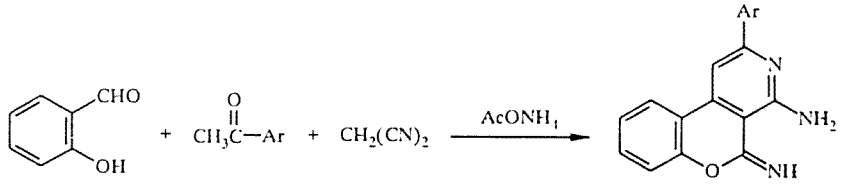
Substituted pyrido[3,4-c]coumarins are obtained in very low yield (5%) from 2-hydroxy-4-methoxybenzaldehyde and aminopropene-1-carbonitrile in the presence of piperidine [58]. The yield of pyridocoumarins in this condensation is increased somewhat (to 20%) when it is carried out in an acidic medium (CH_3COOH).

The 4-oxohexahydropyrido[3,2-c]coumarins (LXXXIII) are formed in yields of 10-62% by the reaction of alkenyl derivatives of acetoacetic ester (LXXXII) with the Schiff's base obtained from salicylic aldehyde and methylamine. The reaction proceeds satisfactorily only in the presence of an excess of methylamine [59].



Aromatization of the piperidinocoumarins (LXXXIII) with dichlorodicyano-p-quinone was unsuccessful. Attempts to synthesize the same pyridocoumarins by the condensation of methylamine with 3-(1-oxo-1-alk-2-enyl)coumarins (LXXXIV) were also negative. According to NMR data these compounds are completely in the enolic form in solution.

The formation of pyridocoumarin systems from salicylic aldehyde may also be effected successfully by using a mixture of ketone and malonic acid derivatives. 4-Amino-2-aryl-5-iminopyrido[3,4-c]coumarin (LXXXV) was obtained in this way in up to 30% yield. Subsequent replacement of the imino group by an oxo group was possible [60].

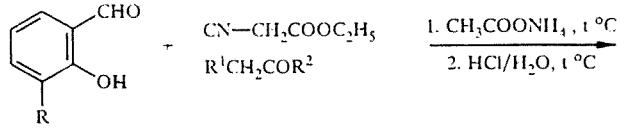


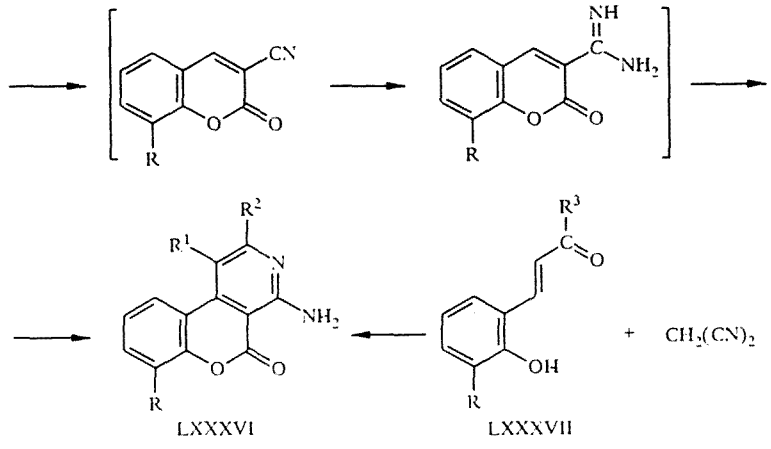
LXXXV

Ar = C_6H_5, $C_6H_4CH_3$-*p*

An analogous benzo-annelated pyrido[3,4-c]coumarin was obtained by the condensation of 1-hydroxy-2-naphthaldehyde with monocyanomalonic ester and ammonia [61].

Boiling (for 1.5-2 h) an equimolar mixture of four components, viz. salicylic aldehyde with ethyl cyanoacetate, various ketones or aliphatic aldehydes, and ammonium acetate, leads to the formation of the 4-aminopyrido[3,4-c]coumarins (LXXXVI) [62-66]



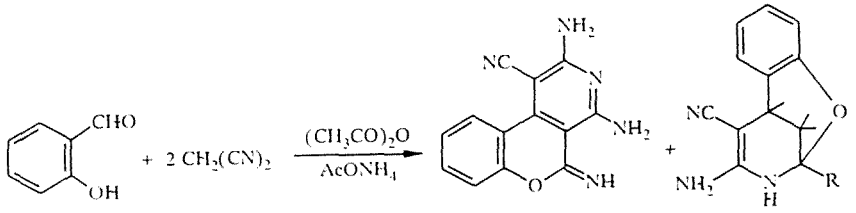


LXXXVI LXXXVII

R = H, OCH_3; R^1, R^2 = H, CH_3, Ar; R^3 = Alk, Ar

It was shown that the formation of these compounds occurs through amidinocoumarins.

A significant improvement in the yield of the analogous amino substituted pyridocoumarins (to 53%) was achieved by changing the order of adding the reactants [65]. The condensation of salicylic aldehyde with acetone or acetophenone was carried out first. Malondinitrile was then introduced. The intermediate 4-amino-5-imino pyridocoumarin derivatives were hydrolyzed to (LXXXVI). With this sequence the byproduct 4-oxo derivatives were not formed. Reaction of the chalcone (LXXXVII) with malondinitrile and ammonium acetate leads to the formation of the intermediate 2-amino-3-cyano-4-(α-hydroxyaryl)pyridine, which readily closes the pyran ring and after hydrolysis gives compound (LXXXVI) [67]. It was noted in [60, 66, 68] that variation of the ketone component in the condensation of salicylic aldehydes with malondinitrile leads to the synthesis of compounds (LXXXV), (LXXXVI), (LXXXVIII), and (LXXXIX). The latter (R = CH_3) was also identified in mixtures with a polycycle of type (LXXIV) (with a [2,3-c]linkage) formed by an analogous condensation with aceto-acetic ester [69].



LXXXVIII LXXXIX

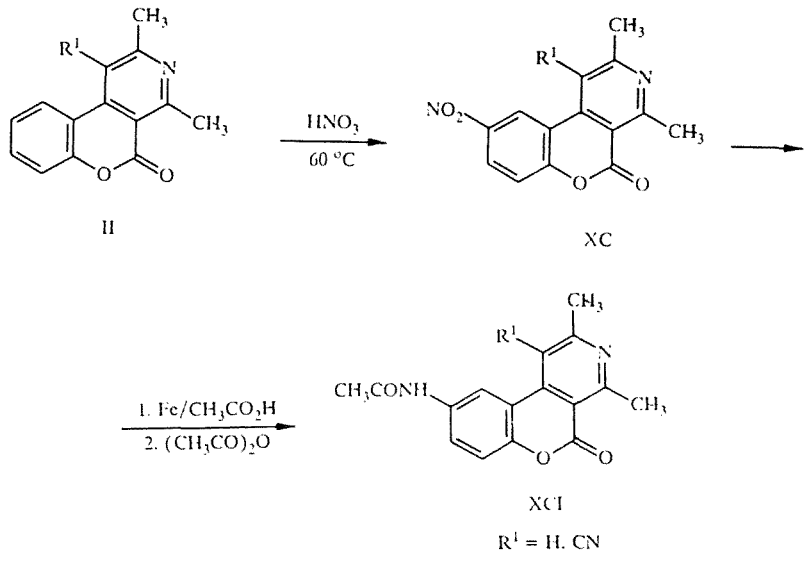
R = CH_3, C_2H_5

2. CHEMICAL CONVERSIONS OF PYRIDOCOUMARINS

2.1. Reactions of the Benzene Fragment

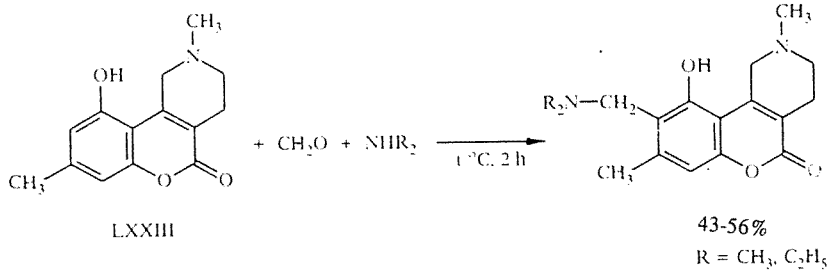
The reactivity of pyridocoumarins has been little studied both theoretically and experimentally. Only nitration and aminomethylation of the electrophilic substitution reactions have been effected. The functionalization of the benzene or pyridine fragments is usually achieved by using the appropriate substituted starting materials when making the pyridocoumarin itself, as considered in the preceding chapter.

The pyridocoumarin (II), unsubstituted in the benzene ring, is nitrated with fuming HNO_3 at the C_9 carbon atom to (XC) in quantitative yield [8].



The position of the nitro group at C_9 was confirmed by an alternate synthesis from 2-methoxy-5-nitrobenzaldehyde and β-aminocrotonitrile. Reduction of the nitro compound (XC) to the corresponding amine (XCI) occurred quantitatively. The yield of amine fell to 62% in the presence of a CN group at C_1. It must be emphasized that after introducing a nitro group at the C_9 position a CN group at C_1 may be hydrolyzed (HBr, 48%) to the acid in low yield (which is not achieved in the absence of activating NO_2 group). Nitration of an unsubstituted pyrido[3,2-c]coumarin is also oriented to the C_9 carbon atom (the yield of nitro compound was 67%) [31].

Mannich aminomethylation of the phenolic fragment of the tetrahydropyridocoumarins (LXXIII) has been effected [70].

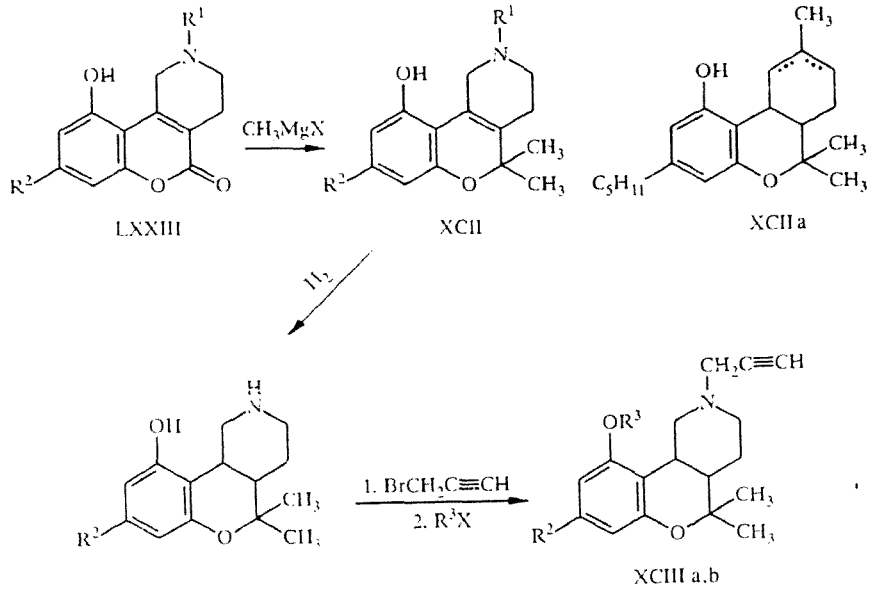


If an OH group is present at C_8 in the benzene nucleus then the aminomethylation occurs at position 7. Cyclic amines such as piperidine, morpholine, and pyrrolidine also react readily. There are no data on the Mannich condensation in the absence of an activating phenolic group.

These two reactions exhaust the literature data on electrophilic substitution in the benzene nucleus of pyridocoumarins.

2.2. Reactions at the Pyrane Fragment

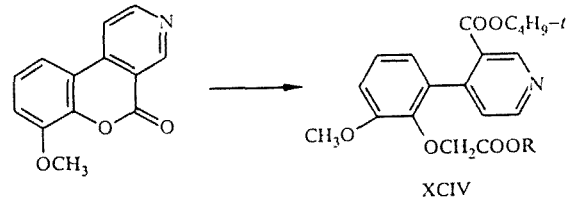
Substituted piperidino[4,3-c]coumarins of the (LXXIII) type are methylated in anisole solution with an excess of methylmagnesium iodide at 50°C to (XCII) (47% yield) [50]. The compounds obtained in this way are considered as physiologically active nitrogen analogs of the natural tetrahydrocannabinols (XCIIa), the active components of marijuana (centrally acting depressants) [51-55]. The synthetic scheme for two of the preparations, viz. nabital (XCIIIa) and A-41988 (XCIIIb) is shown below. These compounds are undergoing extended clinical testing as centrally acting analgesics [71].



LXXIII $R^1 = CH_3, CH_2Ph$; $R^2 = Alk\ (C_5\text{-}C_9)$, ArAlk;
XCII a $R^2 = CH(CH_3)CH(CH_3)C_5H_{11}$; $R^3 = COCH_2CH_2CH_2\text{-}NC_5H_{10}$;
b $R^2 = CH(CH_3)CH_2CH_2CH_2C_6H_4F$; $R^3 = H$

The unsubstituted pyrido[4,3-c]coumarin (V) is converted by the action of phenylmagnesium bromide into a 5,5-diphenyl substituted pyridochromene [13].

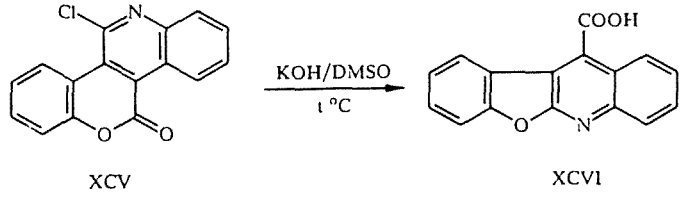
Alkaline reagents readily open the lactone ring. Ring opening reduces the physiological activity of the compounds of type (XCII) and (XCIII) mentioned above. A series of 4-arylnicotinates (XCIV) was obtained in yields up to 96% by the action of potassium t-butylate on 7-methoxypyrido[3,4-c]coumarin at −65°C and subsequent treatment of the reaction mixture with alkyl bromoacetate [19]. Compounds (XCIV) are then used for the synthesis of spiro[benzofuran-3,4′-piperidines] which are codeine analogs.



XCIV

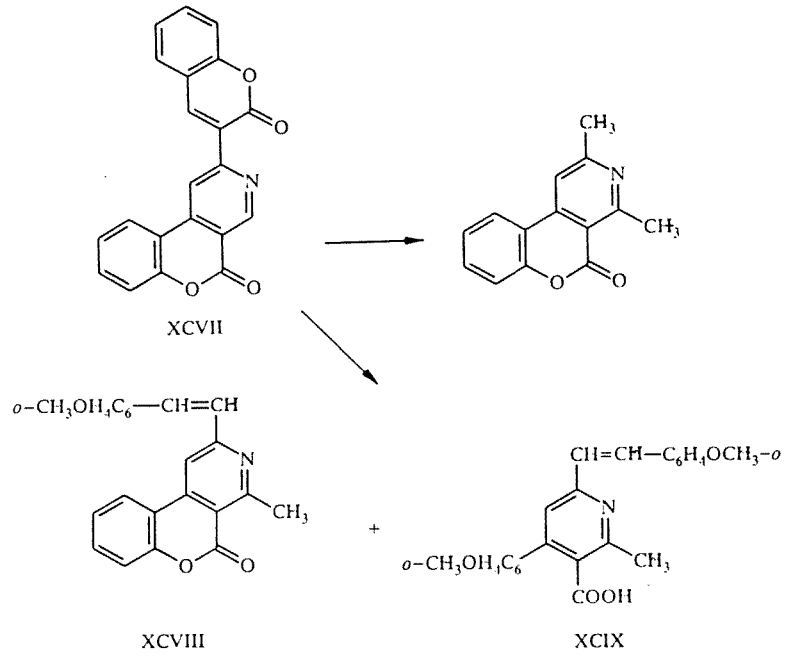
The dihydropyrido[3,4-c]coumarins (LXXVII) are also readily decomposed by K_2CO_3 in ethanol at 25°C into 1,4-dihydro-4-arylpyridines [12].

An interesting conversion of the six-membered lactone ring of the quinolinocoumarin (XCV), having a chlorine atom in the pyridine ring, was observed on heating with alkali in DMSO [16]. Fission of the lactone occurs but the product recyclizes with elimination of the chlorine atom and the formation of benzofuro[2,3-b]quinoline-11-carboxylic acid (XCVI) in 47% yield.



XCV XCVI

By the sequential action of alkali, methyl sulfate, and heating of the isolated dry quaternary salt, 2-(3-coumarinyl)pyridocoumarin (XCVII) is converted into a mixture of two compounds (XCVIII) and (XCIX), formed as a result of the sequential opening of the pyrane rings, initially into a 3-coumarinyl substituent, and then into a pyridocoumarin fragment [33].



XCVII

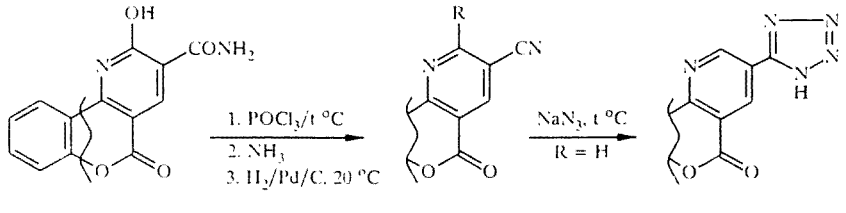
XCVIII

XCIX

Stabilization of the coumarin fragment by condensing it with a pyridine nucleus was shown in a similar way by fusing (XCVII) with alkali (220°C), which leads to the formation of a 2,4-dimethylpyridocoumarin (43% yield). Alkaline oxidation of (XCVII) gave 2,3,4,6-pyridinetetracarboxylic acid.

2.3. Reactions at a Substituted Pyridine Nucleus

Reactions at the unsubstituted pyridine nucleus of pyridocoumarins have not been studied in practice with the exception of its quaternization [13, 44] or aromatization of a dihydropyridine fragment with the aid of an oxidizing agent [57]. Reports mainly cover the conversions of substituents in the pyridine ring. Thus pyridocoumarin-carboxylic acids are readily decarboxylated on short heating above the melting point [7] or on heating in quinoline (170°C, 2 h) [28]. The saponification of amide groups at C_4 to carboxyl, and 2-ethoxyl to a 2-oxo group have been effected in high yield [28]. Conversions of various functional groups at positions 2 and 3 of the pyridocoumarin (C) have been carried out [46].



C

CI

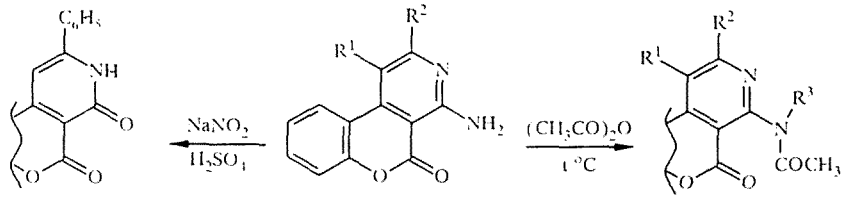
CII

R = H, Cl, NH_2

A hydroxyl group at C_2 is replaced by chlorine (31% yield) by the action of PCl_5 and $POCl_3$ at 120°C. In its turn chlorine may be replaced by an amino group in high yield. The reductive dechlorination of the 2-chloro derivative of the pyridocoumarin (CI, R = Cl) has been effected. It must be noted that on chlorination of 3-carboxamido-2-hydroxypyridocoumarin (C) simultaneous dehydration of the amide group also occurs with the formation of a cyano group. The latter then reacts with sodium azide on heating, being converted into a tetrazole substituent. A cyano group, like an amide, at C_3 of the pyridocoumarin is saponified on heating in 50% sulfuric acid and acetic acid (1:1, 120°C, 4-15 h) to a carboxyl group with a yield of pyridocoumarin-3-carboxylic acid of 56-64%.

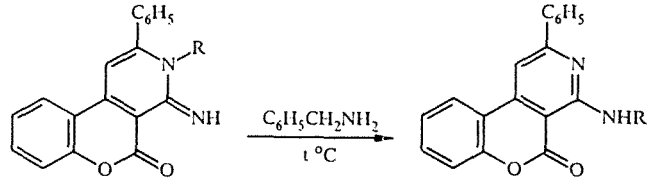
The amination of 1-bromo-4-hydroxypyrido[4,3-c]coumarin has been effected by replacing bromine with butylamine (80% yield) [36]. 4-Aminopyrido[3,4-c]coumarin (CIII), having no substituent in position 2, is acylated by acetic anhydride

in pyridine to the diacetyl derivative (CIV) [63]. When an alkyl or aryl (apart from phenyl) substituent is present in this position acylation under identical conditions forms only a monocylamide. This is probably linked with steric hindrance [62].



CV CIII CIV

The amino group at position 4 of the pyridocoumarin (CIII) is readily replaced by chlorine (70% yield) by the action of sodium nitrite in HCl [42]. If the reaction is carried out in sulfuric acid and then this amino group is replaced by oxygen [compound (CV)]. In the same study the possibility was established of carrying out a Dimroth rearrangement for 3-alkyl(aralkyl) substituted 4-imino-pyrido[3,4-c]coumarins (CVI) on boiling them in benzylamine or in a solution of KOH in ethylcellosolve to compound (CVII). The rearrangement was not observed on heating these compounds with KOH in methanol.



CVI CVII ~70%

R = C_4H_9, $CH_2C_6H_5$

The following conclusions may be drawn from an analysis of the publications on the chemistry of pyridocoumarins.

1. The state of this subdivision of heterocyclic chemistry is characterized by the small number of studies, publications being mainly devoted to the development of methods of synthesizing pyridocoumarins.

2. The reactivity and useful properties of pyridocoumarins and their derivatives have been studied to an insignificant and their derivatives have been studied to an insignificant extent and unsystematically in spite of the obvious promise of this group of compounds, containing coumarin and pyridine fragments, as biologically active substances and dyestuffs for lasers.

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